Single-Dose Pharmacokinetics of Methylphenidate Extended-Release Multiple Layer Beads Administered as Intact Capsule or Sprinkles Versus Methylphenidate Immediate-Release Tablets (Ritalin[®]) in Healthy Adult Volunteers

Akwete Adjei, PhD,¹ Nathan S. Teuscher, PhD,² Robert J. Kupper, PhD,¹ Wei-Wei Chang, PhD,³ Laurence Greenhill, MD,⁴ Jeffrey H. Newcorn, MD,⁵ Daniel F. Connor, MD,⁶ and Sharon Wigal, PhD⁷

Abstract

Objectives: The purpose of this study was to evaluate the relative bioavailability and safety of a multilayer extended-release bead methylphenidate (MPH) hydrochloride 80 mg (MPH-MLR) capsule or sprinkles (37% immediate-release [IR]) versus MPH hydrochloride IR(Ritalin[®]) tablets, and to develop a pharmacokinetic (PK) model simulating MPH concentration-time data for different MPH-MLR dosage strengths.

Methods: This was a single-center, randomized, open-label, three-period crossover study conducted in 26 fasted healthy adults (mean weight $\pm$ standard deviation, 70.4 $\pm$ 11.7 kg) assigned to single-dose oral MPH-MLR 80 mg capsule or sprinkles with applesauce, or Ritalin IR 25 mg (1 $\times$ 5 mg and 1 $\times$ 20 mg tablet) administered at 0, 4, and 8 hours.

Results: MPH-MLR 80 mg capsule and sprinkles were bioequivalent; ratios for maximum concentration ($C_{\max}$), area under plasma drug concentration versus time curve (AUC_{0-t}), and $AUC_{0-\infty}$ were 1.04 (95% confidence interval [CI], 96.3–112.4), 0.99 (95% CI, 95.3–102.8), and 0.99 (95% CI, 95.4–103.0), respectively. MPH-MLR capsule/sprinkles produced highly comparable, biphasic profiles of plasma MPH concentrations characterized by rapid initial peak, followed by moderate decline until 5 hours postdose, and gradual increase until 7 hours postdose, culminating in an attenuated second peak. Based on 90% CIs, total systemic exposure to MPH-MLR 80 mg capsule/sprinkles was similar to that for Ritalin IR 25 mg three times daily, but marked differences in $C_{\max}$ values indicated that MPH-MLR regimens were not bioequivalent to Ritalin. MPH $C_{\max}$ and total systemic exposure over the first 4 hours postdose with MPH-MLR capsule/sprinkles was markedly higher than that associated with the first dose of Ritalin. All study drugs were safe and well tolerated. The PK modeling in adults suggested that differences in MPH pharmacokinetics between MPH-MLR and Ritalin are the result of dosage form design attributes and the associated absorption profiles of MPH.

Conclusions: MPH-MLR 80 mg provides a long-acting biphasic pattern of plasma MPH concentrations with one less peak and trough than Ritalin IR.

Introduction

STIMULANTS SUCH AS METHYLPHENIDATE (MPH) remain first-line treatment options for children, adolescents, and adults with attention-deficit/hyperactivity disorder (ADHD) (National Institute for Health and Care Excellence 2008; Wolraich et al. 2011). Use of

once-daily methylphenidate extended-release (ER) formulations offers major advantages over multiple daily doses of MPH immediate-release (IR) formulations, including reduced medication burden, improved adherence to treatment, lowered abuse liability, avoidance of school day administration, and minimized on/off responses associated with fluctuating drug concentrations, with the

¹Product Development, Rhodes Pharmaceuticals L.P., Coventry, Rhode Island.

²PK/PD Associates, Trophy Club, Texas.

³NuTec Incorporated, Boston, Massachusetts.

⁴Columbia University Medical Center and the New York State Psychiatric Institute, New York, New York.

⁵Mount Sinai Medical Center, New York, New York.

⁶University of Connecticut School of Medicine, Farmington, Connecticut.

⁷AVIDA, Inc., Newport Beach, California.

Statistical consultant: Lisa Diamond.

Funding: This study was funded by Rhodes Pharmaceuticals L.P.

potential for reducing related adverse events (AEs) (Stein et al. 1996; Greenhill et al. 1999; Markowitz et al. 2003a; Steele et al. 2006; Wigal et al. 2006; Rader et al. 2009). The efficacy and safety of a number of MPH ER formulations compared with placebo have been demonstrated both individually and through meta-analyses (Banaschewski et al. 2006; Faraone et al. 2006; Faraone and Buitelaar 2010).

None of the currently marketed MPH ER formulations is bioequivalent to another or to multiple daily doses of MPH IR (González et al. 2002; Markowitz et al. 2003a; Schutz et al. 2009), although some formulations (e.g., Ritalin[®] IR and Ritalin LA[®], Novartis Pharmaceuticals Corporation, East Hanover, NJ) are comparable with respect to total systemic exposure, based on area under the plasma drug concentration versus time curve (AUC) values (Wang et al. 2004). MPH ER formulations were specifically designed to have different pharmacokinetic and pharmacodynamic profiles that result in differing patterns of duration and timing of effect, thus giving clinicians an opportunity to individualize patient treatment (Maldonado 2013).

To varying extents, all of the current second-generation MPH ER formulations were developed to provide a quick pulse of MPH, followed by a subsequent, more prolonged phase of drug delivery (Markowitz et al. 2003a). Initial rapid dissolution of a portion of the MPH dose contained within each ER formula is required, because research suggests that the greatest behavioral improvements may occur during the absorption phase of the pharmacokinetic profile in children with ADHD receiving MPH IR (Swanson et al. 1999; Swanson and Volkow 2002). This so-called ramp or gradient effect coincides with engagement in morning activities (Greenhill 1992; Patrick and Markowitz 1997). The IR component of the total MPH dose of current second-generation ER formulations differs (20%, Quillivant XR[™], NextWave Pharmaceuticals, Cupertino CA; 22%, Concerta[®], Janssen Pharmaceuticals, Inc., Titusville, NJ; 30%, Metadate[®] CD, UCB, Inc., Smyrna, GA; 50%, Ritalin LA, Novartis Pharmaceuticals Corporation, East Hanover, NJ; and 50% [dextromethylphenidate] Focalin XR[®], Novartis Pharmaceuticals Corporation, East Hanover, NJ) (Markowitz et al. 2003a; Quillivant XR [methylphenidate hydrochloride] product information 2013).

