Brief Report

A Post Hoc Comparison of Prior ADHD Medication Dose and Optimized Delayed-release and Extended-release Methylphenidate Dose in a Pivotal Phase III Trial

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ABSTRACT

Purpose: HLD200 is the first evening-dosed, delayed-release and extended-release methylphenidate (DR/ER-MPH) designed to delay initial release of MPH and provide treatment effects throughout the day and into the evening for individuals with attention-deficit/hyperactivity disorder (ADHD). Because DR/ER-MPH is uniquely absorbed in the colon, it cannot be substituted for other ADHD medications on a milligram-per-milligram basis. To provide clinicians with a target dose range for DR/ER-MPH when transitioning patients from a prior ADHD medication, dose conversion ratios (DCRs) between prior medication doses and optimized doses of DR/ER-MPH were determined post hoc from a pivotal Phase III study of children (aged 6−12 years) with ADHD.

Methods: DR/ER-MPH doses were optimized over a 6-week open-label period. DCRs were calculated between optimized doses of DR/ER-MPH at week 6 and prior stable doses of ADHD medication.

Findings: Mean DCRs ranged from 1.8 to 4.3 for optimized DR/ER-MPH dose versus previous stable dose for individuals taking an extended-release stimulant monotherapy. DCRs for those taking an immediate-release stimulant monotherapy ranged from 4.7 to 6.0.

Implications: In a Phase III trial of children with ADHD, optimized doses of DR/ER-MPH were higher than doses of prior ADHD medications, but the adverse event profile was consistent with that of other MPHs. Higher DCRs compared with those predicted by bioavailability differences are consistent with a predicted dose-dependent duration of effect for DR/ER-MPH: with increasing doses, absorption is extended but with an attenuated increase in C_{max} compared with MPH formulations absorbed in the upper bowel. These data may help guide clinicians to optimize DR/ER-MPH doses. ClinicalTrials.gov identifier: NCT02493777. (*Clin Ther*. 2020;42:2332−2340)

Key words: attention-deficit/hyperactivity disorder, delayed-release and extended-release methylphenidate, dose conversion, psychopharmacology, stimulants.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder that affects ~11% of children and 4.4% of adults in the United States.[1,2] Long-acting stimulants are recommended as first-line treatment for ADHD, and commonly prescribed extended-release stimulants are given once daily in the morning to control ADHD symptoms

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into the afternoon or evening, depending on formulation.[3,4] However, current long-acting stimulant formulations may not provide coverage in the early morning (between the time of stimulant administration and onset of effect) and the late afternoon/evening (when the medication wears off) with a single dose.[4] Although symptom control has historically been the primary goal of ADHD treatment, the importance of improving ADHD-related functional impairments has been recognized.[5–7] At a minimum, a person diagnosed with ADHD would exhibit functional impairment in at least 2 settings.[8] Several important functional areas, such as family and social relations and self-care, take prominence outside of school and work settings both in the early morning and in the late afternoon/evening when control of ADHD symptoms and functional impairment may not be optimal.[9–13]

Altogether, there remains an unmet need for control of ADHD symptoms and functional impairment into the evening while also providing control from the time of awakening.[10,11] Delayed-release and extended-release methylphenidate (DR/ER-MPH, formerly HLD200; Jornay PM®; Ironshore Pharmaceuticals & Development, Inc, Grand Cayman, Cayman Islands) is an evening-dosed ADHD medication designed to delay the initial release of MPH by ~8–10 h to provide onset of treatment effect upon awakening and lasting through to the evening.[14] The efficacy and tolerability of DR/ER-MPH have been shown in two pivotal Phase III trials of children with ADHD.[15,16]

Treatment guidelines are increasingly recommending that the goal of treatment should be all-day control of ADHD-related symptoms and functional impairment, and that physicians should change ADHD medications if responses to current medications are not optimal (eg, a lack of all-day coverage).[17,18] Transitioning between stimulants is complex, and each particular medication provides unique drug exposure in each individual patient.[19] For example, long-acting MPHs that provide longer windows of coverage will require more absolute amounts of the active substance than is contained in MPH formulations which provide shorter windows of coverage.[20]

