# Symptomatic and Functional Response and Remission From the Open-Label Treatment-Optimization Phase of a Study With DR/ER-MPH in Children With ADHD

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**ABSTRACT**

**Objective:** Delayed-release and extended-release methylphenidate (DR/ER-MPH), the first stimulant predicted to be absorbed primarily in the colon, demonstrated significant improvements in attention-deficit/hyperactivity disorder (ADHD) symptoms and functional impairment from awakening until evening versus placebo in clinical trials. The clinical significance of these improvements was explored post hoc by examining response and remission thresholds as well as safety in the context of dose optimization.

**Methods:** Data from the open-label, treatment-optimization phase of a phase 3 study of DR/ER-MPH in children (aged 6–12 years) with ADHD, as diagnosed by *DSM-5* criteria and enrolled between July 2015 and March 2016, were analyzed. Thresholds for response (anchored to Clinical Global Impressions–Improvement scale [CGI-I] score of 1 or 2) and remission were applied to ADHD Rating Scale-IV (ADHD-RS-IV), Before School Functioning Questionnaire (BSFQ), and Parent Rating of Evening and Morning Behavior, Revised, Morning Subscale (PREMB-R AM) and Evening Subscale (PREMB-R PM) scores. Rates of response, remission, and treatment-emergent adverse events by starting dose were examined.

**Results:** Mean DR/ER-MPH dose increased from 29.7 mg/d at baseline (51% on 20 mg/d; 49% on 40 mg/d) to 66.2 mg/d at week 6. At week 6, most participants achieved response/remission thresholds (response/remission: ADHD-RS-IV: 97%/89%; BSFQ: 98%/94%; PREMB-R AM: 94%/98%; PREMB-R PM: 91%/84%). More participants starting on a 40-mg versus 20-mg dose achieved thresholds at week 1 (*P* < .02). Weekly treatment-emergent adverse event rates over the open-label period were similar between starting doses.

**Conclusions:** When DR/ER-MPH dosing was optimized for ADHD symptom control throughout the day, the majority of participants achieved thresholds indicating all-day control of ADHD symptoms and functional impairment to the level of their non-ADHD peers.

**Trial Registration:** Data used in this post hoc analysis came from the study with ClinicalTrials.gov identifier: NCT02493777

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Recent guidelines for the treatment of attention-deficit/hyperactivity disorder (ADHD)[1,2] emphasize the importance of treatments with durations of effect that extend beyond the school- and workday. These guidelines also stress the importance of implementing treatments that target functional impairment, commonly the primary cause for seeking treatment for ADHD,[3] in addition to symptom control. Despite formulation improvements, all-day clinical efficacy with a single stimulant dose has remained an unmet need in adults[4] and youth[5,6] with ADHD.

HLD200, a delayed-release and extended-release formulation of methylphenidate (DR/ER-MPH; trade name: JORNAY PM) approved by the US Food and Drug Administration (FDA) for the treatment of ADHD in individuals aged 6 years and older,[7] is the first stimulant that is predicted to be absorbed primarily in the colon following evening administration without an immediate-release component. Because the colon is a less efficient site of absorption compared to the upper gastrointestinal tract,[8] colonic absorption is predicted to underlie several of the pharmacokinetic properties of DR/ER-MPH, including a gradual ascending curve in the early morning, attenuated peak plasma concentration, protracted elimination phase into the evening, and a dose-dependent duration of effect.[9,10] In two phase 3 studies of children with ADHD,[11,12] treatment with DR/ER-MPH improved symptoms as well as functional impairment during the early morning, over a laboratory classroom test day, and in the late afternoon/evening versus placebo.

Primary and secondary efficacy endpoints, including those from the two phase 3 studies of DR/ER-MPH, are typically averages of continuous measures, which summarize a range of individual treatment outcomes. A categorical outcome measure based on a threshold of treatment success (ie, proportion of patients that achieve the thresholds) may be more clinically intuitive than information from a continuous outcome measure based on group averages.[13] As such, applying established cutoffs can help clinicians understand the clinical meaningfulness of an aggregate treatment effect and help predict positive individual patient outcomes.[13,14] A number of thresholds using various symptom scales have been used to determine symptomatic response, including a decrease in ADHD Rating Scale-IV (ADHD-RS-IV) or Swanson, Nolan, and Pelham-IV-18 (SNAP-IV-18) total score of 25%–30%

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### Clinical Points

- Results from clinical trials do not always generate the full complement of information that is relevant to clinicians, such as providing dosing recommendations to achieve optimal outcomes.

- After a 6-week dose optimization period with delayed-release and extended-release methylphenidate (DR/ER-MPH), clinically meaningful improvements were seen in attention-deficit/hyperactivity disorder (ADHD) symptom and functional impairment response and remission rates from early morning to evening in the vast majority of patients. The higher starting dose of 40 mg was associated with earlier improvements without sacrificing safety.

- Optimization of ADHD symptom control in the evening is especially important, as evening improvement lags behind morning improvement during titration due to the dose-dependent duration of effect of DR/ER-MPH. As doses were optimized overall outcomes improved, and optimized doses led to clinically meaningful evening improvements.

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to define response or 40%–50% to define a more robust response, either alone or in combination with a Clinical Global Impressions–Improvement scale (CGI-I) score of 1 (very much improved) or 2 (much improved).[15–24] Weiss and colleagues[25] identified a decrease of 40% in ADHD-RS-IV total score as being most closely aligned with individuals being very much or much improved (CGI-I score = 1 or 2).