After this initial absorption phase, an ideal ER formulation would facilitate: 1) Trough plasma drug concentrations near lunchtime, allowing for a normal appetite; 2) a second increase in plasma drug concentrations 6–8 hours after administration, to allow for symptom control during afternoon activities (e.g., homework for younger patients, afternoon commute for older patients); and 3) a gradual decline in plasma drug concentrations, allowing for a normal dinner appetite and sleep schedule (Markowitz et al. 2003b). None of the currently approved MPH ER formulations meets these three criteria that would optimize the efficacy of MPH while potentially minimizing side effects. For example, Concerta (22% IR, 78% ER), utilizing OROS[®] technology (ALZA Corporation, Vacaville, CA), provides an 8 hour absorption phase over which circulating plasma MPH concentrations rise with a flattened rate of change 1–4 hours postdose (Markowitz et al. 2003a; Patrick et al. 2005). Metadate CD (30% IR, 70% ER), formulated using Diffucaps[®] technology (Aptalis Pharmaceutical Technologies, Bridgewater, NJ), exhibits a linear absorption phase over a 7 hour period without evidence of a plateau in plasma drug concentrations over the lunchtime period (Markowitz et al. 2003a). The variable pharmacokinetic (PK) profile produced by Ritalin LA (50% IR, 50% ER; Novartis Pharmaceuticals Corporation, East Hanover, NJ), which uses SODAS[®] technology (Alkermes Pharma, Gainesville, GA), is similar to that of twice-daily MPH IR, and features

an initial peak at ~1 hour postdose, followed by a second peak at ~5 hours postdose, with the afternoon peak being higher than the morning peak (Markowitz et al. 2003a).

A novel multilayer release (MLR) bead formulation of MPH hydrochloride containing 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, or 80 mg of active ingredient (MPH-MLR hard gelatin capsule, Rhodes Pharmaceuticals L.P., Coventry, RI) has been designed and developed to meet all three of the aforementioned criteria of an ideal ER formulation by providing a biphasic plasma concentration-time profile when given as a single daily dose. The formulation caters to patients who have problems swallowing solid oral dosage forms by making available the option of administering the controlled-release beads intact or sprinkled on applesauce. The MLR bead system was designed to provide rapid initial release of 37% of the total MPH dose with an onset of action comparable with that of MPH IR (Quinn et al. 2007; Reiz et al. 2008). Following the rapid initial pulse of MPH exposure observed in phase 1 trials, there was a noticeable small drop in plasma drug concentrations over the lunchtime period before MPH release from the controlled-release core, which resulted in a gradual increase in concentrations throughout the rest of the day and into the early evening (Quinn et al. 2007; Reiz et al. 2008).

After a second peak in the afternoon, MPH levels gradually decreased through dinner and sleeping hours. In phase 2 studies of ADHD in children and adolescents conducted in the home and school settings (Weiss et al. 2007) or a laboratory classroom-based study setting (Schachar et al. 2008;), and outpatient settings (for adults) (Jain et al. 2007), once-daily MPH-MLR was associated with significant improvements in situational behavior and cognitive measures, with a prolonged duration of effect and minimal side effects.

The current study was designed to evaluate the relative bioavailability and the safety and tolerability of a single dose of MPH-MLR 80 mg administered as a capsule or as sprinkles versus Ritalin IR 25 mg tablets given three times daily under fasted conditions in healthy adult male and female subjects. Using these phase 1 data, we also developed a PK model to simulate MPH concentration-time data for different dosage strengths of MPH-MLR.

Methods

Study conduct

This single-center, single-dose, randomized, open-label, three-period crossover study was approved by the IntegReview Ethics Review Board (protocol number, RP-BP-PK001; approved May 13, 2011). The study was conducted by Frontage Clinical Services (Frontage Laboratories, Inc., Hackensack, NJ), and undertaken in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki.

Subjects

Twenty-six, consenting, nonsmoking male and female subjects ages 18–45 years were enrolled in the study. All subjects were MPH therapy naïve, weighed between 50 and 90 kg, and were within 15% of ideal weight based on height and body frame (based on the Metropolitan Life Insurance Company height and weight tables) (Metropolitan Life Insurance Company 1999). The subjects were in good health, based on the results of physical examinations, vital sign evaluations, routine clinical laboratory tests, and 12 lead electrocardiograms performed within the 21 days before receiving

study drug. Female subjects of childbearing potential were required to use appropriate contraceptive measures throughout the duration of the study, and have a negative urine pregnancy test result at screening and before study drug dosing. In addition, all subjects were required to have had a negative drug and alcohol test result at screening and at each admission to the research facility. Exclusion criteria included: A true allergy to MPH; poorly controlled significant medical illness; infection with hepatitis B or C or HIV; usage of any prescription drug therapy within 14 days, or of any over-the-counter drugs or supplements within the 48 hours before receiving study drug; and the consumption of grapefruit or grapefruit-containing juices within 72 hours, or caffeine-containing foods or beverages within the 24 hours before receiving the study drug.

Study design

Subjects were screened within 3 weeks of initial dosing. Subjects who passed screening were randomly assigned to one of three sequences in a crossover study, each sequence consisting of three 1 day study drug administration periods, with a 7 day interperiod washout (Fig. 1): 1) MPH-MLR 80 mg capsule once daily (period 1), MPH-MLR 80 mg sprinkles once daily (period 2), and Ritalin 25 mg three times daily (period 3); 2) Ritalin 25 mg three times daily (period 1), MPH-MLR 80 mg capsule once daily (period 2), and MPH-MLR 80 mg sprinkles once daily (period 3); and 3) MPH-MLR 80 mg sprinkles once daily (period 1), Ritalin 25 mg three times daily (period 2), and MPH-MLR 80 mg capsule once daily (period 3).