The prescribing information for DR/ER-MPH states that it cannot be substituted for other MPH products on a milligram-per-milligram basis and that an optimized dose of DR/ER-MPH should be established by titration.[21] Several unique features contribute to the need for differential dosing of DR/ER-MPH, including predominant absorption in the colon, exposure in the early morning, and a protracted elimination phase resulting in exposure through the late afternoon and into the evening.[14,22] Absorption that occurs predominantly in the colon is unique to DR/ER-MPH, as it has a delayed release and no immediate-release component; all other currently available MPH formulations are predominantly released and absorbed more proximally, in the small intestine. The colon has a smaller surface area and a lower surface area to volume ratio than the small intestine, resulting in a lower solute absorptive potential.[23] Because of this, the bioavailability of DR/ER-MPH is 73.9% of immediate-release MPH.[22]

Colonic absorption is predicted to affect the C_{max} of MPH; the highest available dose form of DR/ER-MPH (100 mg) is predicted to have a similar C_{max} compared with that of other MPH formulations at their highest available dose form, which is a lower absolute dose (eg, 54 mg of osmotic release oral system MPH).[24] Total MPH exposure, the AUC, is also predicted to be higher for modeled pharmacokinetic profiles of 100 mg of DR/ER-MPH compared with 54 mg of osmotic release oral system MPH.[24] Colonic absorption also extends the period of drug absorption for DR/ER-MPH, with >50% of drug absorption occurring after C_{max} is reached.[14] This suggests that the elimination phase of DR/ER-MPH consists of the sum of continued absorption in the colon and elimination rather than pure elimination[14]; this is in stark contrast with other MPH formulations, which predominantly exhibit elimination kinetics after C_{max} is reached. Consequently, therapeutic levels of MPH are predicted to be maintained later in the evening compared with other MPH formulations.[24] Another outcome of this unique pharmacokinetic profile due to colonic absorption is that DR/ER-MPH is predicted to have a dose-dependent duration of effect without an equivalent effect on absolute C_{max}; higher doses are predicted to provide an extended duration of clinical response without affecting the magnitude of effect over the duration of the day.[24]

Due to these fundamental differences between the pharmacokinetic profiles of DR/ER-MPH and other MPH formulations, determining an equivalent therapeutic dose between DR/ER-MPH and a prior medication is not straightforward. One method by

which health care practitioners can estimate a target (ie, optimized) dose range for a new medication is to calculate a ratio between patients' medication doses before enrolling in a clinical trial and the doses of study medication to which they are eventually optimized. This dose conversion ratio is intended to provide guidance on a target dose range for DR/ER-MPH that would provide optimized patient outcomes and is not intended to estimate a starting dose or to provide guidance on dose titration. As stated in the prescribing information for DR/ER-MPH, patients should initiate DR/ER-MPH at a dose of 20 mg and may titrate weekly in increments of 20 mg/d until optimized efficacy and tolerability outcomes are achieved.[21]

To provide this guidance to clinicians when transitioning from previous ADHD medications to DR/ER-MPH, we conducted a post hoc analysis of a Phase III trial of children with ADHD (A Pivotal Efficacy Trial to Evaluate HLD200 in Children With ADHD in a Classroom Setting; ClinicalTrials.gov identifier: NCT02493777) in which dose conversion ratios were determined by comparing the dose of prior ADHD medications versus the optimized dose of DR/ER-MPH achieved in the trial.

PARTICIPANTS AND METHODS

These post hoc analyses were performed on data from a Phase III, multicenter, randomized, double-blind, placebo-controlled, forced-withdrawal, parallel-group, laboratory classroom study of DR/ER-MPH in children (aged 6−12 years) with ADHD.[15] Key inclusion criteria included but were not limited to: diagnosis of ADHD based on the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition); a baseline ADHD Rating Scale-IV (ADHD-RS-IV) score in at least the 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 ≥26 at baseline; Clinical Global Impression of Severity (CGI-S) score ≥4 and Conners' Global Index−Parent (CGI-P) score >10 at baseline; and prior response to MPH therapy or treatment with the same dose of MPH and clinical response with acceptable tolerability for ≥2 weeks before screening. Key exclusion criteria included but were not limited to: history of or current medical condition or laboratory result that could interfere with study participation, participant safety, or satisfactory completion of the study; any cardiac problems that may place the participant at increased vulnerability to the sympathomimetic effects of a stimulant drug; history of psychosis, bipolar disorder, anorexia nervosa, bulimia, or suicide attempt; and current depression, anxiety, conduct disorder, substance use disorder, or other psychiatric condition that may jeopardize participant safety or interfere with the satisfactory completion of the study.

