CLINICAL PHARMACOLOGY REVIEW

NDA:	**209311**
Related IND:	**118074**
Submission Dates:	**9/30/2016**
PDUFA Date:	**7/30/2017**
Brand Name:	**Jornay PM (proposed)**
Generic Name:	**Methylphenidate MR capsule (HLD200)**
Dosage & Strength:	**Oral Capsule, strength = 20 mg, 40 mg, 60 mg, 80 mg and 100 mg**
Route of administration:	**Oral (dosed at evening/night)**
Indication:	**Treatment for ADHD**
Applicant:	**Ironshore Pharmaceuticals and Development, Inc.**
Submission:	**Original NDA [505(b)(2)]**
Division:	**DCP1**
Reviewers:	**Praveen Balimane, Ph.D. and Xiaofeng Wang, Ph.D.**
Team Leader:	**Hao Zhu, Ph.D. and Kevin Krudys, Ph.D.**

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EXECUTIVE SUMMARY

Ironshore Pharmaceuticals & Development, Inc. (Ironshore) has submitted a New Drug Application (NDA) for Methylphenidate Hydrochloride (MPH) Modified Release Capsules (HLD200) for the indication of treatment of Attention Deficit Hyperactivity Disorder (ADHD). HLD200 is an evening-dosed, delayed-release and extended-release formulation of methylphenidate hydrochloride, for which Ritalin® serves as the listed drug. Within the HLD200 capsules, methylphenidate is incorporated into a delayed release (DR) and extended release (ER) coated core that allows for release of methylphenidate in plasma at a controlled rate following an initial delay of approximately 6 to 8 hours. This DR/ER profile is designed to allow for once-daily dosing during the evening (just prior to sleep) with HLD200, leading to control of symptoms and improved functioning in ADHD patients on the next day. Ironshore is requesting approval for the following strengths of capsule: 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. HLD200 is intended for once-daily oral administration in the evening for patients 6 years of age and older with ADHD.

The clinical program for this application is supported by the following clinical pharmacology, and efficacy and safety trials:

- Relative bioavailability trial (HLD200-110)
- Food-effect trial (HLD200-109)
- Dose-proportionality trial (HLD200-104)
- Pediatric pharmacokinetic trial (HLD200-102)
- Clinical efficacy and safety trial (HLD200-107), 20-100 mg in 6-12 year ADHD patients
- Clinical efficacy and safety trial (HLD200-108), 40-80 mg in 6-12 year ADHD patients

In addition, the sponsor had conducted several other clinical trials with a preliminary formulation which was different from the final to-be-marketed formulation and thus the following clinical trials were not reviewed:

- HLD200-101 (relative BA trial)
- HLD200-103 (food effect trial)
- HLD200-106 (preliminary safety and efficacy trial)

Our findings are summarized as follows:

- An adequate pharmacokinetic link has been established between the HLD200 product and Ritalin, the listed product, through a relative bioavailability trial.
- The pharmacokinetic profile of methylphenidate following the administration of HLD200 is consistent with the expectation for an extended release formulation and is sufficient to support a once daily dosing regimen.
- The shape of the pharmacokinetic profile is similar in all age groups; children 6-12 years of age, adolescents, and adults. Therefore, the pharmacodynamic profile

for effectiveness is also expected to be similar in children 6-12 years of age, adolescents, and adults with ADHD.

- Though exposure to methylphenidate is less in adolescents and adults compared to children after the same dose (in mg) administration of HLD200, optimal clinical response can be achieved by titration. The recommended therapeutic daily dose and timing for dosing should be individualized according to patient's needs, clinical response, and tolerability.
- There was no apparent sign of early release of drug (i.e., concentrations were below 1 ng/mL up to 8 hours post-dosing with $AUC_{0\text{-}10h}$ of less than 5% of total AUC) observed in around 50 subjects from 3 different clinical pharmacology trials (# 104, # 109 and # 110). Similarly, at the mean level, the residual drug exposure at sleep time with the HLD200 product were similar or lower than the residual drug levels at sleep time with previously approved products (e.g., Concerta, Aptensio XR, Quillivant XR, Quillichew ER etc.). However, there were clearly increased incidence of insomnia related AE's with the current product compared to previously approved methylphenidate products. The medical team will assess in greater detail the reasons for this unfavorable AE profile and the ultimate benefit-risk ratio of this product for the target populations.
- At the mean level, the exposure (i.e., Cmax and AUC) observed at the highest dose of 100 mg of HLD200 product were generally lower or similar to the exposures obtained at the highest approved dose of marketed methylphenidate products (e.g., Quillivant XR, Aptensio XR, Concerta etc.)
- HLD200 can be administered with or without food. To ensure consistent clinical responses, advise patients to take HLD200 consistently with food or consistently without food.
- The PK parameters exhibited low intra subject variability (i.e., %CV was 20% based on Cmax and 13% based on AUC) and acceptable inter subject variability (i.e., %CV was 35% based on Cmax and 30% based on AUC).
- Patients should avoid alcohol while taking HLD200.
- In vitro dissolution studies demonstrated that less than 5% of the drug was released for up to 4 hours at pH 6 and up to 2 hours in pH 7.2. Thus, the potential for drug interaction with concomitant medicines which can modulate the gastric pH (for e.g., PPI's) is low.
- No direct study (e.g., gamma scintigraphy study) was performed with the product to assess the effect of bowel movement (e.g., diarrhea, constipation or concomitant administration of drugs that can impact gut-motility) on drug release.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has determined that clinical pharmacology and biopharmaceutics information provided in the NDA is acceptable.

1.2 Post-Marketing Studies

Comment: When this product gets approved in patients 6 years and above, additional clinical pharmacokinetic trial will be requested in younger patients 4 to 5 years of age as a PMR. The shape of pharmacokinetic profile and exposures at the time points of interest (e.g., Tmax and around dinner and bed time) in combination with safety and tolerability information should be assessed in pediatric patients 4-5 years of age. The sponsor may use sparse sampling. The shape of the pharmacokinetic profile may be used to support the extrapolation of the effectiveness findings from patients 6 years and above into patients 4 to 5 years of age. The exposures at the time points of interest can be used to assess the potential safety risk for insomnia and lack of appetite. All patients enrolled in the safety, tolerability, and pharmacokinetic trial should be given the option to be rolled into the long-term safety trial in patients 4-5 years of age.

2 Question Based Review

2.1 Are the formulations used in the key clinical pharmacology trials and clinical efficacy trials the same as the planned "to-be-marketed" formulation?

Yes, all the key clinical pharmacology trials (e.g., Relative bioavailability trial, HLD200-110; Food-effect trial HLD200-109; Dose-proportionality trial HLD200-104) as well as the two pivotal efficacy trials (HLD200-107 and HLD200-108) were all conducted using the same formulation as the planned "to be marketed" formulation. Additionally, though the formulation used in the pediatric pharmacokinetic trial (HLD200-102) was not exactly identical to the "to be marketed" formulation, the minor difference in one of the excipient was determined to be within the SUPAC guidance limits and the formulations also had similar *in vitro* release/dissolution profile. Thus, it was also determined to be acceptable as the "to be marketed" formulation.

2.2 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Methylphenidate is a central nervous system stimulant which has been approved to treat ADHD. Ironshore has developed HLD200 capsules, a novel drug release formulation for methylphenidate. It incorporates both a delayed release (DR) and an extended release (ER) coated core that allows for release of methylphenidate in plasma at a controlled rate following an initial delay of approximately 6 to 8 hours. This DR/ER profile is designed to allow for once-daily dosing during the evening with HLD200, leading to control of symptoms and improved functioning in ADHD patients next day.

2.3 What is the proposed dosage form and route of administration?

The proposed dosage form of the to-be-marketed formulation is Methylphenidate Modified Release (MR) capsule (20 mg, 40 mg, 60 mg, 80 mg and 100 mg) and it is to be administered orally in the evening just prior to sleeping.

2.4 What methylphenidate MR products indicated for the same indication are already approved in the US?

Other previously approved methylphenidate extended-release products indicated for the treatment of ADHD are Aptensio ®, Concerta ®, Ritlain LA ®, Ritlan SR ®, Focalin XR ®, Metadate CD ®, Quillichew®, Contempla XR-ODT ®, and Quillivant ®.

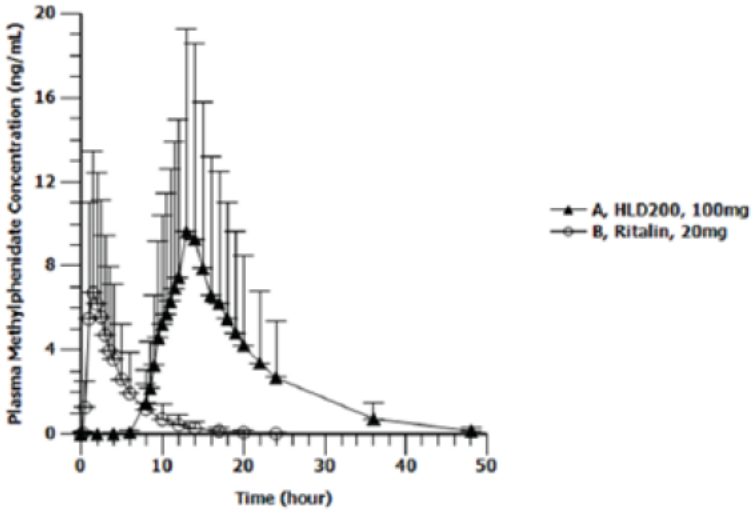
2.5 What are the details of the delayed release (DR) and extended release (ER) formulation of the HLD200 product?