Subjects reattended the research facility the night before the first period of study drug administration (day -1). In the morning after an overnight fast (at ~08:00 hours on day 1), subjects received their first dose of study drug. Study drugs included MPH-MLR oral capsule (Lot No. A71556A) containing 80 mg of MPH hydrochloride, and the contents of the opened capsule sprinkled over 1 tablespoon of applesauce. The applesauce used in this study for the sprinkle dose was Mott's® Original Applesauce (Lot No. 011911WB, Mott's LLP, Rye Brook, NY). The pH of this lot of applesauce was 3.45, as assessed by Rhodes Pharmaceuticals L.P. Ritalin 20 mg (Lot No. F0125) and 5 mg (Lot No. F0103) oral tablets were manufactured by Novartis Pharmaceuticals Corporation. Water (240 mL) was consumed with each dose, including the sprinkles, and allowed *ad libitum*, with the exception of 1 hour pre- and 1 hour postdose. On the day of dosing, standard meals were consumed at ~6 and 11 hours after the study drug dose. An evening snack was offered at ~21:00 hours on the evening of admission and on the day of dosing.

Seated blood pressure and pulse rate were measured within 60 minutes before dosing. Subjects remained sitting upright, and ambulation was limited during the immediate 1 hour postdose period. Subjects were discontinued from the study prematurely if excessive treatment-emergent adverse events (TEAEs) from acute exposure to the drug developed.

Frequent serial blood samples for determination of MPH plasma concentration and PK analysis were obtained on day 1 at time 0 (i.e., within 15 minutes predose) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 12.0, 15.0, 19.0, and 24.0 hours postdose. On day 2 (~24 hours after administration of the study drug), subjects were discharged from the research facility. Subjects reported back to the research facility on the evenings prior to day 8 (period 2) and day 15 (period 3) by ~20:00 hours, fasted overnight, and remained confined to the research facility until ~24 hours after administration of the study drug. A urine drug and saliva alcohol test (all subjects) and a urine pregnancy test (for females of childbearing potential) were performed upon admission to the research facility. Following a wash-out period of 7 days, subjects were crossed over to an alternate MPH formulation on day 8 and day 15, and the same procedures were performed as during period 1. In addition, blood and urine were collected for clinical laboratory tests (chemistry, hematology, and urinalysis) ~24 hours after administration of study drug during period 3, and an abbreviated physical examination was performed and vital signs were collected before subjects were discharged from the study.

Assays

Blood samples (~6 mL) were collected from indwelling catheters or from venipuncture into chilled blood collection tubes containing ethylenediaminetetraacetic acid dipotassium, and were immediately chilled on crushed ice and centrifuged for 10 minutes in a refrigerated centrifuge (4–8°C) at 2000g within 30 minutes after collection. Duplicate plasma samples were transferred into polypropylene tubes (~1.5 mL per tube), and stored at -70°C or lower until ready for analysis by Frontage Laboratories, Inc. An absence of a reaction between collection/storage vessels and MPH was determined as part of the bioanalytical method validation. Harvested plasma samples were extracted into ethylenediaminetetraacetic acid dipotassium and analyzed for total plasma MPH concentration determination using a fully validated liquid chromatography tandem mass spectrometry (LC/MS) analysis method using methylphenidate-d3 hydrochloride as the internal standard (Quinn et al. 2007). Calibrations were performed similarly to the Quinn et al. study (Quinn et al. 2007), with a quadratic regression

FIG.1. Study design. Sequence 1: Multilayer extended-release bead methylphenidate (MPH-MLR) 80 mg capsule once daily (period 1); MPH-MLR 80 mg sprinkles once daily (period 2); and Ritalin® 25 mg three times daily (period 3). Sequence 2: Ritalin 25 mg three times daily (period 1); MPH-MLR 80 mg capsule once daily (period 2); and MPH-MLR 80 mg sprinkles once daily (period 3). Sequence 3: MPH-MLR 80 mg sprinkles once daily (period 1); Ritalin 25 mg three times daily (period 2); and MPH-MLR 80 mg capsule once daily (period 3). PK, pharmacokinetic.

(weighted $1/x$) on the calibration standards for curve determination. The calibrator standards were 0.05, 0.1, 0.5, 1, 5, 12.5, 20, and 25 ng/mL. Curve parameters for the assay method were stable throughout the runs, specifically, coefficient of determination met acceptance criteria ($R^2 \geq 0.99$), lower limit of quantitation was 50 pg/mL, and $> 2/3$ of the analyzed incurred sample reanalysis samples had no more than a $\pm 20\%$ difference when compared with the original analysis results.

PK analysis

Individual plasma concentration-time data were used to calculate MPH PK parameters using standard, noncompartmental methods (WinNonlin version 5.3, Pharsight Corporation, Mountain View, CA). The primary PK end-points were the maximum plasma MPH concentration ($C_{\max}$) and AUC calculated to 4 hours (AUC_{0-4}), to the last measurable observation (AUC_{0-t}), and extrapolated to infinity ($AUC_{0-\infty}$). AUC values were calculated using the linear trapezoidal method. The terminal elimination rate constant (k_{el}) was calculated as the negative gradient of the log-linear terminal portion of the plasma concentration-time curve using linear regression. Secondary MPH PK variables were the respective time to $C_{\max}$, elimination half-life, and k_{el} . The half-life of the terminal elimination phase was estimated by use of the following ratio: $0.693/k_{el}$.

Safety assessments

The incidence, nature, severity, and relationship of each AE to the study drug were monitored by nursing and medical observations of the staff and spontaneous reports throughout the study. Safety was evaluated by performing vital sign measurements, 12 lead electrocardiograms, clinical laboratory testing (hematology, chemistry, and urinalysis), and physical examinations. A TEAE was defined as an AE commonly reported in the literature for MPH when taken orally by healthy volunteers. AEs were coded and summarized using the Medical Dictionary for Regulatory Activities version 13.1.

Analysis populations

The following populations were defined for analyses: 1) The safety analysis set (SAF), defined as the subset of all enrolled subjects who received one or more doses of study drug; and 2) the PK analysis set, defined as the subset of subjects from the SAF who completed two or more drug administration phases and had PK parameters generated.