Some have proposed utilizing more robust thresholds to achieve scores within the range of unaffected individuals, which has been termed symptomatic or functional remission.[26–28] In the context of ADHD, a neurodevelopmental disorder, remission is contextualized within the framework of currently available treatments and does not reference duration of improvement. Symptomatic remission in ADHD has commonly been operationalized as ADHD-RS-IV or SNAP-IV-18 scores of ≤ 18, indicating mean scores of ≤ 1 ("mild or less") per item.[13,26] This threshold for remission captured 88% of children in the control group of the National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA).[13]

Recently, decreases in total score of at least 45%, 49%, and 29% were determined to be clinically meaningful (anchored to CGI-I score = 1 or 2 [very much or much improved]) for the Before School Functioning Questionnaire (BSFQ); Parent Rating of Evening and Morning Behavior, Revised, Morning Subscale (PREMB-R AM); and PREMB-R Evening Subscale (PREMB-R PM), respectively.[29] For the BSFQ, PREMB-R AM, and PREMB-R PM, age-appropriate norm-referenced cutoffs[30] have also been determined to identify severity (screening risk, mild, moderate, and severe) of functional impairment during the early morning and late afternoon/evening. Individuals with scores below screening risk (< 80th percentile) represent a level of functional impairment that is indistinguishable from the general population (ie, functional remission). Indeed, scores below the screening risk threshold on the BSFQ, PREMB-R AM, and PREMB-R PM captured 87%–89% of youth with no ADHD and no comorbidities.[30]

The goal of these post hoc analyses was to examine symptom and functional impairment scores by applying categorical cutoffs for response and remission in the context of DR/ER-MPH dosing during the 6-week, open-label, treatment-optimization period of a phase 3 study.[12] Rates of treatment-emergent adverse events (TEAEs) in the context of DR/ER-MPH dosing were also examined.

## METHODS

### Participants

Children (aged 6–12 years) were enrolled in the study if they met the predefined entry criteria, as described in a previous report.[12] Briefly, key inclusion criteria included diagnosis of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition[31] criteria and confirmed with the Mini-International Neuropsychiatric Interview for Children and Adolescents; baseline ADHD-RS-IV score ≥ 90th percentile normalized for sex and age in at least one of the following categories: inattentive, hyperactive-impulsive, or total score, and a total score of ≥ 26 at baseline; prior response to MPH treatment; and parent/guardian confirmation of before-school functional impairment and difficulties performing morning routine, with a weekday morning routine of at least 30 minutes.

### Study Design

This pivotal phase 3, multicenter, laboratory classroom study (NCT02493777) of DR/ER-MPH in children with ADHD took place between July 2015 and March 2016 and was conducted in 3 distinct phases: (1) a screening/washout phase (up to 4 weeks, with washout of ADHD treatment for ≥ 5 days); (2) a 6-week, open-label, DR/ER-MPH treatment–optimization phase; and (3) a 1-week, double-blind, randomized, placebo-controlled, parallel-group phase concluding with a laboratory classroom test day. At baseline, all participants received DR/ER-MPH, either 20 mg or 40 mg, once daily at 8:00 PM (± 30 minutes), with the starting dose dependent on their previous treatment history. Over the 4 subsequent study visits (weeks 1, 2, 3, and 4), dose titrations were permitted in 20- or 40-mg increments or decrements until an optimal daily dose was achieved or a maximum daily dose of 100 mg/d or 3.7 mg/kg was reached. Adjustments to the evening administration time in 30- to 60-minute increments or decrements were permitted (between 6:30 PM and 9:30 PM).

Optimized dose and administration time were predefined as those that produced meaningful control during the morning and throughout the day while remaining safe and well tolerated with ≥ 33% improvement from baseline in ADHD-RS-IV, BSFQ, and Conners' Global Index–Parent [CGI-P] scores. The final permitted dose and administration time adjustments were made at the week 4 visit, after which dose and administration time were to be maintained from

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the week 5 visit through to randomization at the week 6 visit (after completing the 6-week treatment-optimization phase).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all participants and parents/legal guardians provided informed assent and consent, respectively, under procedures approved by each site's Institutional Review Board.

## Assessments and Statistical Analyses

Descriptions of assessments, including timing and scoring, are listed in Supplementary Table 1. Post hoc analyses were performed in the intent-to-treat (ITT) population, defined as randomized participants who received at least one dose of double-blind study drug and had at least one post-baseline evaluation of the primary efficacy variable. Dose, number of participants at each dose level, ADHD-RS-IV scores, and BSFQ scores were summarized at each time point using descriptive statistics; the PREMB-R AM and PREMB-R PM were administered only at baseline and week 6. Rating scale scores reflected symptoms or functional impairment over the preceding week. Percentage change from baseline for ADHD-RS-IV, BSFQ, and PREMB-R AM/PM (week 6 only) total scores was calculated as

$$100 \times \frac{Baseline\ Score - Visit\ Score}{Baseline\ Score}$$

The response thresholds applied in this study were determined using the same external anchor (CGI-I score = 1 or 2, indicating very much or much improved). The following response thresholds were used: ADHD-RS-IV score, ≥40% decrease from baseline; BSFQ score, ≥45% decrease from baseline, PREMB-R AM score, ≥49% decrease from baseline; and PREMB-R PM score, ≥29% decrease from baseline.[25,29] Similarly, the remission thresholds that were applied were also chosen because they identify the majority of youth without ADHD (Supplementary Table 1).[13,30] For children 6–8 and 9–12 years of age, respectively, the following remission thresholds were used: BSFQ, ≤24 and ≤21; PREMB-R AM, ≤4 and ≤3; and PREMB-R PM, ≤10 and ≤8.[30] The proportion achieving each threshold was compared, using the Fisher exact test, between those who received a starting dose of 20 mg and those who received 40 mg. TEAEs were assessed by general query at weekly visits. TEAEs of special interest included those related to sleep and appetite. Unlike all other TEAEs, which were spontaneously reported, sleep-related TEAEs were directly queried by asking about onset, quality, and quantity of sleep. The number and percentage of participants reporting TEAEs and the number of TEAEs were summarized by baseline dose (ie, those starting on 20 mg vs 40 mg).