The study was conducted in 3 phases: a screening/washout phase lasting up to 4 weeks with washout of ADHD treatment for ≥5 days; a 6-week, open-label, DR/ER-MPH treatment-optimization phase; and a 1-week, randomized, double-blind, placebo-controlled, parallel-group phase ending with a laboratory classroom test day (Figure 1).[15] At the baseline visit, all participants initiated DR/ER-MPH treatment at either 20 mg or 40 mg once daily at 8:00 PM (±30 min), with the starting dose dependent on their previous treatment history and at the discretion of the investigator. Over the first 4 weeks of the open-label treatment-optimization phase, weekly dose titrations were permitted in 20- or 40-mg increments or decrements until an optimized dose was achieved or a maximum daily dose of 100 mg/d or 3.7 mg/kg per day was reached. Adjustments to the administration time in 30- to 60-min increments or decrements were also permitted (between 6:30 PM and 9:30 PM). Optimized dose and administration time were defined as those that produced clinically meaningful control of symptoms and early morning functional impairment while remaining safe and well tolerated. Clinically meaningful control was predefined as ≥33% improvement from the baseline visit in ADHD-RS-IV, Before School Functioning Questionnaire (BSFQ), and CGI-P scores. The final permitted dose and administration time adjustments were made at week 4, after which the dose and administration time were to be maintained from week 5 through to the end of the open-label phase at week 6.

Participants were included in the dose conversion analysis if they were on a stable stimulant dose before the screening visit, defined as the same dose of stimulant for ≥8 days. Despite investigators confirming that all participants met the inclusion criterion of a prior response to MPH therapy, prior ADHD medications were not recorded for 14 participants. Dose conversion ratios were not calculated for these participants, but their DR/ER-MPH dosing information was collected. Participants who reported

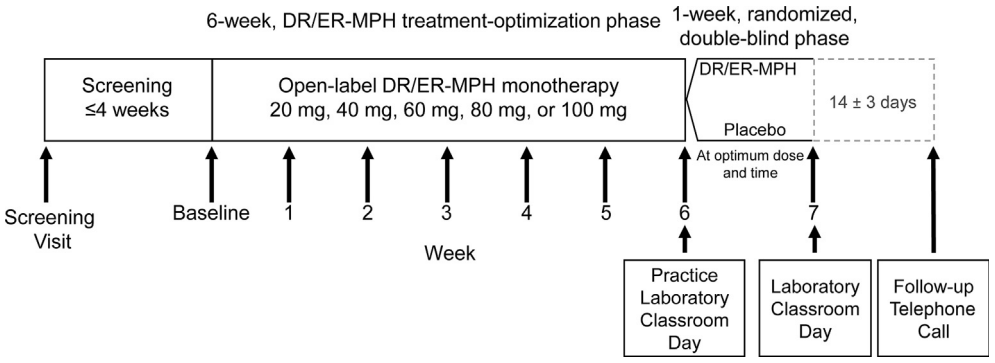

Figure 1. Study design. DR/ER-MPH = delayed-release and extended-release methylphenidate. From Childress et al.[15] (open access under the CC BY 4.0 license [https://creativecommons.org/licenses/by/4.0/]).

taking multiple concurrent medications (ie, combination therapies) were not included in the analysis. If participants reported multiple previous monotherapies, the most recent therapy at a stable dose was used. Prior therapies that were taken once daily were categorized as extended-release formulations. In addition, participants had to achieve an optimized DR/ER-MPH dose at the completion of the open-label treatment-optimization phase of the study (as defined earlier).

Descriptive statistics for previous stimulant monotherapy and optimized DR/ER-MPH daily doses (ie, doses at week 6) were determined. A dose conversion ratio was calculated for each participant using the following equation:

$$\text{Dose conversion ratio} = \frac{\text{DR/ER-MPH dose at week 6}}{\text{prior stimulant dose}}$$

Participants were categorized according to the type of stimulant monotherapy they were taking at screening, and the mean dose conversion ratio was calculated for each type of prior therapy by averaging individual dose conversion ratios.