Statistical analysis

All PK and safety data analyses were performed using descriptive statistics compiled by SAS[®] version 9.1 or higher (SAS[®] Institute Inc., Cary, NC). All plasma concentrations below the lower limit of quantitation were treated as missing in the PK analyses, except those that occurred before the first quantifiable concentration on the day of dosing, or after the last quantifiable concentration, which were set to 0.

There were two study hypotheses: 1) The two MPH-MLR 80 mg preparations were bioequivalent; and 2) the two MPH-MLR 80 mg preparations were not bioequivalent to Ritalin 25 mg administered three times daily. To assess the relative bioavailability of MPH-MLR 80 mg capsule or sprinkles, as well as their relative bioavailability to Ritalin 75 mg daily (normalized to 80 mg), a crossover analysis of variance model was constructed to statistically analyze PK param-

eters. Log-transformed PK parameters AUC_{0-4} , $AUC_{0-\infty}$, and $C_{\max}$ were analyzed using the analysis of variance model with terms for sequence, study drug, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. A confidence interval (CI) on the ratio of untransformed PK parameters was derived through reverse transformation of the 90% CI for the difference in the log scale from the 90% CI for the ratio in the original scale. Bioequivalence was concluded if the 90% CIs for the ratio of the geometric means for the MPH-MLR 80 mg capsule versus sprinkles, or for either MPH-MLR 80 mg capsule or sprinkles versus Ritalin, was within an 80–125% range for all primary PK parameters. Because this study only assessed PKs and not pharmacodynamics, any statements pertaining to bioequivalence between different methylphenidate dosing preparations do not serve as substitutes for the collection of time-response data effects on the subjects' behavior and seatwork performance during a laboratory school protocol (Wigal and Wigal 2006).

PK modeling

Population PK models are useful tools for understanding pharmacokinetic features including dosage adjustments (United States Department of Health and Human Services Food and Drug Administration 1999). Although a single strength of MPH-MLR (80 mg) was used in the present study, additional strengths of this product are intended to be developed. To better understand the kinetics of these intended dose formulations, a PK model was constructed to allow simulations for the other strengths of MPH-MLR capsules. PK data from this study were evaluated using nonlinear mixed effects modeling. The structural model included first-order elimination from a central compartment and two parallel absorption depots. The final model included between-individual variability parameters for clearance, volume of distribution, absorption rate 1, absorption rate 2, and a proportional residual error parameter. No between-individual variability parameters were used for the fraction of drug in the IR layer or lag time. All structural and variability parameters were estimated with high precision. The final model was used to simulate different dosage strengths of MPH-MLR (10–60 mg) and calculate the partial AUC from 0–4 hours ($pAUC_{0-4}$) as a marker of the initial MPH absorption phase in adults (Zirkelbach et al. 2013).

Results

Subject disposition and baseline data

All 26 randomized subjects received one or more doses of the study medication and constituted the SAF population (completed study, $n = 23$). Three subjects voluntarily withdrew from the study for reasons other than AEs. Although these three subjects did not complete the study, there were sufficient data provided by two of these subjects for PK analysis. Hence, the PK analysis set included 25 subjects.

Table 1 shows that more than half (58%) of the subjects in the SAF were male, most (58%) were white, and most of the remaining subjects (38%) were black. The age, weight, and body mass index of all subjects fell within the inclusion criteria defined in the protocol.

PK assessments

The PK profiles of the three MPH administration schemes are shown in Figure 2. Overall, interpatient variability is minimal. The

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Parameter	All volunteers; n=26
Male, n (%)	15 (57.7)
Race, n (%)	
White	15 (57.7)
Black	10 (38.5)
Other	1 (3.8)
Ethnicity, n (%)	
Not Hispanic or Latino	15 (57.7)
Mean (SD) age, years	27.8 (7.3)
Mean (SD) weight, kg	70.4 (11.7)
Mean (SD) BMI, kg/m ²	24.3 (2.9)

BMI, body mass index; SD, standard deviation.

primary outlier with each administration scheme was the same patient. Baseline characteristics were not predictive of this response. Visual inspection of the plasma MPH concentrations associated with MPH-MLR 80 mg capsule and sprinkles revealed curves that were biphasic and almost superimposable over the 24 hour sampling period, suggesting that there was minimal in-

trapatient variability between oral and sprinkle administration. Administration of MPH-MLR as either a capsule or sprinkles resulted in rapidly rising plasma MPH concentrations peaking at 2 hours postdose, followed by a moderate decline in drug concentrations until 5 hours postdose, and then a gradual increase in drug concentrations until 7 hours postdose, culminating in an attenuated second peak. Thereafter, plasma MPH concentrations gradually declined in an apparent log-linear fashion. In contrast, three unique peaks in plasma MPH concentration that corresponded to each dose of Ritalin 25 mg three times daily were observed, and were characterized by a trend of higher peak concentrations throughout the day. The Ritalin three times daily regimen produced its second rise in plasma drug concentrations earlier than the second rises produced by MPH-MLR capsule or sprinkles, and plasma drug concentrations with Ritalin were still increasing 4 hours after they had started to decline with MPH-MLR administered as a capsule or sprinkles at 7 hours postdose. Consequently, mean plasma drug concentrations were ~67% higher with the Ritalin regimen than with the MPH-MLR capsule or sprinkles at 11 hours postdose.

Analysis of the primary PK parameters revealed that total systemic exposure (i.e., AUC_{0-t} and AUC_{0-inf}) were similar for the three study drugs, but that there were differences between either

FIG. 2. (A) Mean plasma methylphenidate concentration-time profiles following single-dose administration of multilayer extended-release bead methylphenidate (MPH-MLR) 80 mg capsule, MPH-MLR 80 mg sprinkles, and Ritalin[®] 25 mg three times daily under fasted conditions. Error bars represent standard deviation. (B) Individual plasma methylphenidate concentration-time profiles following single-dose administration of MPH-MLR 80 mg as intact capsule (fasted conditions). (C) Individual plasma methylphenidate concentration-time profiles following single-dose administration of MPH-MLR sprinkled on applesauce (fasted conditions). (D) Individual plasma methylphenidate concentration-time profiles following administration of Ritalin 25 mg three times daily (fasted conditions).