## RESULTS

### Participants

Participant disposition as well as demographics and baseline characteristics have been previously reported.[12]

Briefly, the ITT population (N = 117), in which all analyses were performed, was 68.4% male (80/117), mean ± SD age was 9.4 ± 1.63 years, and presentation was mostly combined type (86.3%) with some predominantly inattentive (13.7%). The mean ± SD baseline ADHD-RS-IV score was 42.5 ± 6.60. The mean ± SD baseline BSFQ score was 40.7 ± 10.28, which corresponds to meeting the 93rd percentile threshold or moderate severity of early morning functional impairment,[30] and 5 (4.3%) of 117 participants had BSFQ scores below the 80th percentile or screening risk at baseline. The mean ± SD baseline PREMB-R AM score was 5.7 ± 2.44, which corresponds to meeting the 80th percentile threshold or screening risk,[30] and 23 (19.7%) of 117 participants had PREMB-R AM scores below screening risk at baseline. The mean ± SD baseline PREMB-R PM score was 17.2 ± 4.17, which corresponds to meeting the 93rd percentile threshold or moderate severity of late afternoon/evening functional impairment,[30] and 3 (2.6%) of 117 participants had PREMB-R PM scores below screening risk at baseline.

### Dose Titration

Investigators were provided a starting dose manual that prespecified DR/ER-MPH starting doses based on previous methylphenidate dosing. The starting doses were calculated based on available pharmacokinetic and comparative bioavailability data and rounded down to 20 mg or 40 mg of DR/ER-MPH. On the basis of previous dosing history, approximately half of participants (51.3%) received 20 mg and approximately half (48.7%) received 40 mg as their initial dose at baseline (Table 1). The final mean ± SD optimized dose was 66.2 ± 19.56 mg,[12,36] with 87.2% optimized to 40-, 60-, or 80-mg doses (Table 1). At the beginning of the open-label period, the majority of participants (93.2%) had a prescribed administration time of 8:00 PM. At the end of the open-label period, the most common (64.1%) administration time was still 8:00 PM, with most adjustments shifting to administration later in the evening (Table 1).

### Substantial Mean Improvements in ADHD Symptoms and Functional Impairment During the Early Morning and Late Afternoon/Evening

ADHD-RS-IV (Supplementary Figure 1A) and BSFQ (Supplementary Figure 1B) mean scores improved markedly from the baseline assessment (reflecting the previous untreated week) to the week-1 assessment (reflecting the first week of open-label treatment). The randomization criterion of ≥33% improvement on the ADHD-RS-IV and BSFQ was achieved after 1 week of DR/ER-MPH treatment (Supplementary Figure 1); therefore, dose increases over the subsequent weeks (Table 1) were guided by ADHD-RS-IV and BSFQ scores (but not by a specific target) and clinical judgement to optimize treatment effect throughout the day. Following the first week of treatment, ADHD-RS-IV and BSFQ mean scores continued to improve week-over-week during the treatment-optimization period, generally

**Table 1. Weekly Dosage Titration Parameters[a]**

| Parameter | Baseline | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 |
|---|---|---|---|---|---|---|
| Prescribed dose, n (%) | | | | | | |
| 20 mg | 60 (51.3) | 12 (10.3) | 5 (4.3) | 4 (3.4) | 2 (1.7) | 2 (1.7) |
| 40 mg | 57 (48.7) | 67 (57.3) | 39 (33.3) | 31 (26.5) | 24 (20.5) | 24 (20.5) |
| 60 mg | 0 | 38 (32.5) | 53 (45.3) | 42 (35.9) | 40 (34.2) | 40 (34.2) |
| 80 mg | 0 | 0 | 20 (17.1) | 35 (29.9) | 38 (32.5) | 38 (32.5) |
| 100 mg | 0 | 0 | 0 | 5 (4.3) | 13 (11.1) | 13 (11.1) |
| Prescribed dose in mg, mean (SD) | 29.7 (10.04) | 44.4 (12.35) | 55.0 (15.74) | 61.0 (18.73) | 66.2 (19.56) | 66.2 (19.56) |
| Prescribed administration time, n (%) | | | | | | |
| 6:30 PM | 0 | 0 | 0 | 0 | 0 | 0 |
| 7:00 PM | 0 | 1 (0.9) | 1 (0.9) | 1 (0.9) | 1 (0.9) | 1 (0.9) |
| 7:30 PM | 3 (2.6) | 1 (0.9) | 2 (1.7) | 3 (2.6) | 2 (1.7) | 2 (1.7) |
| 8:00 PM | 109 (93.2) | 88 (75.2) | 78 (66.7) | 72 (61.5) | 75 (64.1) | 75 (64.1) |
| 8:30 PM | 5 (4.3) | 17 (14.5) | 23 (19.7) | 22 (18.8) | 19 (16.2) | 19 (16.2) |
| 9:00 PM | 0 | 10 (8.5) | 13 (11.1) | 19 (16.2) | 20 (17.1) | 20 (17.1) |
| 9:30 PM | 0 | 0 | 0 | 0 | 0 | 0 |
| Prescribed administration time, median (range) | 8:00 PM (7:30–8:30 PM) | 8:00 PM (7:00–9:00 PM) | 8:00 PM (7:00–9:00 PM) | 8:00 PM (7:00–9:00 PM) | 8:00 PM (7:00–9:00 PM) | 8:00 PM (7:00–9:00 PM) |

[a]Percentages based on N = 117.

