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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*Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, Nevada*  
*SUNY Upstate Medical University, Syracuse, New York*  
*Highland Therapeutics Inc., Toronto, Ontario, Canada*  
*Ironshore Pharmaceuticals & Development, Inc., Camana Bay, Grand Cayman, Cayman Islands*  
*Ironshore Pharmaceuticals Inc., Durham, North Carolina*  
*Corresponding author: Ann C. Childress, MD, Center for Psychiatry and Behavioral Medicine, 7351 Prairie Falcon Rd, Ste 160, Las Vegas, NV 89128 (drann87@aol.com).*

Recent guidelines for the treatment of attention-deficit/hyperactivity disorder (ADHD) 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, in addition to symptom control. Despite formulation improvements, all-day clinical efficacy with a single stimulant dose has remained an unmet need in adults and youth 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, 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, 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.

In two phase 3 studies of children with ADHD, 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. As such, applying established cutoffs can help clinicians understand the clinical meaningfulness of an aggregate treatment effect and help predict positive individual patient outcomes.

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%.
Children with Attention-Deficit/Hyperactivity Disorder Collaborative Multisite Multimodal Treatment Study of control group of the National Institute of Mental Health threshold for remission captured 88% of children in the 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 this 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 Edition31 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

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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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...
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 based on the 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 thresholds (Figure 1B).

Table 1. Weekly Dosage Titration Parameters

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

aPercentages based on N = 117.

Abbreviations: ADHD-RS-IV = ADHD Rating Scale-IV, BSFQ = Before School Functioning Questionnaire.
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,10 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 2B).

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

### A. ADHD-RS-IV Improvement

<table>
<thead>
<tr>
<th>Dose</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
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<tr>
<td>20 mg</td>
<td>28%</td>
<td>47%</td>
<td>78%</td>
<td>85%</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>40 mg</td>
<td>17%</td>
<td>38%</td>
<td>55%</td>
<td>68%</td>
<td>78%</td>
<td>87%</td>
</tr>
</tbody>
</table>

### B. BSFQ Improvement

<table>
<thead>
<tr>
<th>Dose</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>35%</td>
<td>50%</td>
<td>77%</td>
<td>87%</td>
<td>98%</td>
<td>90%</td>
</tr>
<tr>
<td>40 mg</td>
<td>33%</td>
<td>52%</td>
<td>86%</td>
<td>91%</td>
<td>98%</td>
<td>98%</td>
</tr>
</tbody>
</table>