TABLE 2. RANGE PLASMA PHARMACOKINETIC PARAMETERS OF METHYLPHENIDATE FOLLOWING SINGLE-DOSE ADMINISTRATION OF MPH-MLR 80 MG CAPSULE, MPH-MLR 80 MG SPRINKLES, AND RITALIN® 25 MG THREE TIMES DAILY

Parameter (unit)	MPH-MLR 80 mg capsule; n = 24			MPH-MLR 80 mg sprinkles; n = 25			Ritalin 25 mg 3 times daily; n = 24 ^b		
C _{max} (ng/mL)	23.5	(11.4)	9.7-45.6	21.8	(9.5)	9.9-53.2	29.1	(14.9)	12.4-81.7
AUC ₀₋₄ (ng·hr/mL)	60.1	(27.7)	27.2-125.9	59.6	(22.8)	28.3-112.6	44.8	(22.4)	16.0-116.2
AUC _{0-t} (ng·hr/mL)	262.7	(134.8)	113.9-735.0	262.9	(127.5)	120.0-752.7	271.4	(151.7)	103.2-861.9
AUC _{0-inf} (ng·hr/mL)	258.1	(94.2)	127.2-458.9	258.0	(84.4)	125.6-428.3	281.7	(171.6)	104.1-974.2
t _{max} (hr) ^a	2.0		1.0- 10.0	2.0		1.0-9.0	9.5		1.5- 10.5
t _{1/2} (hr)	5.1	(1.6)	3.2-9.9	5.4	(2.5)	3.5-13.9	3.4	(0.7)	2.7-5.8
K _{el} (L/hr)	0.15	(0.04)	0.07-0.22	0.14	(0.04)	0.05-0.2	0.21	(0.03)	0.12-0.26

Arithmetical mean (SD).

^aMedian.^bData shown for Ritalin represents data over the 24 hour monitoring period.

AUC, area under the plasma drug concentration vs. time curve; AUC₀₋₄, AUC calculated to 4 hours; AUC_{0-inf}, AUC extrapolated to infinity; AUC_{0-t}, AUC to the last measurable observation; C_{max}, maximum plasma drug concentration; k_{el}, terminal elimination rate constant; t_{1/2}, elimination half-life; t_{max}, time to C_{max}; MPH-MLR, multilayer extended-release bead methylphenidate.

MPH-MLR capsules or sprinkles and Ritalin in regard to acute exposure as measured by C_{max} and AUC₀₋₄ (Table 2). The C_{max} values associated with each successive dose of Ritalin were progressively higher (C_{max1}, 16.4 ng/mL at 1.9 hours; C_{max2}, 25.5 ng/mL at 5.8 hours; C_{max3}, 27.3 ng/mL at 10.4 hours), such that the average of the three Ritalin C_{max} values was higher than the averages associated with MPH-MLR capsule and sprinkles (29.1 vs. 23.5 and 21.8 ng/mL, respectively). Notably, not only were the C_{max} values associated with MPH-MLR capsule and sprinkles 33–43% higher, respectively, than the C_{max} value associated with the first dose of Ritalin, but total systemic exposure over the first 4 hours postdose (i.e., AUC₀₋₄) was also markedly greater by ~33% (Table 2). Relative to the C_{max} values associated with the second and third doses of Ritalin, the C_{max} values of MPH-MLR capsule

and sprinkles were lower by 9% and 16%, respectively, and by 17% and 25%, respectively.

As evidenced by the ratio of log-transformed MPH-MLR C_{max}, AUC_{0-t}, and AUC_{0-inf} values, the MPH-MLR capsule and sprinkles were deemed bioequivalent based on 90% CIs (Table 3). Neither the MPH-MLR capsule nor sprinkles was bioequivalent to Ritalin, as both the geometric mean ratio of log-transformed C_{max} values and the lower limit of the 90% CI were below the 80% threshold.

Estimates for fluctuation index (FI) were derived for the respective treatment groups using the relationship FI = (C_{max} - C_{trough})/C_{ave}, where C_{trough} is MPH trough concentrations and C_{ave} is average plasma MPH concentration for the multiphasic profiles. The results are summarized in Table 4.

PK simulations

The PK model demonstrated high precision for all structural parameters, and the percent coefficient of variation was <12% for all parameters. The residual variability was extremely small, indicating that the other model parameters explained a majority of the variability observed in the concentration data. The PK model was used to simulate MPH concentration-time data for lower dosage strengths of MPH-MLR, specifically 10, 15, 20, 30, 40, 50, and 60 mg. The overall mean concentration profiles showed increasing concentrations with increasing dose in a linear fashion, consistent with the known linear pharmacokinetics of MPH (Fig. 3). The partial AUC values (pAUC₀₋₄) were calculated for each strength of MPH-MLR (10–80 mg) to assess systemic exposure relative to the IR comparator, Ritalin. The mean (standard deviation [SD])

TABLE 3. LOG-TRANSFORMED METHYLPHENIDATE PHARMACOKINETIC PARAMETERS FOLLOWING SINGLE-DOSE ADMINISTRATION OF MPH-MLR 80 MG CAPSULE, MPH-MLR 80 MG SPRINKLES, AND RITALIN® 25 MG THREE TIMES DAILY^{a,b}

Parameter (unit)	Geometric mean ratio	90% Confidence interval
MPH-MLR 80 mg capsule vs. Ritalin 25 mg 3 times daily		
C _{max} (ng/mL)	0.74	68.7–80.4
AUC _{0-inf} (ng·hr/mL)	0.98	93.9–101.3
AUC _{0-t} (ng·hr/mL)	0.93	89.3–96.5
MPH-MLR 80 mg sprinkle vs. Ritalin 25 mg 3 times daily		
C _{max} (ng/mL)	0.71	66.1–77.2
AUC _{0-inf} (ng·hr/mL)	0.99	94.9–102.3
AUC _{0-t} (ng·hr/mL)	0.94	90.1–97.3
MPH-MLR 80 mg capsule vs. MPH-MLR 80 mg sprinkles		
C _{max} (ng/mL)	1.04	96.3–112.4
AUC _{0-inf} (ng·hr/mL)	0.99	95.3–102.8
AUC _{0-t} (ng·hr/mL)	0.99	95.4–103.0

^aResults based on an analysis of variance model with terms for sequence, study drug, and period as fixed effects, and subject nested within sequence as a random effect.