RESULTS

Participant Disposition and Characteristics

Of 125 children enrolled in the study, 117 were included in the intention-to-treat (ITT) population (defined as all randomized participants who received at least 1 dose of double-blind study drug and had at least 1 postbaseline evaluation of the primary efficacy assessment). A total of 98 children from the enrolled study population were included in the dose conversion analysis. Demographic and baseline characteristics of the enrolled study population have been described in detail elsewhere.[15] Briefly, 68% of participants were male, the mean age was 9.4 years, and 79.2% of participants were White. The majority of participants (86.4%) had combined-type ADHD, the mean baseline ADHD-RS-IV total score was 42.7, and the baseline CGI-S score was 5 (ie, markedly ill) in 42% of participants. The mean baseline CGI-P score was 22.1. At the screening visit (when participants were still taking their previous medication), mean ADHD-RS-IV total score was 33.9, mean CGI-P was 16.9, and CGI-S was 5 in 32% of participants.

DR/ER-MPH Dose Optimization

At baseline, the mean (SD) starting dose of DR/ER-MPH in the ITT population was 29.7 (10.04) mg/d, with starting doses split evenly between 20 mg and 40 mg (51.3% and 48.7%, respectively) (Figure 2). At the end of the open-label, treatment-optimization phase, the mean (SD) optimized dose of DR/ER-MPH in the ITT population was 66.2 (19.56) mg/d; 87.2% of participants were prescribed a daily dose of either 40 mg (20.5%), 60 mg (34.2%), or 80 mg (32.5%).

The mean percent reductions in ADHD-RS-IV, BSFQ, and CGI-P scores between baseline and the end of the open-label, treatment-optimization phase in the ITT population were 74.0%, 82.2%, and 75.1%, respectively. This outcome shows that the doses achieved at the end of the treatment-optimization phase resulted in substantial improvements in ADHD-

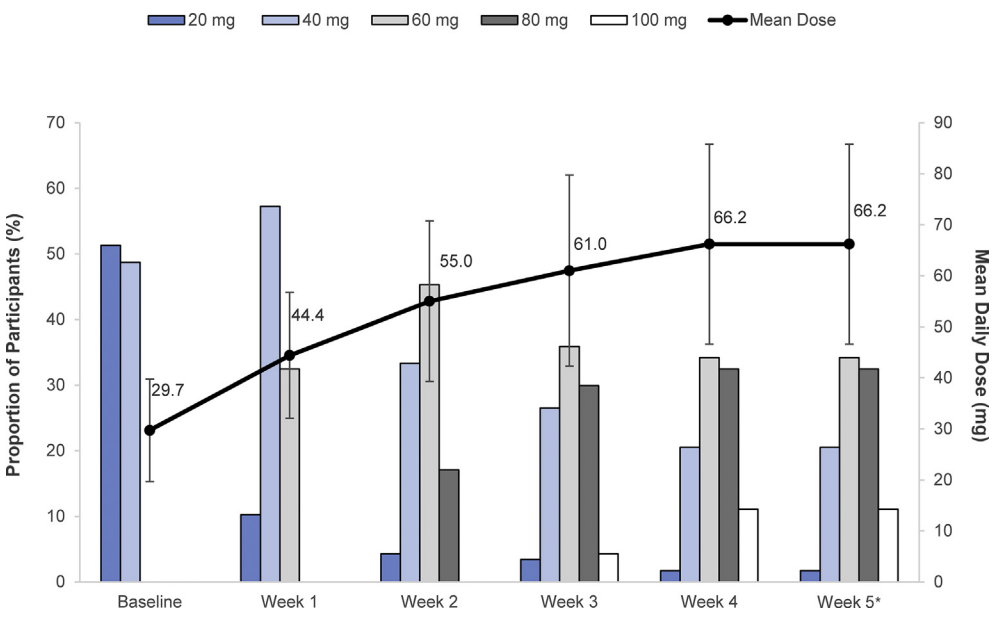

Figure 2. Mean (SD) and distribution of delayed-release and extended-release methylphenidate doses over the 6-week open-label phase. The dose prescribed at the baseline visit was the dose during the first week of open-label treatment, the dose prescribed at the week 1 visit was the dose during the second week of open-label treatment, and so forth. *No dose adjustments were permitted on the last week of the open-label period.