**Figure 1. Proportion of Study Participants Achieving (A) Symptomatic and (B) Early Morning Functional Impairment Response and Remission Thresholds at Each Open-Label Visit**
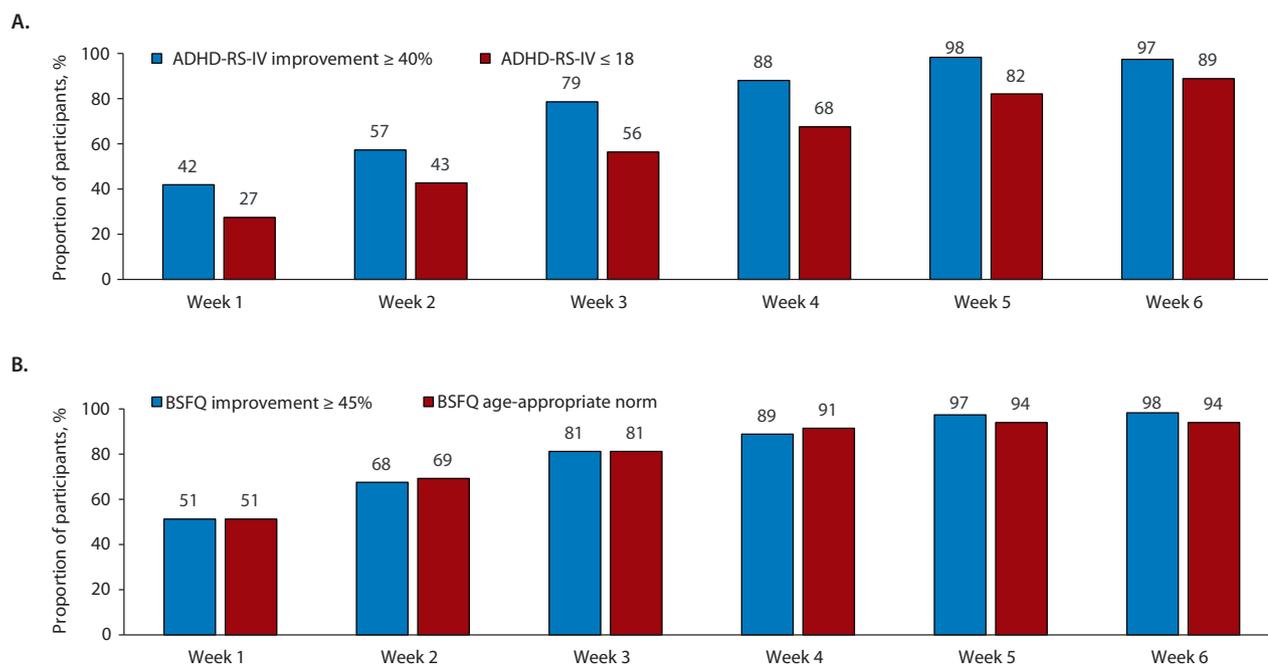


Abbreviations: ADHD-RS-IV = ADHD Rating Scale-IV, BSFQ = Before School Functioning Questionnaire.

mirroring increases in mean doses (Table 1). PREMB-R AM and PREMB-R PM scores also improved substantially from baseline to week 6 (not measured in intervening weeks): mean ± SD PREMB-R AM scores improved from 5.7 ± 2.44 at baseline to 0.8 ± 1.11 at week 6, and PREMB-R PM scores improved from 17.2 ± 4.17 at baseline to 5.3 ± 4.20 at week 6.
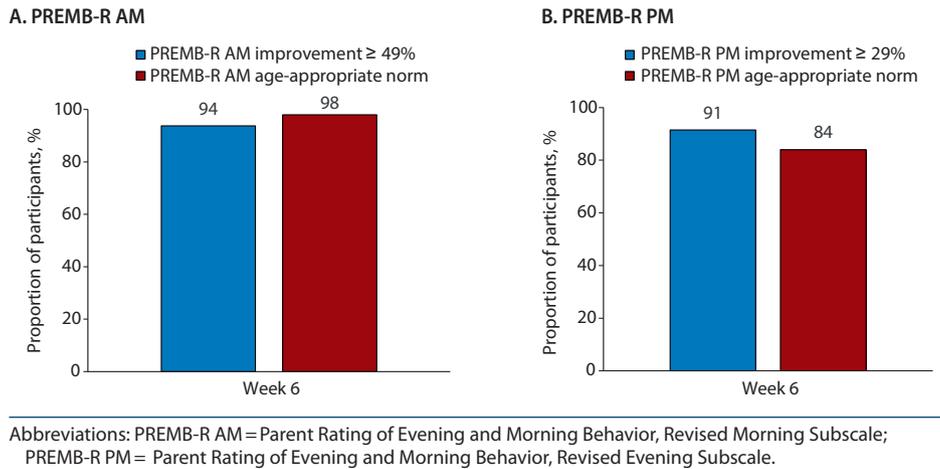
**Achievement of Response and Remission Thresholds After the 6-Week, Open-Label, DR/ER-MPH Treatment-Optimization Phase**

Achievement of response and remission thresholds increased from the beginning to the end of the treatment-optimization period. After 1 week of treatment with open-label DR/ER-MPH, 42% of participants achieved symptomatic response and 27% achieved symptomatic remission by ADHD-RS-IV thresholds (Figure 1A). After 6 weeks of treatment with open-label DR/ER-MPH, 97% of participants achieved symptomatic response and 89% achieved symptomatic remission by ADHD-RS-IV thresholds (Figure 1A). After 1 week of treatment with open-label DR/ER-MPH, 51% of participants achieved response and 51% achieved remission in early morning functional impairment by BSFQ thresholds (Figure 1B). After 6 weeks of treatment with open-label DR/ER-MPH, 98% and 94% of participants achieved response and remission, respectively, in early morning functional impairment based on the BSFQ

Figure 2. Proportion of Study Participants Achieving Response and Remission Thresholds of (A) Early Morning and (B) Late Afternoon/Evening Functional Impairment at Week 6



Abbreviations: PREMB-R AM = Parent Rating of Evening and Morning Behavior, Revised Morning Subscale; PREMB-R PM = Parent Rating of Evening and Morning Behavior, Revised Evening Subscale.