HLD 200 Capsules are composed of [redacted] (b) (4) capsule filled with methylphenidate hydrochloride delayed release/extended release (DR/ER) coated cores. [redacted] (b) (4) are manufactured by [redacted] (b) (4) [redacted] Additional details are provided in the CMC review.

2.6 What are the key pharmacokinetic features of the Methylphenidate MR capsule (HLD200) product?

The mean plasma MPH concentration-time profiles after administration of a single, oral, 100 mg dose of HLD200 or a single, oral, 20 mg dose of Ritalin in a crossover manner to healthy adult subjects was studied in a relative BA study HLD200-110. The mean MPH concentration-time profiles are shown in Figure 1. Due to the delayed release nature of the novel formulation, the MPH concentrations rise very slowly with a delay of approximately 6 to 8 hours. Time to reach maximal observed mean plasma concentration was 13 hours following HLD200. The T1/2 was determined to be around 6 hours.

Figure 1: Methylphenidate concentration-time profile following a single oral dose of HLD200 or Ritalin.



2.7 Can the HLD200 product be taken with or without food?

Yes. HLD200 can be taken with or without food. To ensure consistent clinical outcomes, patients should be advised to take HLD200 with food consistently or without food consistently. In addition, HLD can be taken as a whole capsule or the contents of the capsule can be sprinkled on apple sauce.

The effect of food intake at night time (dinner) on the PK of 100 mg of HLD200, methylphenidate HCl modified release capsules in healthy adult volunteers was studied in a 3-way cross-over study conducted under fasted, fed and sprinkled state(on apple sauce) at night time.

For food effect at night time (dinner), mean Cmax after the high-fat meal was 14% lower than after the fasted dose, and median Tmax after the high-fat meal was 2.5 hours longer than after the fasted dose (Table 1). Visual inspection shows a change in pharmacokinetic profile (delayed Tmax) of methylphenidate when HLD200 is given with high fat meal (Figure 2). Since there is a strong pharmacokinetic-pharmacodynamic relationship, patients should be advised to take HLD200 with food consistently or without food consistently in order to ensure consistent clinical response. Additionally, mean AUC, Cmax, and median Tmax after the sprinkled dose (on apple sauce) were similar to those after taking HLD200 as a whole capsule under fasted condition. In addition, the mean pharmacokinetic profiles are similar between sprinkled dose (on apple sauce) versus whole capsule under fasted condition.

Figure 2: MPH Plasma Concentration after 100 mg HLD200 in Fed, Sprinkled on Food and Fasted State.

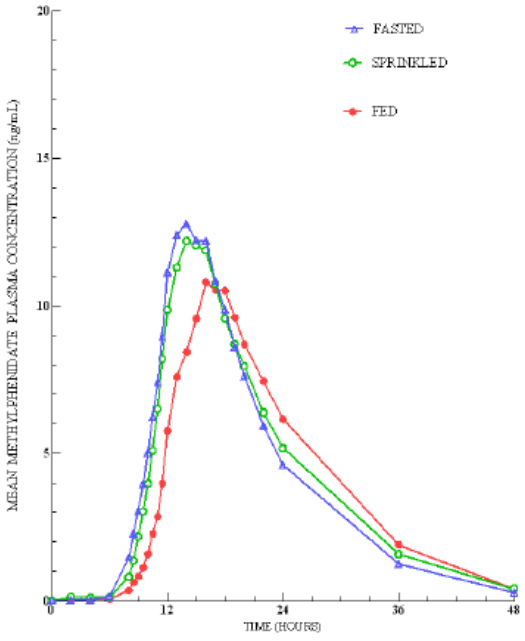


Table 1: MPH Pharmacokinetic Parameters after 100 mg HLD200 in Fed, Sprinkled, and Fasted State.

Parameter	HLD200 100 mg Treatment Group		
	A (Fed) N = 18	B (Sprinkled) N = 18	C (Fasted) N = 18
C_{max} (ng/mL), mean (CV%)	12.21 (41.3)	13.71 (39.5)	14.17 (46.5)
T_{max} (hours), median (range)	16.50 (13.00-20.00)	14.00 (11.50-20.02)	14.00 (11.50–18.05)
$T_{1/2}$ (hours), mean (CV%)	5.94 (23.5)	6.25 (27.2)	5.90 (41.6)
λ_z (1/hour), mean (CV%)	0.1216 (19.1)	0.1187 (27.0)	0.1307 (28.8)
AUC_{0-t} (ng•hr/mL), mean (CV%)	174.8 (41.9)	182.5 (39.6)	179.8 (44.7)
$AUC_{0-\infty}$ (ng•hr/mL), mean (CV%)	178.7 (43.4)	187.4 (40.0)	183.0 (44.3)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time; AUC_{0-t} = area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration; C_{max} = peak observed plasma concentration; CV = coefficient of variation; λ_z = terminal phase rate constant; $T_{1/2}$ = terminal phase half-life; T_{max} = time to teak observed plasma concentration.

Additionally, an alternate trial assessed the effect of food intake at morning time (breakfast) on the PK of 100 mg of HLD200. The 2 treatment arms compared the PK after a “low fat breakfast” vs. “medium fat breakfast”. There was negligible change in Cmax, AUC and Tmax due to the type of morning time breakfast.

In summary, the PK data indicate that HLD200 capsules can be administered with food consistently or without food consistently, and that the contents of the capsules may be sprinkled on apple sauce.

2.8 Was dosage strength proportionality demonstrated for the HLD200 product?

Yes. Strength proportionality was assessed in a cross-over clinical trial conducted at 20 mg and 100 mg strength levels of HLD200 in healthy adult subjects. The mean PK parameters (Table 2) and the concentration time curves (normalized for dose) (Figure 3) are similar between the 20 mg and 100 mg strength levels demonstrating strength proportionality across the proposed strength range.

Figure 3: MPH Plasma Concentration after 20 and 100 mg HLD200

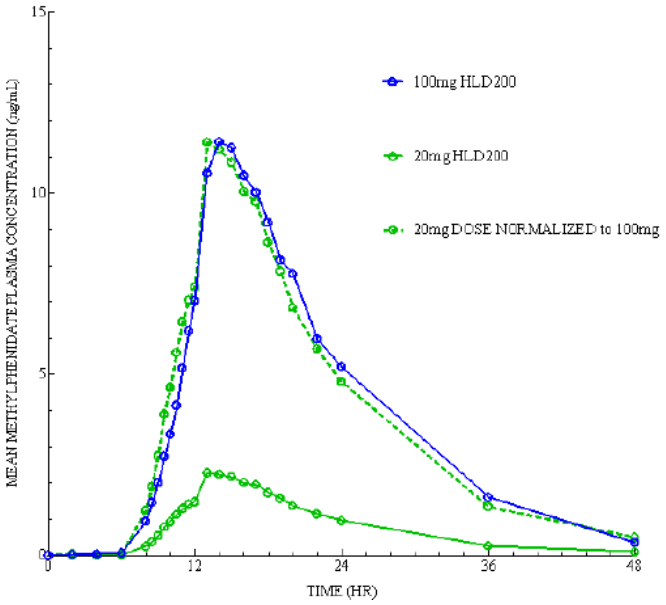


Table 2: MPH Pharmacokinetic Parameters after 20 and 100 mg HLD200.

Parameter	HLD200 Treatment Group A N = 20	B N = 20
C_{max} (ng/mL), mean (CV%)	12.31 (36.5)	2.56 (34.4)
T_{max} (hours), median (range)	14.00 (13.00–20.00)	14.00 (13.00–19.00)
$T_{1/2}$ (hours), mean (CV%)	6.40 (34.5)	6.51 (32.3)
λ_z (1/hour), mean (CV%)	0.1192 (29.3)	0.1166 (29.4)
AUC_{0-t} (ng•hr/mL), mean (CV%)	171.4 (33.0)	33.4 (38.9)
$AUC_{0-\infty}$ (ng•hr/mL), mean (CV%)	176.7 (34.0)	34.7 (40.5)

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast;
B = 20 mg followed by a low to moderate-fat/high-calorie breakfast;

2.9 Was the efficacy of HLD200 product demonstrated in dedicated efficacy studies?

The efficacy results for HLD200 were supported by the following studies in the NDA submission (Table 3).