related symptoms and functional impairment, well beyond the 33% improvement from baseline prespecified as meaningful control.[15] Mean (SD) ADHD-RS-IV scores improved from 42.5 (6.60) at baseline to 11.0 (7.14) at week 6, mean (SD) BSFQ scores improved from 40.7 (10.28) at baseline to 7.3 (6.45) at week 6, and mean (SD) CGI-P scores improved from 22.0 (5.11) to 5.5 (4.08) at week 6.[15]

Comparison of Optimized DR/ER-MPH Dose to Previous Medication Dose

The mean dose conversion ratios indicated that participants required, on average, 1.8 to 4.3 times higher doses of DR/ER-MPH compared with their previous extended-release stimulant monotherapies (Table). Mean dose conversion ratios for previous immediate-release stimulant medications were even higher; on average, participants required 4.7 to 6.0 times higher doses of DR/ER-MPH compared with that of their previous immediate-release stimulant medication. Mean dose conversion ratios for the D-enantiomer MPH formulations were at the upper end of these ranges (extended-release, 4.3; immediate-release, 6.0). The mean optimized DR/ER-MPH dose for participants whose prior ADHD medication was not recorded was 68.6 mg/d, in line with the optimized doses of other participants in the study.

DISCUSSION

In this post hoc analysis, doses of optimized DR/ER-MPH were compared with previous doses of stimulant monotherapy in children with ADHD. These data may provide guidance to clinicians when transitioning from a previous ADHD medication to help estimate an appropriate target dose range for DR/ER-MPH. As noted previously, the dose conversion ratio is meant to be an estimate of the final (ie, optimized) dose of DR/ER-MPH and is not intended to guide the starting dose or the titration process, both of which are set out in the prescribing information for DR/ER-MPH.

The dose conversion ratios between optimized DR/ER-MPH doses and prior stimulants were higher than what would be expected given the

Table. Dose comparisons between delayed-release and extended-release methylphenidate (DR/ER-MPH) at week 6 and prior attention-deficit/hyperactivity disorder (ADHD) monotherapies.

Previous ADHD Medication*	Sample Size (n)	Mean (SD) Prior Stimulant Dose (mg/d)	Mean (SD) Optimized DR/ER-MPH Dose at Week 6 (mg/d)	Mean Dose Conversion Ratio (95% CI)
MPH ER				
OROS MPH	26	38.1 (16.0)	69.2 (19.8)	2.0 (1.7–2.4)
d-MPH ER	10	17.5 (10.3)	62.0 (25.7)	4.3 (2.3–6.3)
MPH CD	15	37.3 (13.9)	58.7 (17.7)	1.8 (1.3–2.3)
MEROS	11	34.3 (12.2)	65.5 (12.9)	2.2 (1.5–2.9)
MPH HCI ER	5	18.0 (8.4)	48.0 (17.9)	3.5 (0.1–6.8)
ER MPH	2	15.0 (7.1)	40.0 (0.0)	3.0 (–9.7 to 15.7)
MPH IR				
d-MPH	8	19.4 (6.8)	85.0 (9.3)	6.0 (1.2–10.7)
IR MPH	3	16.7 (5.8)	73.3 (11.6)	4.7 (2.8–6.5)
MPH HCL	1	10.0 (NA)	60.0 (NA)	6.0 (NA)
AMP				
LDX	14	45.0 (25.9)	60.0 (20.8)	1.9 (1.2–2.6)
MAS ER	3	20.0 (0.0)	80.0 (0.0)	4.0 (4.0–4.0)
Prior ADHD medication not recorded	14	NA	68.6 (18.8)	NA