^bAll calculations based on dose-normalized values.

AUC, area under the plasma drug concentration vs. time curve; AUC_{0-t}, AUC to the last measurable observation; AUC_{0-inf}, AUC extrapolated to infinity; C_{max}, maximum plasma drug concentration; MPH-MLR, multilayer extended-release bead methylphenidate.

TABLE 4. FLUCTUATION INDEX FOLLOWING SINGLE-DOSE ADMINISTRATION OF MPH-MLR 80 MG CAPSULE, MPH-MLR 80 MG SPRINKLES, AND RITALIN® 25 MG THREE TIMES DAILY

	MPH-MLR 80 mg capsule	MPH-MLR 80 mg sprinkle	Ritalin 25 mg 3 times daily
1st peak	0.6277	0.4876	0.4027
2nd peak	0.0423	0.0696	0.7861
3rd peak	NA	NA	0.9181

NA, data not available; MPH-MLR, multilayer extended-release bead methylphenidate.

FIG. 3. Mean simulated concentration-time profiles for multi-layer extended-release bead methylphenidate (MPH-MLR) dose strengths between 10 mg and 80 mg.

pAUC_{0-4} for Ritalin IR 25 mg (from observed data) was 44.83 (22.44). The mean (SD) pAUC_{0-4} (from simulated drug levels) for the 60 mg dose was 42.66 (3.10). The variability for the observed data was much higher than the simulated data, because of the difference in sample size ($n = 26$ for real-life data observed; $n = 100$ for 60 mg simulated). The pAUC_{0-4} results demonstrated that MPH-MLR 60 mg, which contains ~ 22 mg of MPH in the IR layer, provides early MPH exposure equivalent to Ritalin IR 25 mg.

Safety assessments

Fourteen (53.8%) subjects experienced one or more TEAEs during the study. Eight (33.3%), 8 (32.0%), and 9 (36.0%) subjects reported one or more TEAEs following administration of MPH-MLR 80 mg capsule, MPH-MLR 80 mg sprinkles, and Ritalin, respectively. The most common TEAEs recorded were headache, dizziness, dry mouth, nausea, and anxiety. All TEAEs were mild or moderate in intensity, no serious AEs were reported during the study, and no subject discontinued study participation because of an AE. Furthermore, there were no clinically significant findings from clinical laboratory test results, or from physical examination or electrocardiogram evaluations. No trends or changes in vital sign assessments were noted.

Discussion

There are several findings from this three-way crossover PK study of MPH-MLR 80 mg capsule or sprinkles administered once in the morning, and Ritalin IR 25 mg tablets given three times daily in fasted healthy adults. First, the study demonstrated through comparisons of C_{max} , AUC_{0-t} , and $\text{AUC}_{0-\text{inf}}$ ratios that MPH-MLR 80 mg administered either as a capsule or as sprinkles on apple-sauce were bioequivalent. The plasma MPH concentration-time curves of MPH-MLR 80 mg capsule or sprinkles were almost identical, to the extent that the secondary PK parameters time to C_{max} , half-life, and K_{el} were also highly comparable. These data show that MPH-MLR 80 mg sprinkles can be directly substituted for MPH-MLR 80 mg capsule in patients with ADHD who have difficulty swallowing solid oral dosage forms.

Second, once-daily doses of either MPH-MLR 80 mg capsule or sprinkles were not bioequivalent to Ritalin IR 25 mg tablets administered three times daily based upon acute systemic exposure,

C_{max} . Whereas MPH-MLR 80 mg administered as a capsule or sprinkles provided equivalent total systemic exposure to MPH based on AUC_{0-t} and $\text{AUC}_{0-\text{inf}}$ that was similar to three divided doses of Ritalin IR 25 mg tablets administered at time 0, 4 hours, and 8 hours, MPH-MLR 80 mg capsule and sprinkles yielded lower C_{max} values than the average C_{max} associated with taking 75 mg of Ritalin IR tablets in three evenly divided 25 mg doses. Hence, the design objective for the MPH-MLR bead formulation achieved the intended PK profile for MPH (which was characterized by higher pAUC_{0-4} than that associated with the first dose of Ritalin IR 25 mg tablet). Specifically, the profiles exhibited an initial peak followed by declining plasma concentrations to ~ 5 hours postdose, followed by increasing concentrations throughout the afternoon until early evening, and terminating toward the end of the day, with gradually decreasing concentrations through dinner and night sleeping hours. In contrast, the PK profile for MPH following three times daily dosing with Ritalin IR 25 mg tablets was triphasic, and therefore, not as steady throughout the day. Importantly, lower plasma MPH concentrations were observed throughout the morning with the Ritalin IR 25 mg regimen than with the MPH-MLR 80 mg regimens, and vice versa, and far higher drug concentrations were observed with the Ritalin IR 25 mg regimen over lunchtime and in the early evening. MPH-MLR 80 mg capsule or sprinkles maintained average plasma methylphenidate concentrations of > 10 ng/mL until 15 hours postdose, at which time, a continuous and gradually decreasing slope was observed up to the last sampling time of 24 hours. A minor caveat of the bioavailability data is that the total daily dose of Ritalin IR tablets used in this study, 75 mg administered as three doses of 25 mg/day, represented the daily dose that is closest to the MPH-MLR 80 mg daily dose. Relative bioavailability calculations were based on dose normalization, which was hypothetical, and thus are not conclusive.

Third, the MPH plasma concentration-time course yielded a two-parallel input, one-compartment PK model with first-order elimination that simulated dose-linear plasma MPH concentrations for the 10, 15, 20, 30, 40, 50, and 60 mg dose strengths. The findings are expected, not only based on design targets for MPH-MLR, but also because the eight product strengths are made from a single common multiple layered bead formulation that is filled gravimetrically into various sized gelatin capsules.