Table 3: Efficacy and Safety Studies submitted in the HLD200 NDA 209311

Study Number	Study Type	Formulation
Completed Studies - Efficacy		
HLD200-108	Pivotal efficacy and safety (naturalistic study design; no PK)	HLD200 (proposed to-be-marketed formulation)
HLD200-107	Pivotal efficacy and safety (classroom design; no PK)	HLD200 (proposed to-be-marketed formulation)
HLD200-106	Supportive efficacy and safety (classroom design; no PK); contributed to the study designs of HLD200-107 and HLD200-108	B-HLD200 (b) (4) (b) (4) formulation)

The two pivotal efficacy studies, 108 and 107 were performed using the to-be-marketed formulation. Study 106 used a preliminary formulation.

Study HLD200-108 was a pivotal phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study that evaluated the safety and efficacy of evening-dosed HLD200 (40 mg- 80 mg) on post-waking, early morning function in children aged 6 through 12 years with ADHD. The study was conducted in the U.S. A total of 163 subjects were enrolled in the study; 82 were randomized to receive HLD200 and 81 were randomized to receive placebo. Blinded study drug was taken for 3 weeks (through study day 22), and weekly study assessments were conducted. The primary endpoint was improvements in ADHD symptoms throughout the day and was assessed using the ADHD-RS-IV. Key secondary endpoints were improvements in ADHD symptoms and function during the post-waking, early morning routine (6:00 am to 9:00 am) using the clinician-rated BSFQ assessment (b) (4) The study met its primary end-point by showing a statistically significant improvement in the ADHD-RS-IV total score at week 3 in the HLD treated group compared to the placebo group (p of 0.002).

Study HLD200-107 was a pivotal phase 3, multicenter, open-label, treatment-optimized, double-blind, randomized, placebo-controlled, forced-withdrawal, parallel-group study that evaluated the safety and efficacy of evening doses of HLD200 (20 mg- 100 mg)in children aged 6 through 12 years with ADHD in a laboratory classroom setting. The

study was conducted in the U.S. A total of 161 subjects were enrolled in the study and titrated to an effective dose of HLD200 over a 6-week period; at Visit 8 (43 days), 155 were randomized to receive either HLD200 (83 subjects) or placebo (72 subjects). Following randomization, blinded study drug was taken for 1 week, with a classroom assessment conducted at Visit 9 (50 days). The primary endpoint was the model-adjusted average of all post-dose SKAMP CS from 8:00 am to 8:00 pm measured on the laboratory classroom day (Visit 9). The key secondary endpoint was the PREMB-R AM, a parent-completed daily questionnaire intended to evaluate the child's functioning during the early morning period. (b) (4) ; the SKAMP CS by time point (symptoms); and SKAMP subscale analyses. The study met its primary end-point by showing a statistically significant improvement in the SKAMP CS during the 12-hour period from 8:00 am to 8:00 pm measured on the laboratory classroom day in the HLD treated group compared to the placebo group (p of 0.010).

The details of the clinical efficacy and safety are covered in the medical review.

2.10 Was there any evidence of any early release of drug from this product in the pharmacokinetic clinical trials conducted by the sponsor?

No apparent pattern of early release of methylphenidate for HLD200 was identified in the pharmacokinetic clinical trials. HLD200 is intended to be a delayed release (DR) and extended release (XR) product designed to allow for a delay of approximately 6-8 hours prior to the gradual rise of concentrations in the plasma. Since the product is administered at night time (just prior to sleeping), it is important to assess the extent of early release of drug (post-dosing) to ensure that drug concentrations do not rise sharply interfering with the process of sleeping. The early release concentrations of methylphenidate were assessed using data from all relevant clinical pharmacokinetic trials which used the final "to be marketed" formulation and incorporated early sampling times (i.e., 0-8 hrs). Data from approximately 50 subjects in clinical trials: 104, 109 and 110 were normalized to the highest dose of 100 mg and used for assessing the early release concentrations. Table 4 demonstrates that mean drug concentrations were very low with levels rising only up to 1% of the Cmax levels at 6 hours post-dosing (and less than 10% of Cmax even up to 8 hours post-dosing). Therefore, such low concentrations up to 6-8 hours post-dosing (in the night) are unlikely to interfere with sleep.

Table 4: Mean and Standard Deviation of Methylphenidate Concentration Pre-Dose, 2, 4, 6, and 8 Hours after a Single Dose of HLD200 100 mg for Studies HLD200-104 (N=20), HLD200-109 (N=18), and HLD200-110 (N=11)

Time (hours)	Mean (ng/mL)	Standard Deviation (ng/mL)
0	0	0
2	0.04	0.12
4	0.04	0.07
6	0.11	0.16
8	1.13	1.25

Data Source: HLD200-104 PK Report Table 1, Table 2, and Table 18; HLD200-109 PK Report Table 1, Table 2, and Table 3; HLD200-110 Clinical Study Report Listing 16.2.6.1

2.11 What are the anticipated residual concentrations at sleep time for the highest dose of HLD200 versus the highest approved doses of the RLD Ritalin-IR product? How do these residual drug concentrations compare to levels for other approved methylphenidate products such as Concerta, Quillivant XR, Aptensio XR etc.?

The comparison of the residual drug concentration at hours when the patients are likely to go to bed for HLD200 vs. Ritalin was performed. The analysis was performed using data from relevant clinical pharmacokinetic trials which used the "to be marketed" formulation and had adequate sampling times at the latter-end (i.e., 24 hrs). Data from all subjects in studies: 104, 109 and 110 were normalized to the highest dose of 100 mg of HLD200 and contrasted with the data for highest approved dose of 30 mg BID for Ritalin-IR. Since the HLD product is administered at night, the sleep time for it was 24 hr post-dosing. Since Ritalin is BID dosing with the 1st dose given in the morning , the sleep time for Ritalin-IR was 12 hr post 1st dose (with the 1st dose at 8 am and the 2nd dose at noon).The mean residual drug concentrations at sleep time are listed below:

HLD200 (100 mg) = 4.91 (±2.66) ng/mL

Ritalin (30 mg- BID) = 2.47 (±1.58) ng/mL

The comparison of mean exposure demonstrates that mean drug levels at sleep times are 2-times higher for 100 mg of HLD200 vs. the highest approved dose of Ritalin IR. Additionally, out of a total of 62 subjects with data for HLD200, around 10% of the subjects had concentrations above 10 ng/mL (which is more than 4- fold higher than Ritalin) and almost 50% of the subjects had concentrations above 5 ng/mL (which is 2-fold higher than Ritalin). These significantly higher sleep time exposures with the HLD200 product compared to sleep time exposures with Ritalin can be a potential concern due to methylphenidate's potential to interfere with sleep..

However, to get a true sense of the residual concentrations at sleep times, the concentrations with the HLD200 product were compared to the residual drug concentrations with other commercially approved methylphenidate products. Based on the published labels, the anticipated residual mean drug concentrations for other marketed methylphenidate products are listed in Table 5. Concerta, Quillivant XR, Aptensio XR, and Quillichew ER are all XR formulation that are dosed in the morning. Therefore, the residual drug concentration at sleep time will be concentrations at 12 hr post-dosing.

Table 5: Residual drug concentration at sleep time for approved methylphenidate products

Approved Product Name	Max. approved dose (mg)	Mean concentration at 12 hr post-dose
Concerta	72 mg	~ 9 ng/mL
Aptensio XR	60 mg	~9.4 ng/mL
Quillivant XR	60 mg	~ 5 ng/mL
Quillichew ER	60 mg	~ 6 ng/mL

Therefore, though the residual drug concentration (at sleep time) is higher for the HLD200 product compared to Ritalin, the absolute levels with HLD200 are similar (and even lower) compared to several other approved methylphenidate products such as Concerta, Quillivant XR, Aptensio XR and Quillichew ER. In addition to a single time assessment, if partialAUC (pAUC) from sleep time up to 6- 8 hr after sleep is assessed, the pAUC for HLD200 is again likely to be similar or lower than other approved methylphenidate products. However, these observations are for only for mean drug concentrations and it is always possible that individual subjects may have higher or lower concentrations comparted to these average values leading to a different efficacy and safety profile for an individual.

2.12 How does the exposure (i.e., Cmax and AUC) compare for the highest dose of 100 mg HLD200 vs. the highest approved dose of the RLD Ritalin-IR as well as other approved methylphenidate products?

In terms of drug-load per day, the highest dose level for HLD200 is 100 mg which is higher compared to the highest approved dose levels for both Ritalin IR (30 mg-BID,

which is 60 mg per day) and for Ritalin LA (60 mg per day). Therefore, a systematic assessment of exposure levels (i.e., Cmax and AUC) achieved for the highest dose of 100 mg HLD200 vs. the highest approved dose of 30 mg-BID of the RLD Ritalin-IR was performed. The table below clearly demonstrates that in spite of a higher drug-load per day, the Cmax with HLD200 is lower than the Cmax obtained with Ritalin. The AUC was ~25% higher with HLD200 compared to Ritalin, but that can be explained by the sustained exposure levels achieved with the XR formulation and the lack of a dip in exposure as is seen for the Ritalin IR.