(Figure 1B). Similarly, 94% and 98% achieved response and remission, respectively, in early morning functional impairment based on the PREMB-R AM (Figure 2A). After 6 weeks of treatment with open-label DR/ER-MPH, 91% and 84% of participants achieved response and remission, respectively, in late afternoon/evening functional impairment based on PREMB-R PM thresholds (Figure 2B).

### Improvement in ADHD Symptoms and Early Morning Functional Impairment by Starting Dose

After 1 week of DR/ER-MPH treatment, participants with a starting dose of 40 mg versus 20 mg were more likely to achieve thresholds for symptomatic response by ADHD-RS-IV score (56% vs 28%; $P = .0028$), symptomatic remission by ADHD-RS-IV score (39% vs 17%; $P = .0122$), early morning functional response by BSFQ score (68% vs 35%; $P = .0004$), and early morning functional remission by BSFQ score (70% vs 33%; $P < .0001$) (Figures 3A and 3B). After 2 weeks of DR/ER-MPH treatment, participants who started on 40 mg versus 20 mg were still more likely to achieve symptomatic response (68% vs 47%, $P = .0246$), early morning functional response (86% vs 50%; $P < .0001$), or early morning functional remission (88% vs 52%; $P < .0001$). By week 4 through to week 6, there were no longer significant differences in achievement of symptomatic or functional thresholds based on starting dose.

### Adverse Events by Starting Dose

Safety results over the 6-week, open-label phase have been reported in detail elsewhere.[12] As previously reported, the most common TEAEs (> 5%) during the open-label phase were any insomnia, decreased appetite, affect lability, headache, upper respiratory tract infection, upper abdominal pain, nausea or vomiting, increased diastolic blood pressure, tachycardia, and irritability.[12] Three participants reported 5 TEAEs that led to the premature discontinuation of DR/ER-MPH during the open-label period: affect lability; aggression and agitation; and anxiety and panic attack.[12]

Among these 3 participants who discontinued, the starting dose was 20 mg in 2 participants and 40 mg in 1 participant. No serious TEAEs were reported during the open-label period or during the rest of the trial. When TEAEs were examined by starting dose, there were no obvious differences in the number or rate of TEAEs (Figure 4). For both starting doses, a larger proportion of participants reported TEAEs after the first week of treatment (45% and 49% for 20 and 40 mg, respectively) with a decreasing trend during the 6 weeks of treatment optimization (27% and 30%, respectively, during the sixth week of treatment). The types of TEAEs reported after 1 week of treatment were consistent with the overall TEAE profile; these early TEAEs did not prevent investigators from increasing doses for most participants (Table 1).

### DISCUSSION

In this post hoc analysis of a phase 3 trial of DR/ER-MPH in children with ADHD, almost all participants at the end of the 6-week, open-label, DR/ER-MPH treatment optimization period achieved thresholds of clinically meaningful response and remission, respectively, on measures of symptoms based on the ADHD-RS-IV (97% and 89%), early morning functional impairment based on the BSFQ (98% and 94%) and PREMB-R AM (94% and 98%), and late afternoon/evening functional impairment based on the PREMB-R PM (91% and 84%) with a final optimized mean dose of 66.2 mg.

As described previously,[20] the achievement of response (percentage improvement) and remission (endpoint score) thresholds must be considered in the context of baseline severity, as an individual with severe symptoms may achieve a threshold percentage improvement but still have impairing symptoms. On the other hand, an individual with mild symptoms or functional impairment may achieve remission but not achieve the percent improvement indicating response. These different scenarios are seen in this study: for the ADHD-RS-IV (Figure 1A) and PREMB-R PM (Figure