AMP = amphetamine; CI = confidence interval; d-MPH = dexmethylphenidate (Focalin® [Novartis Pharmaceuticals Corporation, East Hanover, New Jersey]); d-MPH ER = dexmethylphenidate extended-release (Focalin XR® [Novartis Pharmaceuticals Corporation); ER = extended-release; IR = immediate-release; LDX = lisdexamfetamine dimesylate (Vyvanse® [Takeda Pharmaceuticals America, Inc, Deerfield, Illinois]); MAS ER = mixed amphetamine salts extended-release (Adderall XR® [Takeda Pharmaceuticals America, Inc, Deerfield, Illinois]); MEROS = methylphenidate extended-release oral suspension (Quillivant XR® [Tris Pharma, Inc, Monmouth Junction, New Jersey]); MPH = methylphenidate; MPH CD = methylphenidate controlled-release delivery (Metadate CD® [UCB, Inc., Smyrna, Georgia]); MPH HCl = methylphenidate hydrochloride (Ritalin® [Novartis Pharmaceuticals Corporation]); MPH HCl ER = methylphenidate hydrochloride extended-release (Ritalin LA® [Novartis Pharmaceuticals Corporation]); NA = not applicable; OROS MPH = osmotic release oral system methylphenidate (Concerta® [Janssen Pharmaceuticals, Inc, Titusville, New Jersey]).
* Includes branded and generic formulations.

73.9% bioavailability of DR/ER-MPH[22] (ie, ~1.3 for racemic MPH formulations and ~2.7 for D-enantiomer MPH formulations[19]). This discrepancy likely occurs because MPH absorption after DR/ER-MPH dosing is predicted to be extended over a longer duration of time compared with other MPH formulations: extended evening absorption as a result of colonic release and absorption, and release earlier in the morning as a result of evening dosing and the delayed-release properties of DR/ER-MPH.[24] An extended MPH absorption window without an increased C_{max} and with a higher AUC (when comparing the highest dose form of DR/ER-MPH vs the highest dose forms of other MPH formulations) is consistent with clinical trials of DR/ER-MPH, which have documented improvements in symptoms and functional impairment during the early morning, throughout the day, and into the evening.[15,16]

In the present study, DR/ER-MPH was well tolerated despite doses being much higher than those of the participants' previous ADHD medications.[15] This outcome reinforces that dosing with DR/ER-MPH is different than with other stimulants and should be treated as such. An optimized dose was predefined as a ≥33% reduction

from baseline scores in ADHD-RS-IV, BSFQ, and CGI-P in this trial. In clinical practice, optimization will refer to the dose at which there is no further benefit and will not be limited by a predefined 33% reduction from baseline scores but from efficacy and safety over time, and it may benefit from targeting normalized scores on functional scales such as the BSFQ and the Parent Rating of Evening and Morning Behavior—Revised Scale.[12] Despite the predefined 33% criteria for optimized dose, investigators continued titrating well beyond 33% improvement to achieve improvements of 74.0%, 82.2%, and 75.1% in ADHD-RS-IV, BSFQ, and CGI-P scores, respectively[15]; however, the limited time frame and the 4 weekly dose adjustments may have limited full optimization and potentially higher magnitudes of improvement with DR/ER-MPH.

The approach used in the treatment-optimization phase of this study (ie, weekly assessments of symptoms and functional impairment and possible adverse events to inform dose adjustments) may serve as a guide for optimizing DR/ER-MPH dosing. In particular, objective rating scales of ADHD-related symptoms and functional impairment such as the ADHD-RS-IV, BSFQ, and Parent Rating of Evening and Morning Behavior—Revised Scale are important tools for optimizing dose, as patients' responses to treatment throughout the day can be monitored over time as doses are adjusted. Due to interpatient variability, clinicians will still need to titrate doses on an individual basis; however, the dose conversion ratios reported in this study can help clinicians target an appropriate dose range for optimized treatment with DR/ER-MPH.

The analyses presented here have several limitations. This analysis was performed post hoc and should be viewed within the framework of its conceptualization. The findings are affected by small sample sizes. However, all mean dose conversion ratios were at least 1.8, suggesting that clinicians should generally expect that patients will require higher doses (above what is predicted by bioavailability differences) when transitioning to DR/ER-MPH. The dose conversion ratios were calculated for both amphetamines and MPHs, which are different chemical entities. In addition, differences between racemic and D-enantiomer MPH formulations, or between racemic and D-enantiomer amphetamine formulations, may have affected the dose conversion ratio calculations. This should be taken into account when using the dose conversion ratios in clinical practice. A fixed-dose study design may have resulted in more participants achieving higher (and potentially more optimized) DR/ER-MPH doses. It is also possible that participants were not dose-optimized on their previous stimulant medication, despite being on a stable dose before screening. However, enrollment in the study was not predicated on the inefficacy of previous medications. The dose conversion ratios presented here should therefore be viewed as a guide for clinicians, and optimized DR/ER-MPH doses should be determined individually using titration and, whenever possible, objective scales as previously stated.