Additionally, the exposure (i.e., both Cmax and AUCinf) obtained with the highest 100 mg dose level of HLD200 were determined to be generally lower than the exposure obtained with previously approved methylphenidate products (Table 6).

Table 6: Mean exposure (Cmax and AUCinf) data at the highest dose for HLD200 Product compared to approved methylphenidate products

Product Name	Highest Dose (mg)	Cmax (ng/mL)	AUC inf (ng.hr/mL)
HLD200 (Jornay)	100 mg (proposed)	10.46	122
Quillivant XR	60 mg	17	163
Aptensio XR	60 mg	17.6	193
Concerta	72 mg	14.8	167

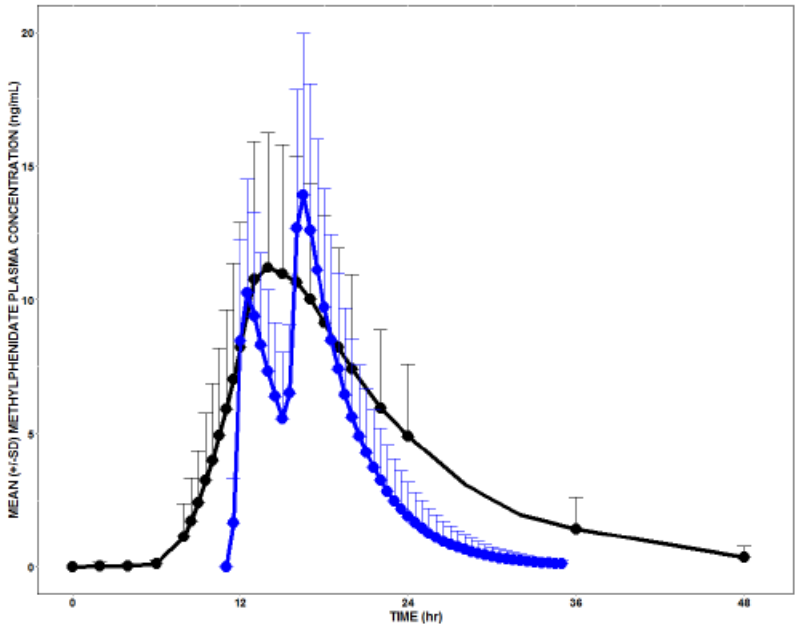
Table 7: Exposure levels of methylphenidate Observed with HLD200 (100 mg) compared with Simulated levels for Ritalin 30 mg BID (*dosed at 8 am and then noon)* in Study HLD200-110

	Ritalin 30 mg BID (N = 12)		HLD200 100 mg (N = 11)	
	C_{max} (ng/mL)	AUC_{0-t} (ng·hr/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng·hr/mL)
HLD200-110 (b) (6)	20.8	127	NA	NA
HLD200-110	12.2	82.2	4.61	71.6
HLD200-110	29.0	213	16.17	242
HLD200-110	10.4	74.8	7.38	74.4
HLD200-110	7.44	51.0	3.85	51.9
HLD200-110	9.14	56.9	6.15	64.5
HLD200-110	17.0	98.4	10.93	139
HLD200-110	18.1	119	13.94	174
HLD200-110	11.9	74.1	15.66	118
HLD200-110	9.37	66.8	3.39	73.7
HLD200-110	11.9	89.3	13.54	106
HLD200-110	13.3	84.8	19.46	208
Mean (±SD)	14.2(±6.10)	94.8(±43.7)	10.46(±5.64)[1]	120(±63.5)[1]

AUC = area under the curve; C = concentration; NA = not applicable; SD = standard deviation

[1]Data Source: HLD200-110 Clinical Study Report Table 14.2.2

Figure 4: Average Concentration Time Profile after a Single Dose of HLD200 100 mg for Studies HLD200-104 (N=20), HLD200-109 (N=18) and HLD200-110 (N=11) and Simulated Average Concentration Time Profile after Ritalin 30mg BID *(dosed at 8 am and then noon)* (N = 12)



Average concentration of HLD200 is represented by black lines and dots and the simulated average concentration of Ritalin is represented by blue lines and dots in Figure 4.

Note: Error bars in the figure represent the corresponding standard deviations. (Data Source: HLD200-104 PK Report Table 1, Table 2, and Table 18; HLD200-109 PK Report Table 1, Table 2, and Table 3; Study HLD200-110 Clinical Study Report Listing 16.2.6.1)

2.13 What is the sponsor's dosing recommendations for the to-be-marketed formulation?

The sponsor has proposed the following dosing recommendations for the to-be-marketed formulation:

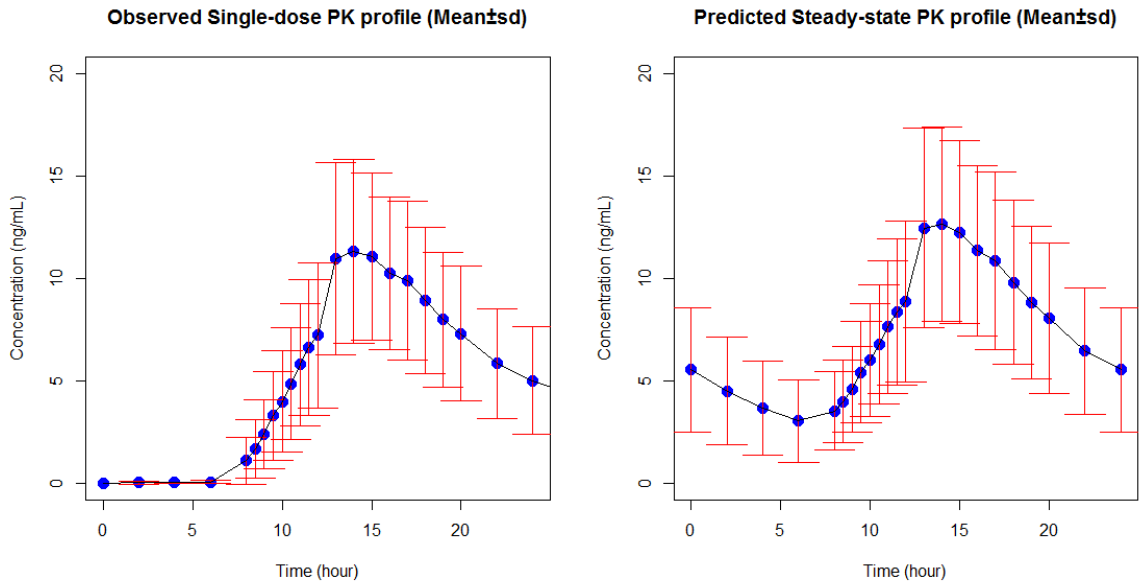
- Recommended starting dose for patients 6 years and above: 20 mg daily in the evening with or without food.
- Dosage may be increased weekly in increments of 20 mg per day. Daily dosage above 100 mg is not recommended.
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce.

2.14 What are the pharmacokinetic characteristics of the product at steady-state following multiple-dosing?

No dedicated multiple-dose PK data was conducted for the HLD200 product. To evaluate the steady-state methylphenidate exposures following multiple doses of HLD200, nonparametric superposition using single-dose PK data form study HLD200-104, which is a phase I, single-dose, open-label, crossover study in healthy adult volunteers, was conducted. The observed Cmax and Cmin (dose-normalized to 100 mg) after a single dose in study HLD200-104 are 11.3 ng/mL and 5.0 ng/mL, respectively. The predicted steady-state Cmax and Cmin (dose-normalized to 100 mg QD) following multiple doses

using superposition approach are 12.7 ng/mL and 5.5 ng/mL, respectively. The results are graphically presented in Figure 5. The accumulation ratio based on the nonparametric superposition analysis is 1.1 for both Cmax and Cmin, indicating minimal accumulation of methylphenidate following QD doses of HLD200. Such result is consistent with expectation based on the 6 hours half-life of HLD200.

Figure 5: Single-dose PK profile (Observed) versus Steady-state PK profile (Predicted)



Note: both single-dose and steady-state PK profiles are dose-normalized concentrations at 100 mg HLD200 level.