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**Figure 3. Proportion of Study Participants Achieving Response and Remission Thresholds of (A) Symptoms and (B) Early Morning Functional Impairment Stratified by Starting Dose**
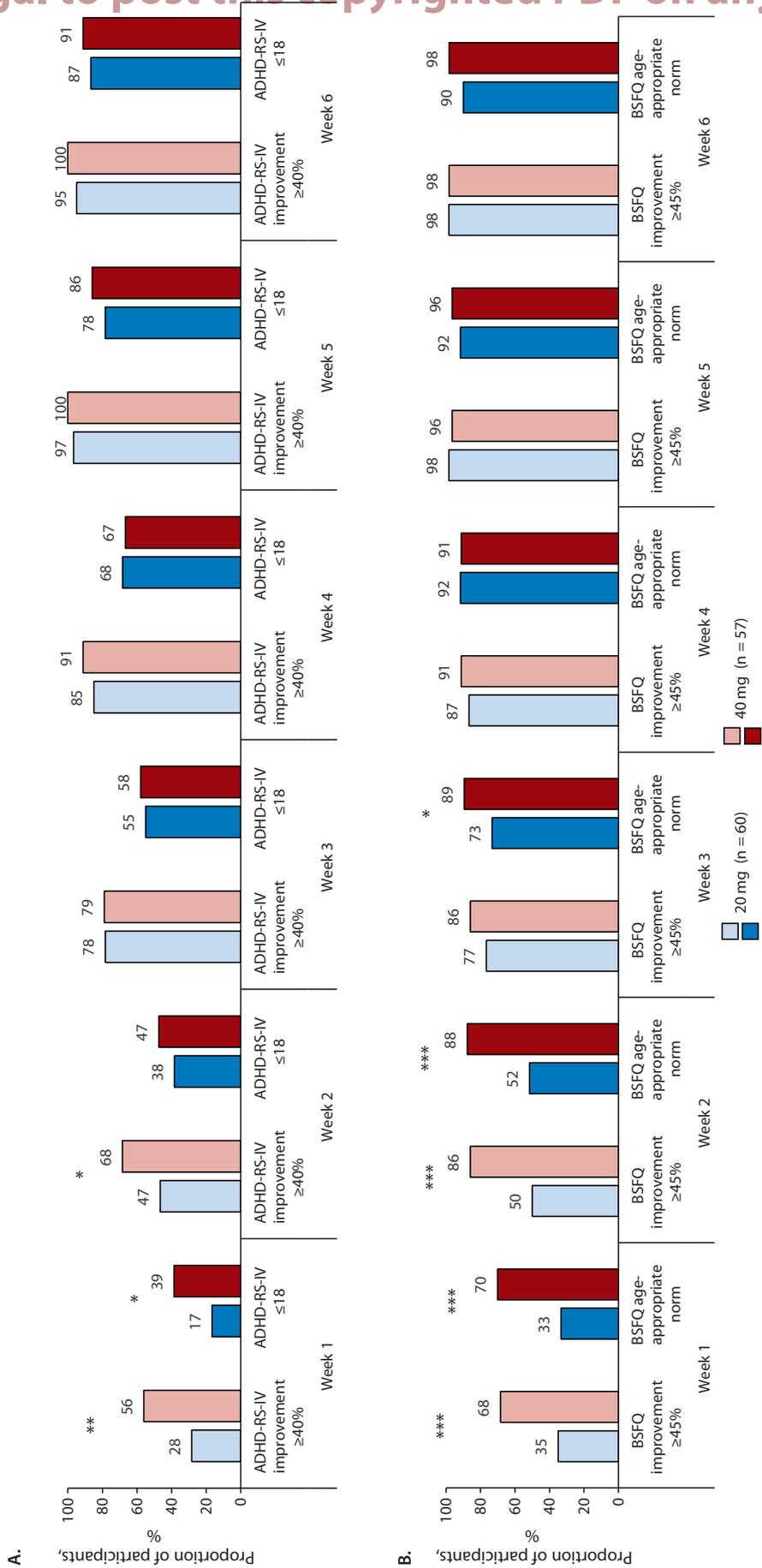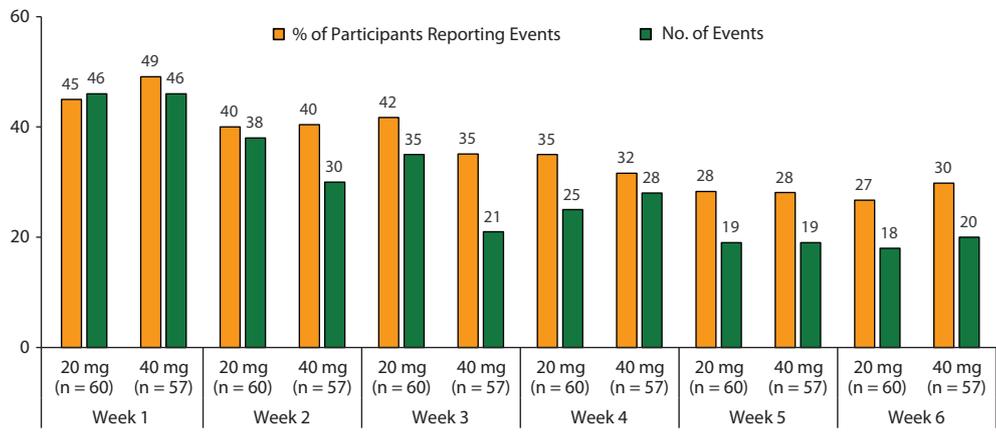


Abbreviations: ADHD-RS-IV = ADHD Rating Scale-IV, BSFQ = Before School Functioning Questionnaire.

*P < .05
**P < .01
***P < .001

Figure 4. Treatment-Emergent Adverse Events Stratified by Starting Dose

2B), the response thresholds were achieved at higher rates than remission thresholds; for the BSFQ, response and remission thresholds were achieved approximately equally (Figure 1B); for the PREMB-R AM, on which the mean baseline score indicated a severity of only screening risk, the remission threshold was achieved at a greater rate than response (Figure 2A). In contrast, mean BSFQ baseline scores indicated moderate severity in early morning functional impairment. The difference in baseline severities between the two scales is consistent with the previous hypothesis that the 20-item BSFQ is a more sensitive scale for determining severities of early morning functional impairment than the 3-item PREMB-R AM.[30] Lower baseline ADHD-RS-IV and BSFQ scores were associated with numerically higher rates of response and remission over the first weeks of the dose-titration period; however, by week 6, similarly high rates of response and remission were achieved for participants with lower or higher than median baseline symptoms or early morning functional impairment (data not shown).