Fourth, the pAUC_{0-4} results suggest that systemic exposure to MPH from a 25 mg dose of Ritalin IR from hours 0 to 4 is most closely approximated by a single dose of MPH-MLR 60 mg (which contains ~ 22.2 mg of MPH in the IR layer) from hours 0 to 4.

Lastly, significant differences in peak-to-trough concentration profile variations, estimated by FI, were noted in favor of MPH-MLR 80 mg when compared with Ritalin IR 75 mg administered in three divided doses. In addition, the minimal inpatient variability that was noted between the oral and sprinkle administration, although not truly identical dosing, adds to the published literature on ER MPH formulations. PK variability within and between individuals receiving MPH has frequently been described, and contributes to the need for dose titration with these products (Ermer et al. 2010).

This study was not designed to evaluate the clinical efficacy of MPH-MLR. Additional studies are required to determine whether the biphasic plasma MPH concentration-time profile produced after administration of once-daily dosing translates into an improved efficacy and safety profile, and improved level of patient adherence, relative to Ritalin IR 25 mg tablets and other MPH ER formulations. The study was also not designed to detect safety differences among the three study drug regimens, although all study drugs were

extremely well tolerated by these healthy male and female subjects, with low rates of AEs reported, and no major safety concerns. AEs were consistent with the known safety profile of MPH.

Conclusions

Administration of MPH-MLR 80 mg capsule or sprinkles on applesauce produced highly comparable biphasic profiles of plasma MPH concentrations, characterized by rapid initial drug release throughout the morning, delayed secondary release over the afternoon and early evening, and similar C_{max} values in both periods. Total systemic exposure to MPH provided by MPH-MLR 80 mg capsule and sprinkles was similar to that provided by Ritalin IR 25 mg tablets administered three times daily, with marked differences in C_{max} values, demonstrating that the MPH-MLR regimens were not bioequivalent to the Ritalin regimen. PK modeling suggested that a 60 mg dose of MPH-MLR produces an early exposure equivalent to Ritalin IR 25 mg tablets.

Clinical Significance

The American Academy of Pediatrics recommends that treatment of child and adolescent patients with ADHD with MPH therapy be tailored according to patient age and clinical circumstance (Wolraich et al. 2011). The results of this study show that administration of MPH-MLR 80 mg capsule or sprinkles on applesauce results in plasma MPH concentrations that are timed to correspond with common activities undertaken by most individuals during the morning and early afternoon. The MPH-MLR 80 mg capsules and sprinkles are interchangeable, and provide equivalent plasma profiles, notably average plasma concentrations with a much lower fluctuation index than with the IR. Maximal sustained plasma MPH concentrations are achieved over the first 4 hours postdose, coincident with early morning activities such as preparing for and attending school or driving to work. The C_{max} of the MPH-MLR 80 mg capsule and sprinkles, which was lower than both the second or third peaks produced following the administration of a Ritalin IR 25 mg tablet, may decrease side effects. Gently increasing plasma MPH concentrations over the sampling period of 24 hours modulates the impact of any sudden decrease in plasma drug concentrations. Additional investigations using MPH-MLR in clinical populations will be needed to fully understand whether the PK profile translates to positive clinical outcomes.

Acknowledgments

This study was conducted at Frontage Laboratories, Exton, PA. A.A. was the study director. A.A., R.J.K., L.G., and S.W. designed the study and created the study protocol. N.S.T. designed and executed the pharmacokinetic modeling. W.C. provided statistical support. All authors analyzed and interpreted the study data, contributed to the content of the manuscript, critically reviewed drafts, and approved the final version for submission. The authors acknowledge the contribution of Lisa Diamond of Frontage Laboratories for her contribution to the conducting of this study. Medical writing support was provided by Malcolm Darkes and Linda Wagner, medical writers at Excel Scientific Solutions, and funded by Rhodes Pharmaceuticals L.P.

Disclosures

Dr. Adjei is the Executive Director of Product Development at Rhodes Pharmaceuticals L.P. and was study director for this study. Dr. Teuscher is a consultant for Rhodes Pharmaceuticals L.P. Dr.

Kupper is an employee of Rhodes Pharmaceuticals L.P. Dr. Chang is a consultant for Rhodes Pharmaceuticals L.P. Dr. Greenhill has received research support from the National Institute on Drug Abuse/National Institutes of Health and Shire, and is on the advisory board for BioBehavioral Diagnostics. Dr. Newcorn receives or has received research grant support from the National Institute of Mental Health and Shire. He is also a consultant and/or advisor for Alcobra Pharma, BioBehavioral Diagnostics, Enzymotec, GencoSciences LLC, Lupin, Neurovance, Sunovion, and Shire. Dr. Connor receives grant support from and is an ADHD consultant for Rhodes Pharmaceuticals L.P. and Shire. He receives additional support from the National Institute of Mental Health and the state of Connecticut. He receives royalties from the Guilford Press and W.W. Norton. Dr. Wigal is an advisory board member/consultant/speakers bureau member for Eli Lilly, Ironshore, Neos Therapeutics Inc., NextWave Pharmaceuticals, Noven, NuTec Incorporated, Pfizer Inc, Purdue Pharma L.P., Rho, Rhodes Pharmaceuticals L.P., Shionogi Inc., Shire, and Vernalis, and has received grant and research support from Eli Lilly, Forest Laboratories, the National Institutes of Health, NextWave Pharmaceuticals, Noven, NuTec Incorporated, Rhodes Pharmaceuticals L.P., Shire, Sunovion, and Tris Pharma.