2.15 What are the pharmacokinetic characteristics of the product in children and adolescents?

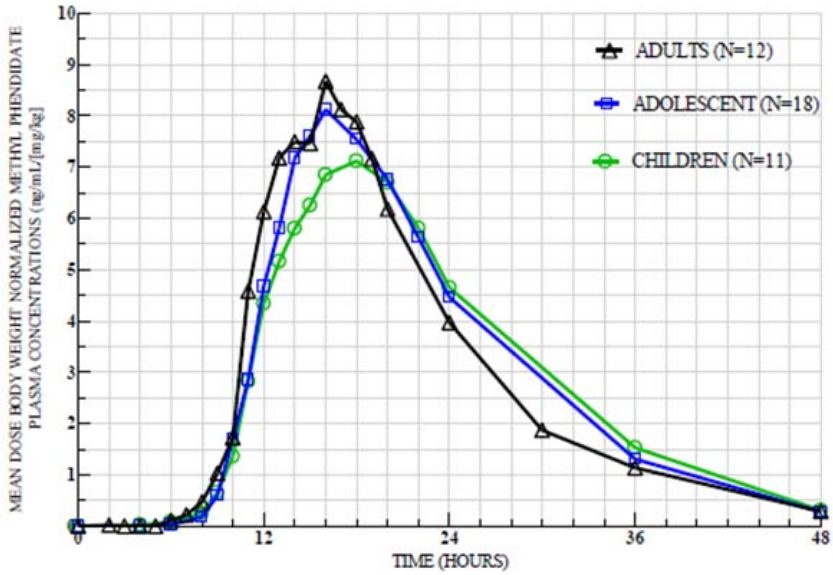
Based on dedicated pharmacokinetic study, the mean PK data i.e., both the shape of the PK profile as well as the PK parameters were determined to be similar across all age groups (children, adolescents and adults) after normalizing for body-weight (Figure 6).

HLD200-102 was an open label, single dose PK study in children (6-12 years) and adolescents (13-17 years) with ADHD. The comparison of mean PK data (normalized for body weight and dose) demonstrated that PK characteristics were similar across children, adolescents and adults.

A detailed visual assessment of the PK data for all the individual subjects (children and adolescents) clearly demonstrated that the PK profiles in pediatric subjects was similar in shape to the profile seen in adults. All the pediatric subjects demonstrated a delayed

release of the drug with plasma exposures beginning to rise only at 6-8 hours similar to what was observed in adults. Similarly, the Tmax observed in pediatric subjects (16.3 hour in adolescents and 18.2 hour in children) was in line with the Tmax of around 16 hour observed in adults.

Figure 6: Mean body weight dose normalized methylphenidate plasma concentrations (ng/mL) for Children, Adolescents and Adults.



2.16 Can the efficacy observed in pediatric patients (6-12 years) be extrapolated to adolescents and adults?

Yes. Two pivotal efficacy studies, 108 and 107, established the efficacy of the product in children 6-12 years in age with ADHD. Based on dedicated pharmacokinetic study, the mean PK data i.e., both the shape of the PK profile as well as the PK parameters were determined to be similar across all age groups (children, adolescents and adults) after normalizing for body-weight. It is also anticipated that similar mean pharmacodynamics profiles will be observed in adolescents and adults if exposures are matched to the exposure level in children (6-12 years). Additionally, as a common clinical practice, doses in all patient groups (including adolescents and adults) will be titrated based on individual clinical response. Thus, even if the exposure to methylphenidate is less in adolescents and adults compared to children after the same dose (in mg) of HLD200 is administered; optimal clinical response can be achieved by titration. Hence, the combination of all the aspects: similarity in PK across age groups, clinical practice of dose-escalation based on individual response, and prior precedence of extrapolation across age with other approved methylphenidate products (e.g., Quillivant XR, Ritalin

LA) support the extrapolation of the indication from pediatric patients to adolescents and adults for the HLD200 product.

2.17 Is this product likely to have drug interactions with gastric pH modulators (e.g., PPI's)?

A dedicated clinical study assessing the effect of PPI's on the PK of this product was not performed. However, in vitro dissolution studies demonstrated that that less than 5% of the drug was released for up to 4 hours at pH 6 and up to 2 hours in pH 7.2. Thus, the likelihood of drug interaction with concomitant medicines which can modulate the gastric pH (for e.g., PPI's) is unlikely.

2.18 Is the absorption of this product likely to be impacted due to diarrhea, constipation or concomitant administration of drugs that impact gut motility?

No direct gamma scintigraphy studies were performed with the product to assess the effect of bowl movement (e.g., diarrhea, constipation or concomitant administration) on drug release or the pharmacokinetics of the product. With a complex formulation (delayed release as well as an extended release) (b) (4) it is hard to predict the effect of changes in bowel movement on the absorption and PK of methylphenidate from the product.

3 Analytical Methods

3.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes.
The active moiety, methylphenidate, was appropriately measured in biological fluids. The PK analysis and results were presented for the total methylphenidate level (i.e., D+L form) which is consistent with the guidance and is acceptable.

3.2 Are bioanalytical methods used to assess concentrations of methylphenidate acceptable?

Yes.
A liquid chromatography/tandem mass spectroscopy (LC-MS/MS) method was used for the detection of methylphenidate in human plasma at a range of 20 pg/mL to 100,000 pg/mL. Two separate methods: High range 100 pg/mL to 100000 pg/mL and Low range 20 pg/mL to 20,000 pg/mL were developed and validated. Thus, a fully validated bioanalytical methodology was used for sample analysis and it was acceptable.

Table 8: Bioanalytical Method: High range and Low range

HIGH RANGE Methylphenidate 100.00 to 100000.00 pg/mL	
Parameter	**Result**
Method Summary/Description:	Supported liquid-liquid extraction: In a 96-well plate, each 80 µL aliquot of plasma standard and QC sample was mixed with 100 µL of internal standard working solution). After vortexing, 200 µL of 0.2 M sodium carbonate solution was added. Following further vortexing, the sample and buffer mixture was transferred to a Cleanert SLE 96-well extraction plate (400 mg) and 800 µL methyl tert-butyl ether was added followed by a further 600 µL of methyl tert-butyl ether. The organic solvent was evaporated to dryness and the dry residue was reconstituted with 500 µL of reconstitution solution. Following vortexing, a 3 µL aliquot was then injected onto an LC-MS/MS system for analysis.
Method Name:	V1: Determination of Methylphenidate in Human Sodium Fluoride/ Potassium Oxalate Plasma (100 - 100,000 pg/mL) by LC-MS/MS (b) (4) 2012.1.00 Draft).
Analyte:	Methylphenidate
Internal Standard:	Methylphenidate-d_9
Matrix:	Human sodium fluoride/potassium oxalate plasma
Limits of Quantitation:	LLOQ 100.00 pg/mL to ULOQ 100000.00 pg/mL
Average Recovery of Analyte Average Recovery of Internal Standard:	70.8% 76.2%
Standard Curve Concentrations:	100.00, 200.00, 1000.00, 2000.00, 5000.00, 10000.00, 20000.00, 60000.00, 90000.00 and 100000.00 pg/mL
LLOQ Concentration:	100.00 pg/mL
LLOQ QC Intra-batch precision (%CV)	6.1%
LLOQ QC Inter-batch precision (%CV)	7.1%
LLOQ QC Intra-batch accuracy (%bias)	-7.7%
LLOQ QC Inter-batch accuracy (%bias)	-0.4%
QC Intra-Run Precision (%CV):	Low, medium, high, upper = 0.6% to 2.0%
QC Intra-Run Accuracy (%Bias):	Low, medium, high, upper = 0.1% to 4.7%
QC Inter-Run Precision (%CV):	Low, medium, high = 1.7% to 4.3%
QC Inter-Run Accuracy (%Bias):	Low, medium, high = 0.5% to 3.0%
Bench Top Stability in Human Plasma:	24 hours at 4°C
Stock, IS Stock, Working Solution Stability:	67 hours at room temperature
Freeze-Thaw Stability:	3 cycles (-20°C/room temperature) and (-20°C/4°C) 3 cycles (-70°C/room temperature) and (-70°C/4°C)
Frozen Storage Stability in Human Plasma:	16 days at -20°C 16 days at -70°C
Specificity for OTC Interference (%Bias):	2.1% to 10.8% Selectivity shows no significant interference in blank plasma samples.