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

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

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Potential conflicts of interest: Dr Childress has received research support from Aevi Genomic Medicine; Akili Interactive Laboratories; Allergan; Arbor; Emalex; Forest; Ironshore Pharmaceuticals & Development, Inc.; KemPharm; Neos Therapeutics; Neurovance; Otsuka; Pearson; Pfizer; Purdue; Rhodes; Servier; Shire; Sunovion; Supernus; Takeda; Tris Pharma; and US Food and Drug Administration; serves on the advisory boards of Adlon; Akili Interactive Laboratories; Arbor; Cingulare Therapeutics; Ironshore Pharmaceuticals & Development, Inc.; Neos Therapeutics; Neurovance; NLS Pharma; Otsuka America; Pfizer; Purdue; Rhodes; Shire; Sunovion; Supernus; Takeda; and Tris Pharma; has consulted for Arbor; Ironshore Pharmaceuticals & Development, Inc.; Jazz; KemPharm; Neos Therapeutics; Neurovance; Purdue; Rhodes; Sunovion; Supernus; Tris Pharma; and has participated in speaker bureaus for Arbor; Ironshore Pharmaceuticals Inc.; Neos Therapeutics; Pfizer; Purdue; Rhodes; Shire; Sunovion; Supernus; Takeda; and Tris Pharma; and has received writing support from Arbor; Ironshore Pharmaceuticals & Development, Inc.; Neos Therapeutics; Pfizer; Purdue; Rhodes; Shire; Sunovion; Takeda; and Tris Pharma. Dr Cutler has received research support from Aevi Genomic Medicine; Akili Interactive Laboratories; Allergan; Arbor; Ironshore Pharmaceuticals & Development, Inc.; KemPharm; Lundbeck; MedAvante-ProPhase; Neos Therapeutics; NLS Pharma; Noven; Otsuka America; Purdue; Rhodes; Shire; Sunovion; Supernus; Takeda; and Tris Pharma; and has served on the advisory board or as a consultant for Aevi Genomic Medicine; AiCure; Akili Interactive Laboratories; Allergan; Arbor; Atentiv; Cingulare; Ironshore Pharmaceuticals & Development, Inc.; KemPharm; Lundbeck; MedAvante-ProPhase; Neos Therapeutics; NLS Pharma; Noven; Otsuka America; Purdue; Rhodes; Shire; Sunovion; Supernus; Takeda; and Tris Pharma; has participated in speaker bureaus for AbbVie; Allergan; Arbor Pharmaceuticals; Ironshore Pharmaceuticals Inc.; Neos Therapeutics; Noven; Otsuka America; Shire; Sunovion; Supernus; Takeda; and Tris Pharma; and is a board member for the Neuroscience Education Institute. Dr Po is an employee of Highland Therapeutics Inc. Dr Warrington is an employee of Ironshore Pharmaceuticals Inc. Dr Sallee is an employee of Ironshore Pharmaceuticals Inc. and serves on the advisory board/board of directors of PD Bioscience. Mr De Sousa and Dr Incledon are employees of Ironshore Pharmaceuticals & Development, Inc.

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Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES


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.
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

Author(s): Ann C. Childress, MD; Andrew J. Cutler, MD; Michelle D. Po, PhD; Norberto J. DeSousa, MA; Lewis E. Warrington, MD; Floyd R. Sallee, MD, PhD and Bev Incledon, PhD

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List of Supplementary Material for the article

1. Table 1  Symptom and Functional Impairment Assessments and Thresholds
2. Figure 1 ADHD-RS-IV and BSFQ Scores with DR/ER-MPH Treatment

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

<table>
<thead>
<tr>
<th>Scale description</th>
<th>Early Morning Functional Impairment</th>
<th>Symptoms</th>
<th>Late Afternoon/Evening Functional Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>BSFQ</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Items rated from 0 (none) to 3 (severe); total scores range from 0 to 60. Scores reflected functional impairment over the preceding week.32</td>
<td>PREMB-R AM</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Assessed at each open-label visit; ≥33% improvement from baseline was required for randomization.</td>
<td>ADHD-RS-IV</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Change from baseline of ≥45%.29</td>
<td>Change from baseline of ≥49%.29</td>
<td>Change from baseline of ≥40%.25</td>
<td>Change from baseline of ≥29%.29</td>
</tr>
<tr>
<td>≤24 for individuals 6–8 years of age and ≤21 for individuals 9–12 years of age.30</td>
<td>≤4 for individuals 6–8 years of age and ≤3 for individuals 9–12 years of age.30</td>
<td>Score ≤18.13</td>
<td>≤10 for individuals 6–8 years of age and ≤8 for individuals 9–12 years of age.30</td>
</tr>
<tr>
<td>Cut-offs for severity thresholds of temporal functional impairment10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–8 years</td>
<td>25 33 36 43</td>
<td>5 6 6 8</td>
<td>11 15 16 19</td>
</tr>
<tr>
<td>9–11 years</td>
<td>22 30 36 43</td>
<td>4 6 6 8</td>
<td>9 13 16 19</td>
</tr>
<tr>
<td>12–14 years</td>
<td>22 30 34 42</td>
<td>4 6 6 7</td>
<td>9 13 15 18</td>
</tr>
<tr>
<td>15–17 years</td>
<td>21 28 31 42</td>
<td>4 6 6 7</td>
<td>9 13 15 18</td>
</tr>
</tbody>
</table>

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.