The results should also be considered in light of limitations of the study design discussed previously[15]: the inclusion of children aged 6—12 years, without significant comorbidities, and at least a partial response to MPH limit the applicability to children in other age groups, ADHD profiles, and MPH-naive patients, respectively. In addition, a short duration limits extrapolation of findings over the long term. The definition of optimized dosing used in the trial does not necessarily reflect optimized doses in a clinical setting; therefore, the clinician's judgment should be used when applying these dose conversion ratios in a clinical setting and with different patient characteristics.

CONCLUSIONS

In this post hoc analysis of a Phase III trial of children with ADHD, optimized doses of DR/ER-MPH were much higher than prior stimulant doses, with dose conversion ratios for stimulant monotherapies ranging from 1.8 to 6.0. The adverse event profile of DR/ER-MPH was consistent with that of other MPH formulations.[15] DR/ER-MPH is distinct from other stimulants in terms of delivery and absorption profile; high optimized doses of DR/ER-MPH in this trial were consistent with lower bioavailability plus the predicted dose-dependent duration of effect that extends MPH absorption into the evening from the time of awakening.[24] The data presented here may help guide clinicians to target an appropriate dose range when optimizing DR/ER-MPH in their practice.

DISCLOSURES

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Arbor Pharmaceuticals, LLC, Emalex, Forest Laboratories, Ironshore Pharmaceuticals & Development, Inc, KemPharm, Inc, Neos Therapeutics, Neurovance, Inc, Otsuka America Pharmaceutical, Inc, Pearson, Pfizer, Purdue Pharma, Rhodes Pharmaceuticals, Servier, Shire, Sunovion Pharmaceutical, Inc, Supernus Pharmaceutical, Inc, Takeda Pharmaceutical Company Ltd, Tris Pharma, and the U.S. Food and Drug Administration. She has served on advisory boards for Adlon, Akili Interactive Labs, Arbor Pharmaceuticals, LLC, Cingulate Therapeutics, Ironshore Pharmaceuticals & Development, Inc, Neos Therapeutics, Neurovance, Inc, NLS Pharma, Otsuka America Pharmaceutical, Inc, Pfizer, Purdue Pharma, Rhodes Pharmaceuticals, Shire, Sunovion Pharmaceuticals, Inc, Supernus Pharmaceuticals, Inc, Takeda Pharmaceutical Company Ltd., and Tris Pharma; and has been a consultant for Arbor Pharmaceuticals, LLC, Ironshore Pharmaceuticals & Development, Inc, Jazz, KemPharm, Inc, Neos Therapeutics, Neurovance, Inc, Purdue Pharma, Rhodes Pharmaceuticals, Sunovion Pharmaceuticals, Inc, Supernus Pharmaceuticals, Inc, and Tris Pharma. She has also served on speaker bureaus for Arbor Pharmaceuticals, LLC, Ironshore Pharmaceuticals Inc, Neos Therapeutics, Pfizer, Shire, Takeda Pharmaceutical Company Ltd, and Tris Pharma; and has received writing support from Arbor Pharmaceuticals, LLC, Ironshore Pharmaceuticals & Development, Inc, Neos Therapeutics, Pfizer, Purdue Pharma, Rhodes Pharmaceuticals, Shire, Sunovion Pharmaceuticals, Inc, Takeda Pharmaceutical Company Ltd, and Tris Pharma. Drs. Uchida and Po are employees of Highland Therapeutics Inc. Mr. DeSousa and Dr. Incledon are employees of Ironshore Pharmaceuticals & Development, Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The study sponsor was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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Dr. Childress was the principal investigator of the clinical trial and contributed to the writing and editing of the manuscript. Dr. Uchida performed the data analysis and wrote the first draft of the manuscript. Dr. Po performed the data analysis and contributed to the writing and editing of the manuscript. Mr. DeSousa performed the data analysis and reviewed/edited the manuscript. Dr. Incledon conceptualized the study, supervised the data analysis, and reviewed/edited the manuscript. All the authors read and approved the final manuscript. The authors thank Justin Barnes, PhD, and Victor Otcheretko, MD, both of Ironshore Pharmaceuticals Inc (Durham, North Carolina) for critically reviewing and editing the manuscript.

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