Parameter	Result
Dilution Integrity:	200000.00 pg/mL diluted 10-fold
Matrix Effect:	6 lots of plasma at low and high levels: Accuracy 95.8% to 110.0%
Matrix Factor Analyte, (CV%):	Low concentration: 2.08% High concentration: 2.04%
Matrix Factor, IS (CV%):	Low concentration: 1.87% High concentration: 2.71%
Matrix Factor, IS-normalized (CV%):	Low concentration: 0.99% High concentration: 0.97%
Reinjection Reproducibility:	42 hours at room temperature 120 hours at 4°C
Post-Preparative Processed Sample Stability:	49 hours at room temperature 120 hours at 4°C
Whole Blood Stability:	2 hours in an ice-water bath
Method Robustness (%CV):	LLOQ = 5.6% Low, medium, high = 1.6% to 8.3%

Parameter	Result
Method Name:	V2: Methylphenidate in Human Plasma, (b) (4) 2012.1.00 (Abbreviated as: *Meth* HP 2012.1.00)
Calibration Range:	100.00 to 100000.00 pg/mL
Stock, IS Stock and Working Solution Stability:	46 days at -20°C
Frozen Storage Stability in Human Plasma:	244 days at -20°C 244 days at -70°C

LOW RANGE Methylphenidate 20.00 to 20000.00 pg/mL

Parameter	Result
Method Summary/Description:	Supported liquid-liquid extraction: In a 96-well plate, each 100 µL aliquot of plasma standard and QC sample was mixed with 100 µL of internal standard working solution. After vortexing, 200 µL of 0.2 M sodium carbonate solution was added. Following further vortexing, the sample and buffer mixture was transferred to a Cleanert SLE 96-well extraction plate (400 mg) and 800 µL methyl tert-butyl ether was added followed by a further 800 µL of methyl tert-butyl ether. The organic solvent was evaporated to dryness and the dry residue was reconstituted with 200 µL of reconstitution solution. Following vortexing, a 10 µL aliquot was then injected onto an LC-MS/MS system for analysis.
Method Name:	V3: Determination of Methylphenidate in Human Sodium Fluoride/ Potassium Oxalate Plasma (20 - 20,000 pg/mL) by LC-MS/MS (b) (4) _2015.1.00 Draft).
Analyte:	Methylphenidate
Internal Standard:	Methylphenidate-d_9
Matrix:	Human sodium fluoride/potassium oxalate plasma
Limits of Quantitation:	LLOQ 20.00 pg/mL to ULOQ 20000.00 pg/mL
Average Recovery of Analyte Average Recovery of Internal Standard:	80.8% 84.3%
Standard Curve Concentrations:	20.00, 40.00, 500.00, 1000.00, 2000.00, 3200.00, 4000.00, 12000.00, 18000.00 and 20000.00 pg/mL
LLOQ Concentration:	20.00 pg/mL
LLOQ QC Intra-batch precision (%CV)	1.8%
LLOQ QC Inter-batch precision (%CV)	5.6%
LLOQ QC Intra-batch accuracy (%Bias)	4.1%
LLOQ QC Inter-batch accuracy (%Bias)	1.7%
QC Intra-Run Precision (%CV):	Low, medium, high, upper = 0.8% to 2.2%
QC Intra-Run Accuracy (%Bias):	Low, medium, high, upper = -2.0% to 5.1%
QC Inter-Run Precision (%CV):	Low, medium, high = 1.0% to 4.1%
QC Inter-Run Accuracy (%Bias):	Low, medium, high = -0.8% to 3.0%
Bench Top Stability in Human Plasma:	47 hours at 4°C
Stock Solution Stability:	67 hours at room temperature 46 days at -20°C
IS Stock, Working Solution Stability:	22 hours at room temperature
Freeze-Thaw Stability:	3 cycles (-20°C/4°C) 3 cycles (-70°C/4°C)
Frozen Storage Stability in Human Plasma:	4 days at -20°C 4 days at -70°C

Parameter (continued)	Result (continued)
Specificity for OTC Interference (%Bias):	-1.5% to 7.6% Selectivity shows no significant interference in blank plasma samples.
Dilution Integrity:	40000.00 pg/mL diluted 10-fold
Matrix Effect:	6 lots of plasma at low and high levels: Accuracy 96.7% to 108.2%
Matrix Factor, Analyte (CV%):	Low concentration: 1.90% High concentration: 1.96%
Matrix Factor, IS (CV%):	Low concentration: 1.90% High concentration: 1.96%
Matrix Factor, IS-normalized (CV%):	Low concentration: 2.00 High concentration: 2.02%
Reinjection Reproducibility:	59 hours at room temperature 83 hours at 4°C
Post-Preparative Processed Sample Stability:	119 hours at room temperature 119 hours at 4°C
Whole Blood Stability:	2 hours in an ice-water bath
Method Robustness (%CV):	LLOQ = 5.3% Low, medium, high = 0.9% to 4.0%

Parameter	Result
Method Name:	V4: Methylphenidate in Human Plasma, (b) (4) 2015.1.00 (Abbreviated as: *Meth* HP 2015.1.00)
Calibration Range:	20.00 to 20000.00 pg/mL
Stock and Working Solution Stability:	230 days at -20°C
Frozen Storage Stability in Human Plasma:	231 days at -20°C did not meet SOP acceptance criteria 231 days at -70°C

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report # HLD200-110 **Study Period:** 06-July-2016 to 30-July-2016

NDA 209311

Title	A Phase I, Single Center, Single-Dose, Open-Label, Randomized, Crossover, Comparative Bioavailability Study of HLD200, Methylphenidate HCl Delayed and Extended Release Capsules, to an Immediate Release Methylphenidate HCl Marketed Formulation in Healthy Adult Volunteers
Objectives :	**Primary:** The primary objective was to compare the bioavailability of HLD200 (100 mg) to immediate release Ritalin® (20 mg). **Secondary:** The secondary objectives were to determine safety and tolerability in healthy adult volunteers.

Study Design:

This study was a Phase I, single-center, single-dose, open-label, randomized, crossover, comparative bioavailability study of HLD200 and Ritalin® in healthy adult volunteers. A total of 12 subjects were randomly assigned to 2 treatment sequence cohorts of 6 subjects each in crossover fashion (table below).

Treatment Sequence	Period 1	Period 2
1 AB	A	B
2 BA	B	A

Treatment A is HLD200, 100 mg and Treatment B is reference Ritalin®, 20 mg.

There was approximately 7 days washout period between periods. The Screening Phase was conducted within -28 to -2 days of admission to the Clinical Research Unit (CRU).

Subjects were admitted to the CRU the day before dosing (Day 0) for final qualification assessments. The subjects were domiciled in the CRU through discharge for a minimum of 24 to 48 hours following receipt of each treatment, depending upon treatment received.

Blood samples for pharmacokinetic (PK) analysis were obtained at the following time points:

- Following HLD200 dose: 2, 4, 6, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 36 and 48 hours post dosing (± 2 mins)
- Following Ritalin® dose: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 17, 20, and 24 hours post dosing (± 2 mins)

Safety was assessed by reports of adverse events (AEs), clinical laboratory parameters, vital signs, and electrocardiograms (ECGs), following each dose. Abnormalities identified by physical exam were reported as AEs.

HLD200 is dosed at 100 mg which is the highest to-be-marketed strength.

Duration of Treatment: Individual subject participation was ~40 days: screening (up to 28 days), 2 doses administered 7 days apart, and last visit at day 9 ± 1 day

Name of Sponsor Company: Ironshore Pharmaceuticals & Development, Inc.
Name of Test Product: HLD200 (Methylphenidate Hydrochloride)
Name of Active Ingredient: Methylphenidate hydrochloride (MPH)

Route of Administration	Oral
Sampling Times	PK sample collection times Blood samples for pharmacokinetic (PK) analysis were obtained at the following time points: - Following HLD200 dose: 2, 4, 6, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 36 and 48 hours post dosing (± 2 mins) - Following Ritalin® dose: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 17, 20, and 24 hours post dosing (± 2 mins)
PK and safety Parameters	**PK:** - C_{max}: maximum plasma drug concentration - C_{max} DN: dose-normalized C_{max} - T_{max}: time of maximum plasma drug concentration - AUC_{last}: area under the plasma concentration time curve from time zero to the last time point with measureable plasma concentration - AUC_{last} DN: dose-normalized AUC_{last} - AUC_{inf}: AUC from time zero to infinity - $\%AUC_{extrap}$: percent of AUC extrapolated to infinity - λz: apparent terminal elimination rate constant - $t_{½}$: apparent terminal half-life **Safety:** - AEs - Clinical laboratory tests - Vital signs - ECGs
PK Moieties	Methylphenidate (D+L)
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	**Sample Size:** No formal sample size calculations were performed. The sample size of 12 subjects follows the general design for relative bioavailability and is deemed sufficient to meet the primary and secondary objectives. **PK:** Descriptive statistics of the methylphenidate hydrochloride (MPH) plasma concentrations and PK parameters were reported for each treatment group. If 90% confidence intervals (CIs) for ln-transformed AUC_{last} and C_{max} for MPH were within 80.00 to 125.00, the treatments were determined to have comparable bioavailability. **Safety:** Summary statistics (number [n], mean, standard deviation [SD], minimum, median, and maximum) were reported for safety parameters. In addition, summary statistics were reported for change from baseline in clinical laboratory parameters and vital signs.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Methylphenidate (D+L)		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population

Number of Subjects: **Planned**: 12
Analyzed: 12

Diagnosis and Main Criteria for Inclusion: Healthy adult volunteers

All but 1 subject (sequence B-A) competed the study per protocol. Subject (b) (6) withdrew consent (work schedule changed) prior to Period 2, Treatment A. Treatment A. Therefore, there were finally N=11 for treatment A (HLD200) and N=12 for Treatment B (Ritalin).

Table 1: Demography of subjects in both treatment arms (Treatment A =HLD200 at 100 mg and Treatment B = Ritalin at 20 mg).