In the present study, rates of response and remission increased week-over-week (Figure 1) and roughly mirrored mean dose increases during the DR/ER-MPH optimization phase (Table 1), which corroborates previous studies that showed adequate dosing is necessary to achieve symptomatic remission.[37,38] Previous studies have also shown that functional impairment does not necessarily improve at the same rate or to the same extent as symptoms.[20,39] In the current study, higher rates of response and remission were achieved for early morning functional impairment compared to symptoms (Figure 1) during the first few weeks of the treatment-optimization period, indicating a robust morning effect even with low doses of DR/ER-MPH. However, even though 50% of participants achieved remission of early morning functional impairment after 1 week of treatment with their starting dose, the other participants required increased doses to achieve remission thresholds in the early morning, highlighting that dose titration can further optimize outcomes (Figure 1B). Because PREMB-R PM was not administered at every visit, it was not possible to evaluate how late afternoon/evening functional impairment

decreased with DR/ER-MPH dose titration. Consistent with the dose-dependent duration of effect that has been predicted from pharmacokinetic/pharmacodynamic modeling,[9] with higher doses increasing duration of effect mainly by extending evening efficacy, one might expect achievement of response and remission of late afternoon/evening functional impairment to require higher doses than for the early morning thresholds. Nevertheless, with optimized doses at week 6, remission rates were similarly high for symptoms (89%), early morning functional impairment (94%–98%), and late afternoon/evening functional impairment (84%), indicating control of ADHD symptoms and functional impairment throughout the day to the level of non-ADHD peers.

After 1 week of DR/ER-MPH treatment, mean ADHD-RS-IV and BSFQ scores improved beyond the 33% prespecified randomization criterion. Therefore, further dose adjustments were guided by weekly ADHD-RS-IV and BSFQ assessments as well as clinical judgment for optimizing control throughout the day. The final optimized DR/ER-MPH doses (mean = 66.2 mg) skewed toward the higher end of the approved dose range (20–100 mg) and were higher than what would have been predicted solely from bioavailability differences between formulations, due to the extended window of exposure from morning to the evening with DR/ER-MPH.[36] Notably, investigators in this trial did not have access to the normative data or response thresholds for the BSFQ, PREMB-R AM, or PREMB-R PM. However, the recent identification of these thresholds adds tools that can be implemented to aid optimization of treatment for ADHD over the duration of the day. The norm-referenced severity cutoffs used to determine remission thresholds for early morning and late afternoon/evening functional impairment are unique in two ways: (1) they reference normative scores in the population and are adjusted for age; and (2) although only the threshold indicating children below screening risk was applied in this study, the multiple severity (percentile) cutoffs (screening risk [< 80th], mild [≥ 80th], moderate [≥ 93rd], severe [≥ 98th]) identified in the normative study[30] allow clinicians to monitor incremental

improvements, to optimize dosing (Supplementary Table 1), and to target further improvement. Furthermore, the results presented here using response and remission thresholds can provide them with a degree of predictability before initiating treatment.

Starting dose significantly affected the achievement of early response and remission on both measures of symptoms and measures of early morning functional impairment (Figure 3). In this study, investigators could prescribe a starting dose of either 20 mg or 40 mg of DR/ER-MPH based on previous treatment history, and approximately half of participants were started on each dose (Table 1). After 1 and 2 weeks of DR/ER-MPH treatment, significantly higher rates of symptomatic and early morning functional impairment thresholds were achieved in participants who started with a 40-mg dose versus a 20-mg dose (Figure 3), indicating a quicker and more robust response for the higher staring dose without an effect on TEAE rates (Figure 4). By the end of the 6-week treatment-optimization period, participants who started on 20 mg achieved similar symptomatic and functional outcomes compared to those who initially received 40 mg, suggesting that with careful monitoring and dose optimization almost complete response and remission were achieved regardless of starting dose. TEAEs were more prevalent early (Figure 4), but they rarely led to discontinuation or prevented dose increases (Table 1), indicating tolerability of treatment during dose optimization.

Selecting doses associated with improved rates of response and remission may be especially important considering that dose optimization in clinical practice may not occur at weekly intervals or be based on weekly administered rating scales, as was done in this study.

Indeed, fewer than half of children prescribed medication have contact with their pediatrician within the first month of prescribing.[40] Here, dose optimization based on weekly assessment of the entire day resulted in most children achieving response and remission thresholds for both symptoms and functional impairment at the bookends of the day by 6 weeks. The recent availability of these thresholds provides objective targets that may improve optimization of treatment for ADHD.

Interpretation of the study is limited by its post hoc nature and the treatment-optimization phase being open-label, which could have biased ratings but also reflects clinical experience. As mentioned previously,[12] the inclusion of only methylphenidate responders with few comorbidities may limit generalization of findings. The analysis was limited to a 6-week treatment-optimization phase, and therefore long-term duration of response and remission remains to be tested prospectively.

In summary, the post hoc analyses reported here demonstrate that previously reported statistically significant mean improvements translate into clinically meaningful individual outcomes, with the majority of participants achieving response and remission of ADHD symptoms and early morning and late/afternoon functional impairment after 6 weeks when doses were appropriately titrated (final optimized dose was 66.2 mg). Improved early response and remission rates (by ADHD-RS-IV and BSFQ thresholds) were seen with a 40-mg versus a 20-mg starting dose without an increase in TEAEs. The results presented here are consistent with symptom and functional response and remission being realistic and achievable outcome goals with DR/ER-MPH when doses are optimized for control of ADHD symptoms and functional impairment throughout the day.

*Supplementary material:* Available at PSYCHIATRIST.COM.