References

- Banaschewski T, Coghill D, Santosh P, Zuddas A, Asherson P, Buitelaar J, Danckaerts M, Dopfner M, Faraone SV, Rothenberger A, Sergeant J, Steinhausen HC, Sonuga-Barke EJ, Taylor E: Long-acting medications for the hyperkinetic disorders. A systematic review and European treatment guideline. *Eur Child Adolesc Psychiatry* 15:476–495, 2006.
- Ermer JC, Adeyi BA, Pucci ML: Stimulants in the treatment of children and adults with attention-deficit hyperactivity disorder. *CNS Drugs* 24:1009–1025, 2010.
- Faraone SV, Biederman J, Spencer TJ, Aleardi M: Comparing the efficacy of medications for ADHD using meta-analysis. *MedGenMed* 8:4, 2006.
- Faraone SV, Buitelaar J: Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. *Eur Child Adolesc Psychiatry* 19:353–364, 2010.
- González MA, Pentikis HS, Anderl N, Benedict MF, DeCory HH, Dirksen SJ, Hatch SJ: Methylphenidate bioavailability from two extended-release formulations. *Int J Clin Pharmacol Ther* 40:175–184, 2002.
- Greenhill LL: Pharmacologic treatment of attention deficit hyperactivity disorder. *Psychiatr Clin North Am* 15:1–27, 1992.
- Greenhill LL, Halperin JM, Abikoff H: Stimulant medications. *J Am Acad Child Adolesc Psychiatry* 38:503–512, 1999.
- Jain U, Hechtman L, Weiss M, Ahmed TS, Reiz JL, Donnelly GA, Harsanyi Z, Darke AC: Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *J Clin Psychiatry* 68:268–277, 2007.
- Maldonado R: Comparison of the pharmacokinetics and clinical efficacy of new extended-release formulations of methylphenidate. *Expert Opin Drug Metab Toxicol* 9, 1001–1014, 2013.
- Markowitz JS, Straughn AB, Patrick KS: Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: Focus on methylphenidate formulations. *Pharmacotherapy* 23:1281–1299, 2003a.
- Markowitz JS, Straughn AB, Patrick KS, DeVane CL, Pestreich L, Lee J, Wang Y, Muniz R: Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. *Clin Pharmacokinet* 42:393–401, 2003b.

- Metropolitan Life Insurance Company: Metropolitan height and weight tables. Stat Bull Metrop Life Insur Co 1999.
- National Institute for Health and Care Excellence: Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults, 2008. Available at <http://publications.nice.org.uk/attention-deficit-hyperactivity-disorder-cg72>. Accessed June 13, 2013.
- Patrick KS, Gonzalez MA, Straughn AB, Markowitz JS: New methylphenidate formulations for the treatment of attention-deficit/hyperactivity disorder. *Expert Opin Drug Deliv* 2:121–143, 2005.
- Patrick KS, Markowitz JS: Pharmacology of methylphenidate, amphetamine enantiomers and pemoline in attention-deficit hyperactivity disorder: A review. *Hum Psychopharmacol* 12:527–546, 1997.
- Quillivant XR (methylphenidate hydrochloride) product information: NextWave Pharmaceuticals, New York, NY. January 2013. Available at <http://www.quillivantxr.com> Accessed July 24, 2013.
- Quinn D, Bode T, Reiz JL, Donnelly GA, Darke AC: Single-dose pharmacokinetics of multilayer-release methylphenidate and immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Clin Pharmacol* 47:760–766, 2007.
- Rader R, McCauley L, Callen EC: Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder. *Am Fam Physician* 79:657–665, 2009.
- Reiz JL, Donnelly GA, Michalko K: Comparative bioavailability of single-dose methylphenidate from a multilayer-release bead formulation and an osmotic system: a two-way crossover study in healthy young adults. *Clin Ther* 30:59–69, 2008.
- Schachar R, Ickowicz A, Crosbie J, Donnelly GA, Reiz JL, Miceli PC, Harsanyi Z, Darke AC: Cognitive and behavioral effects of multilayer-release methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 18:11–24, 2008.
- Schutz H, Fischer R, Grossmann M, Mazur D, Leis HJ, Ammer R: Lack of bioequivalence between two methylphenidate extended modified release formulations in healthy volunteers. *Int J Clin Pharmacol Ther* 47:761–769, 2009.
- Steele M, Weiss M, Swanson J, Wang J, Prinzo RS, Binder CE: A randomized, controlled effectiveness trial of OROS-methylphenidate compared to usual care with immediate-release methylphenidate in attention deficit-hyperactivity disorder. *Can J Clin Pharmacol* 13:e50–e62, 2006.
- Stein MA, Blondis TA, Schnitzler ER, O'Brien T, Fishkin J, Blackwell B, Szumowski E, Roizen NJ: Methylphenidate dosing: twice daily versus three times daily. *Pediatrics* 98:748–756, 1996.
- Swanson J, Gupta S, Gupta D, Flynn D, Agler D, Lerner M, Williams L, Shoulson I, Wigal S: Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 66:295–305, 1999.
- Swanson JM, Volkow ND: Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. *Behav Brain Res* 130:73–78, 2002.
- United States Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Population pharmacokinetics. 1999 Available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133184.pdf> Accessed July 2, 2014.
- Wang Y, Lee L, Somma R, Thompson G, Bakhtiar R, Lee J, Rekhi GS, Lau H, Sedek G, Hossain M: In vitro dissolution and in vivo oral absorption of methylphenidate from a bimodal release formulation in healthy volunteers. *Biopharm Drug Dispos* 25:91–98, 2004.
- Weiss M, Hechtman L, Turgay A, Jain U, Quinn D, Ahmed TS, Yates T, Reiz JL, Donnelly GA, Harsanyi Z, Darke AC: Once-daily multilayer-release methylphenidate in a double-blind, crossover comparison to immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 17:675–688, 2007.
- Wigal SB, Wigal TL: The laboratory school protocol: its origin, use, and new applications. *J Atten Disord* 10:92–111, 2006.
- Wigal SB, Wigal TL, Kollins SH: Advances in methylphenidate drug delivery systems for ADHD therapy. *Advances in ADHD* 1:4–7, 2006.
- Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S: ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 128:1007–1022, 2011.
- Zirkelbach JF, Jackson AJ, Wang Y, Shuirmann DJ: Use of partial AUC (PAUC) to evaluate bioequivalence—a case study with complex absorption: Methylphenidate. *Pharm Res* 30:191–202, 2013.

Address correspondence to:

Akwete Adjei, PhD
Rhodes Pharmaceuticals L.P.
498 Washington St.
Coventry, RI 02816

E-mail: Akwete.Adjei@pharma.com