Variable	Treatment Sequence	
	A-B N=6	B-A N=6
Age (years)		
Mean (SD)	27.0 (5.66)	29.2 (7.94)
Min, Max	22, 36	20, 41
Sex, n (%)		
Female	4 (66.7%)	4 (66.7%)
Male	2 (33.3%)	2 (33.3%)
Race n (%)[a]		
White/Caucasian	5 (83.3%)	6 (100.0%)
Black or African American	1 (16.7%)	0 (0.0%)
Ethnicity, n (%)		
Not Hispanic or Latino	6 (100.0%)	6 (100.0%)
Weight (kg)		
Mean (SD)	82.80 (11.385)	69.55 (15.462)
Min, Max	69.5, 94.9	51.7, 95.2
BMI (kg/m^2)		
Mean (SD)	27.02 (3.587)	22.68 (3.252)
Min, Max	22.0, 31.7	18.5, 27.0

Treatment: A= HLD200, 100 mg, B= Ritalin, 20 mg

BMI = [weight (kg)] / [height (cm) × 0.01]^2

a. Subjects allowed to check multiple responses for race

Results

Pharmacokinetic Results

The mean plasma MPH concentration-time profiles after administration of a single, oral, 100 mg dose of HLD200 (n =11) or a single, oral, 20 mg dose of Ritalin (n=12) in a crossover manner to healthy subjects are shown in Figure 1. Time to reach maximal observed mean plasma concentration was 13 hours following HLD200 dosing and 1.5 hours following Ritalin® dosing. Detectable plasma MPH concentrations were reported for all 11 subjects through 48 hours post-dose following HLD200 dosing and in at least 10 of 12 subjects through 24 hours post-dose following Ritalin® dosing.

Figure 1: **Arithmetic Mean (+ SD, linear) Plasma MPH Concentrations following a Single Oral Dose of HLD200 or Ritalin®**

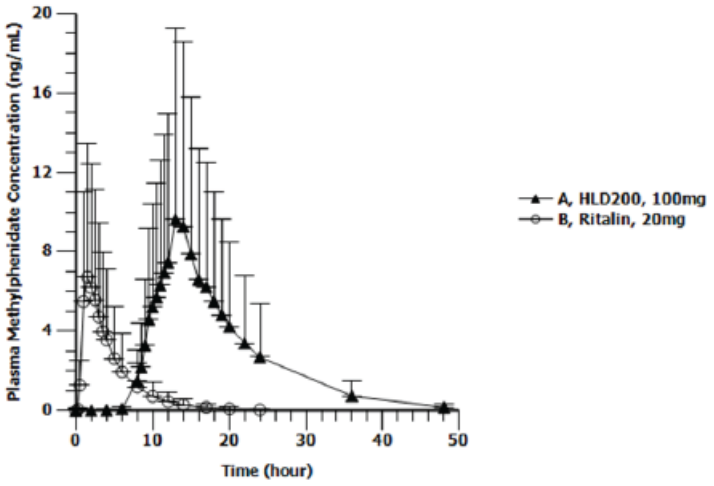


Table 2: Mean PK parameters in HLD200 (100 mg) vs. Ritalin (RLD; 20 mg)

Plasma MPH PK parameters following administration of a single, oral, 100 mg dose of HLD200 or a single, oral, 20 mg dose of Ritalin® in a crossover manner are summarized by treatment in the table below.

MPH PK Parameters by Treatment

PK Parameter	Treatment A HLD200, 100 mg N=11	Treatment B Ritalin, 20 mg N=12
C_{max} (ng/mL), mean (SD)	10.46 (5.64)	7.05 (2.84)
C_{max} DN [(ng/mL)/mg] [a], mean (SD)	0.105 (0.0564)	0.352 (0.142)
AUC_{last} (h·ng/mL), mean (SD)	120 (63.5)	32.3 (15.0)
AUC_{last} DN [(h·ng/mL)/mg] [b], mean (SD)	1.20 (0.635)	1.62 (0.748)
AUC_{inf} (h·ng/mL), mean (SD)	122 (63.8)	32.7 (15.2)
T_{max} (h), median (min, max)	14.00 (10.5 – 15.0)	1.50 (1.00 – 2.00)
$t_{1/2}$ (h), mean (SD)	6.02 (2.10)	3.79 (0.746)

Peak plasma MPH levels were attained within 10.5 to 15 hours after HLD200 dosing and within 1.00 to 2.00 hours after Ritalin® dosing. Higher mean (dose-normalized) C_{max} DN and AUC_{last} DN values were observed following a single oral dose of Ritalin® relative to a single oral dose of HLD200. The mean terminal half-life was approximately 2.2 hours longer following a single dose of HLD200 relative to a single dose of Ritalin®.

MPH AUC_{last} DN was lower following HLD200 dosing relative to Ritalin® dosing in 10 of the 11 subjects who completed both periods of the study; C_{max} DN was lower following HLD200 dosing relative to Ritalin® dosing in all 11 subjects who completed both periods of the study.

The estimate of MPH bioavailability from a single dose of HLD200, 100 mg, relative to a single dose of Ritalin®, 20 mg, based on dose-normalized AUC_{last} was 73.9%. Consistent with the formulation differences, HLD200 exhibited a longer T_{max} relative to immediate release Ritalin®.

Table 3: Analysis of relative bioavailability

Parameter	LS Geometric Means [a]		Geometric Mean Ratio (A:B)	90% CI for Ratio of LS Geometric Means	%CV [b]
	Treatment A HLD200, 100 mg N=11	Treatment B Ritalin®, 20 mg N=12			
AUC_{last} DN [(h·ng/mL)/mg]	1.107	1.498	0.739	0.635 – 0.860	19.6
C_{max} DN [(ng/mL)/mg]	0.093	0.329	0.282	0.219 – 0.363	33.6

LS = Least Squares

a LS means were estimated from the ANOVA model which included sequence, period, and treatment as fixed factors, and subject within sequence as a random factor.

b Estimated intra-subject coefficient of variation, CV%=100*Square root (e^{MSE}-1), where MSE is the mean square error term from the ANOVA.

All but 1 subject (sequence B-A) completed the study per protocol. Subject (b) (6) withdrew consent (work schedule changed) prior to Period 2, Treatment A. Therefore, there were finally N=11 for treatment A and N=12 for Treatment B.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

There were more AEs reported in subjects receiving a single oral dose of HLD200, 100 mg, than those receiving a single oral dose of Ritalin®, 20 mg.

No safety effects were observed related to clinical laboratory, blood pressure, temperature, respiration, or ECG results. Mean pulse increased for both HLD200 and Ritalin® about the time of Tmax and lasting ~10 to 12 hours. This increase in pulse is consistent with the expected pharmacological results of the sympathomimetic mechanism of action of MPH.

Conclusions:

The estimate of MPH bioavailability from a single dose of HLD200, 100 mg, relative to a single dose of immediate release Ritalin®, 20 mg, based on dose normalized AUC_{last} was 73.9%. Consistent with the formulation differences, HLD200 exhibited a longer T_{max} relative to Ritalin®.

The AE profile of HLD200 and Ritalin® was consistent with the established side effect profile and dose of MPH.

Table 4: Overall summary table of AE's by treatment

Overall Summary Table	Treatment A HLD200, 100 mg N=11	Treatment B Ritalin®, 20 mg N=12
Subjects with AEs, n (%)	4 (36.4%)	2 (16.7%)
Number of AEs	9	2
Subjects with SAEs, n (%)	0 (0.0%)	0 (0.0%)
Subjects with Drug-Related AEs, n (%)	3 (27.3%)	2 (16.7%)
Number of Drug-Related AEs	8	2
Subjects Withdrawn due to AEs, n (%)	0 (0.0%)	0 (0.0%)
Subjects with at least 1 AE severity no greater than Moderate, n (%)	4 (36.4%)	2 (16.7%)
Subjects with at least 1 AE severity no greater than Mild, n (%)	3 (27.3%)	2 (16.7%)

Overall Sponsor Conslusions

The estimate of MPH bioavailability from a single dose of HLD200, 100 mg, relative to a single dose of Ritalin®, 20 mg, based on dose normalized AUClast was 73.9%. Consistent with the formulation differences, HLD200 exhibited a longer Tmax relative to immediate release Ritalin®.

There were more AEs reported in subjects receiving a single oral dose of HLD200, 100 mg, than those receiving a single oral dose of Ritalin®, 20 mg. The AE profile of HLD200 and Ritalin® was consistent with the established side effect profile and dose of MPH.

No safety effects were observed related to clinical laboratory, blood pressure, temperature, respiration, or ECG results.

Reviewer Comments

1. *Study Design:*

This 2-way crossover study was designed to compare the relative bioavailability of MPH following evening administration of HLD200 to that of immediate release Ritalin® administered in the morning. The study design (cross-over), dose level (highest to-be-marketed strength of HLD200), study subjects, bioanalytical method, PK and statistical method for data analysis were all acceptable for the primary objective of the study.