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*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

# Supplementary Material

**Article Title:** Symptomatic and Functional Response and Remission From the Open-Label Treatment-Optimization Phase of a Study With DR/ER-MPH in Children With ADHD

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## List of Supplementary Material for the article

## Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

**Supplementary Table 1. Symptom and Functional Impairment Assessments and Thresholds**

| | Early Morning Functional Impairment | | Symptoms | Late Afternoon/Evening Functional Impairment |
|---|---|---|---|---|
| | BSFQ | PREMB-R AM | ADHD-RS-IV | PREMB-R PM |
| Scale description | Validated 20-item clinician-rated scale based on a structured parent interview assessing early morning functional impairment between the time of awakening and getting to school or other morning activities (ie, from 6:00 AM to 9:00 AM) in children with ADHD.[32] | Validated 3-item clinician-rated subscale based on structured parent interview assessing functional impairment during the early morning (eg, getting up and out of bed).[33,34] | Validated 18-item clinician-rated scale evaluating ADHD symptomology based on the DSM-IV diagnostic criteria for ADHD.[35] | Validated 8-item clinician-rated subscale based on structured parent interview assessing functional impairment during the late afternoon/evening (eg, doing/completing homework, getting to bed, and falling asleep).[34] |
| Scale scoring | Items rated from 0 (none) to 3 (severe); total scores range from 0 to 60. Scores reflected functional impairment over the preceding week.[32] | Items rated from 0 (none) to 3 (a lot); total scores range from 0 to 9. Scores reflected the last two school days prior to the study visit.[33,34] | Items rated from 0 (no symptoms) to 3 (severe symptoms); total scores range from 0 to 54. Scores reflected symptoms over the preceding week.[35] | Items rated from 0 (none) to 3 (a lot); total scores range from 0 to 24. Scores reflected the last two school days prior to the study visit.[34] |
| Schedule | Assessed at each open-label visit; ≥33% improvement from baseline was required for randomization. | Assessed at the beginning and end of the 6-week open-label phase as well as following one week of double-blind treatment, which was included as a secondary endpoint. | Assessed at each open-label visit; ≥33% improvement from baseline was required for randomization. | Assessed at the beginning and end of the 6-week open-label phase as well as following one week of double-blind treatment, which was included as a secondary endpoint. |
| Response threshold (anchored to CGI-I of 1 or 2) | Change from baseline of ≥45%.[29] | Change from baseline of ≥49%.[29] | Change from baseline of ≥40%.[25] | Change from baseline of ≥29%.[29] |
| Remission threshold (corresponding to less than screening risk) | ≤24 for individuals 6–8 years of age and ≤21 for individuals 9–12 years of age.[30] | ≤4 for individuals 6–8 years of age and ≤3 for individuals 9–12 years of age.[30] | Score ≤18.[13] | ≤10 for individuals 6–8 years of age and ≤8 for individuals 9–12 years of age.[30] |

| Cut-offs for severity thresholds of temporal functional impairment[30] | SR 80th | Mild 90th | Mod 93rd | Sev 98th | SR 80th | Mild 90th | Mod 93rd | Sev 98th | | SR 80th | Mild 90th | Mod 93rd | Sev 98th |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6–8 years | 25 | 33 | 36 | 43 | 5 | 6 | 6 | 8 | | 11 | 15 | 16 | 19 |
| 9–11 years | 22 | 30 | 36 | 43 | 4 | 6 | 6 | 8 | | 9 | 13 | 16 | 19 |
| 12–14 years | 22 | 30 | 34 | 42 | 4 | 6 | 6 | 7 | | 9 | 13 | 15 | 18 |
| 15–17 years | 21 | 28 | 31 | 42 | 4 | 6 | 6 | 7 | | 9 | 13 | 15 | 18 |

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale-IV; BSFQ, Before School Functioning Questionnaire; CGI-I, Clinical Global Impressions-Improvement; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; Mod, moderate; PREMB-R AM, Parent Rating of Evening and Morning Behavior, Revised, Morning subscale; PREMB-R PM, Parent Rating of Evening and Morning Behavior, Revised, Evening subscale; Sev, severe; SR, screening risk.

**Supplementary Figure 1. ADHD-RS-IV and BSFQ Scores with DR/ER-MPH Treatment**
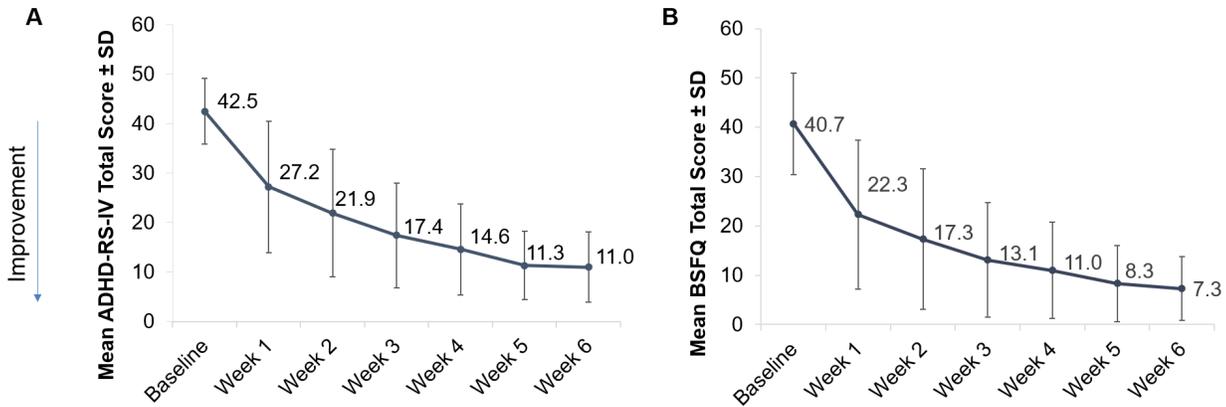


Note: Scores reflect symptoms and functional impairment over the preceding week. Therefore, baseline scores reflect the previous untreated week.

Abbreviations: ADHD-RS-IV, ADHD Rating Scale-IV; BSFQ, Before School Functioning Questionnaire; DR/ER-MPH, delayed-release and extended-release methylphenidate; SD, standard deviation.