2. *Protocol deviation:*

No major or minor protocol deviations were reported and all subjects met the eligibility criteria for the study. This was acceptable

1. *Data Analysis (i.e., any outliers etc.):*

All but 1 subject (sequence B-A) completed the study per protocol. Subject (b) (6) *withdrew consent (work schedule changed) prior to Period 2, Treatment A. Therefore, there were finally N=11 for treatment A and N=12 for Treatment B. This was acceptable since Subject* (b) (6) *was dosed with only Ritalin (with Ritalin exposure levels in this subject similar to other subjects) and they were never dosed with the HLD200 product at all .*

2. *Bioanalytical Method:*

A validated bio-analytical methodology was used which was acceptable.

3. *Pharmacokinetic findings:*

We agree with the sponsor's PK analysis and conclusions from the study.

Additionally, we note, that for the same dose administered (in mg), the following were the key PK characteristics for the HLD200 vs. Ritalin (RLD):

- *AUClast for HLD200 was 73.9 % of Ritalin*
- *Cmax for HLD200 was 28.2% of Ritalin*

Overall Reviewer Conslusions:

The realtive BA study was succesful in providing a PK bridge from the sponsor's product (HLD200) to the RLD (Ritalin).

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report # HLD200-109 **Study Period:** 20-May-2015 to 31-July-201

NDA 209311

Title	A Phase I, Single Center, Clinical Trial Examining the Pharmacokinetic Effects of 100 mg of HLD200, Methylphenidate HCl Modified Release Capsules in Healthy Adult Volunteers in a Fasted, Fed and Sprinkled State under a Randomized Three-way Cross-over Design
Objectives	**Primary:** To determine the rate and extent of absorption of HLD200 following single treatment (100 mg) in healthy adult volunteers in fasted, fed, and sprinkled states. **Secondary:** To determine safety and tolerability in healthy adult volunteers.

Study Design:

Methods:

This study was a single-dose, 3-way, Latin square crossover clinical trial of modified-release (MR) methylphenidate HCl (MPH) capsules. Healthy volunteers between 18 and 55 years of age were screened within 28 days of randomization. Eighteen subjects who met all entry criteria were randomized in equal proportions to one of the following 6 treatment sequences of a single 100 mg dose of MPH MR capsules (HLD200) in conditions A (fed), B (sprinkled), and C (fasted):

Treatment Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Treatment A: fed (after a high-fat meal beginning 30 minutes and ending 5 minutes pre-dose)
Treatment B: sprinkled (contents of capsule on applesauce)
Treatment C: fasted (for a minimum of 8 hours)

The 6 subjects who withdrew or were withdrawn after administration of at least 1 dose of investigational product (IP) were replaced to achieve 3 evaluable subjects per treatment sequence, so a total of 24 subjects were enrolled in the study.

In each Treatment Period, subjects were admitted to the clinical research unit (CRU) on the day before dosing, and eligible subjects were dosed at approximately 9 pm on Days 0, 7, and 14. All subjects received a standard high-fat/high-calorie meal approximately 11 hours post-dose the next morning (not specified in the protocol but information on file at the Sponsor). Subjects remained in the CRU for 48 hours after the dose for pharmacokinetic (PK) sampling and safety assessments (reporting of adverse events [AEs], clinical laboratory evaluations, vital signs, physical examinations, and electrocardiogram [ECGs]). There was a 7-day (± 1 day) Washout Period

Test Product, Dose/Strength/Concentration, Mode of Administration, and Batch Number: MPH MR (HLD200) 100 mg capsules, oral, batch number: 3125683
Duration of Treatment: 3 doses 7 days apart (approximately 15 days)

Route of Administration	Oral
Sampling Times	PK sample collection times: Pre-dose and at 2, 4, 6, 8, 8.5, 9, 9.5 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 36, and 48 hours post-dose
PK and safety Parameters	**Pharmacokinetics:** • C_{max}: peak observed plasma concentration • T_{max}: time to peak observed plasma concentration • λ_z: terminal phase rate constant • $T_{1/2}$: terminal phase half-life • AUC_{0-t}: area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration • $AUC_{0-\infty}$: area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time **Safety:** AEs, clinical laboratory results, vital signs, ECG results, C-SSRS findings
PK Moieties	Methylphenidate (D +L)
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	PK data analysis and the statistical analysis of bioequivalence were performed using the computer program Phoenix WinNonlin version 6.4. A mixed effects model analysis based on the US Food and Drug Administration Guidance for Industry: *Statistical Approaches to Establishing Bioequivalence* was performed on the logarithmic transformation of determined primary PK exposure metrics C_{max} and AUC_{0-t}. The fasted state (Treatment C) was regarded as the reference state for the statistical comparisons with fed (Treatment A) and sprinkled (Treatment B) states. The fed and sprinkled states were also compared to each other. AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) and summarized by treatment for frequency and severity. Clinical laboratory results were summarized by mean, median, standard deviation (SD), and range. Laboratory abnormalities were analyzed by summarizing frequency, severity, and changes from baseline. Shift tables were also created for hematology and chemistry results. Vital signs were listed with the clinically significant values denoted; data were summarized by treatment using raw data and change from Baseline values by treatment by mean, median, SD, and range. Abnormal ECG results were listed. C-SRSS were displayed in subject listings.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Methylphenidate (D+L)		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population

Table 1: Summary of demographics

Characteristic	Treatment Sequence					
	A-B-C N = 5	A-C-B N = 4	B-A-C N = 3	B-C-A N = 5	C-A-B N = 4	C-B-A N = 3
Sex, n (%)						
Male	4 (80.0)	3 (75.0)	2 (66.7)	3 (60.0)	1 (25.0)	2 (66.7)
Female	1 (20.0)	1 (25.0)	1 (33.3)	2 (40.0)	3 (75.0)	1 (33.3)
Age (years)						
Mean (SD)	37.2 (8.64)	46.8 (8.10)	37.0 (15.72)	36.6 (13.81)	38.5 (12.56)	48.3 (5.03)
Range: min, max	25, 46	35, 53	23, 54	21, 50	24, 49	43, 53
Race, n (%)						
White	2 (40.0)	2 (50.0)	2 (66.7)	4 (80.0)	2 (50.0)	3 (100.0)
Black (of African descent)	3 (60.0)	2 (50.0)	1 (33.3)	1 (20.0)	2 (50.0)	0
Ethnicity, n (%)						
Not Hispanic/Latino	5 (100.0)	4 (100.0)	3 (100.0)	5 (100.0)	4 (100.0)	2 (66.7)
Hispanic/Latino	0	0	0	0	0	1 (33.3)
Weight (kg)						
Mean (SD)	90.61 (7.366)	81.04 (15.469)	74.50 (15.702)	81.51 (18.997)	74.37 (4.007)	83.60 (13.161)
Range: min, max	80.5, 96.9	61.0, 98.7	65.2, 92.6	57.0, 103.7	70.0, 79.2	75.8, 98.8
Body mass index (kg/m^2)						
Mean (SD)	28.580 (2.1557)	26.825 (4.4101)	23.900 (3.4871)	25.900 (4.4615)	27.900 (2.4290)	27.033 (3.7072)
Range: min, max	25.80, 31.70	20.40, 29.90	19.90, 26.30	21.70, 31.70	24.30, 29.50	22.80, 29.70

A = fed (high-fat meal); B = sprinkled on applesauce; C = fasted (8-hour fast).
Abbreviations: SD = standard deviation.

Results

Pharmacokinetic Results

Pharmacokinetics: Mean C_{max} after the high-fat meal was 16% lower than after the fasted dose, and median T_{max} after the high-fat meal was 2.5 hours longer than after the fasted dose. Mean C_{max} and median T_{max} after the sprinkled dose were similar to the results after the fasted dose. Mean C_{max} after the high-fat meal was 12% lower than after the sprinkled dose, and median T_{max} after the high-fat meal was 2.5 hours longer than after the sprinkled dose. Mean AUC and $T_{1/2}$ were similar among the 3 dosing conditions.

The women weighed less than the men on average, and the mean AUC_{0-t} values in women were consequently higher than in men for all 3 dosing conditions in this study.

Bioequivalence was demonstrated for all 3 dosing conditions on the basis of total exposure (AUC_{0-t}) and for the dosing conditions after fasting (whole capsule administration and sprinkled on food) on the basis of C_{max}, but the lower bounds of the confidence intervals of C_{max} for the fed state were below the limit for bioequivalence to both the fasted and sprinkled states.

Safety: The fed treatment condition was associated with a lower number of AEs, subjects with AEs, drug-related AEs, subjects with drug-related AEs, and subjects with the more common types of AEs compared to the 2 treatments (capsule and sprinkled) administered after fasting. The AE profile of HLD200 of the 3 treatments was consistent with the established side effect profile of MPH. No safety effects were noted in the laboratory, ECG, or suicidality data. Substantial elevations from Baseline in mean pulse rate were seen starting a few hours before T_{max} and lasting through 24 hours post-dose. The AEs and elevated pulse rate observed were consistent with the expected pharmacological results of the sympathomimetic mechanism of action of MPH.

Figure 1: MPH Plasma Concentration after 100 mg HLD200 in Fed, Sprinkled on Food and Fasted State.

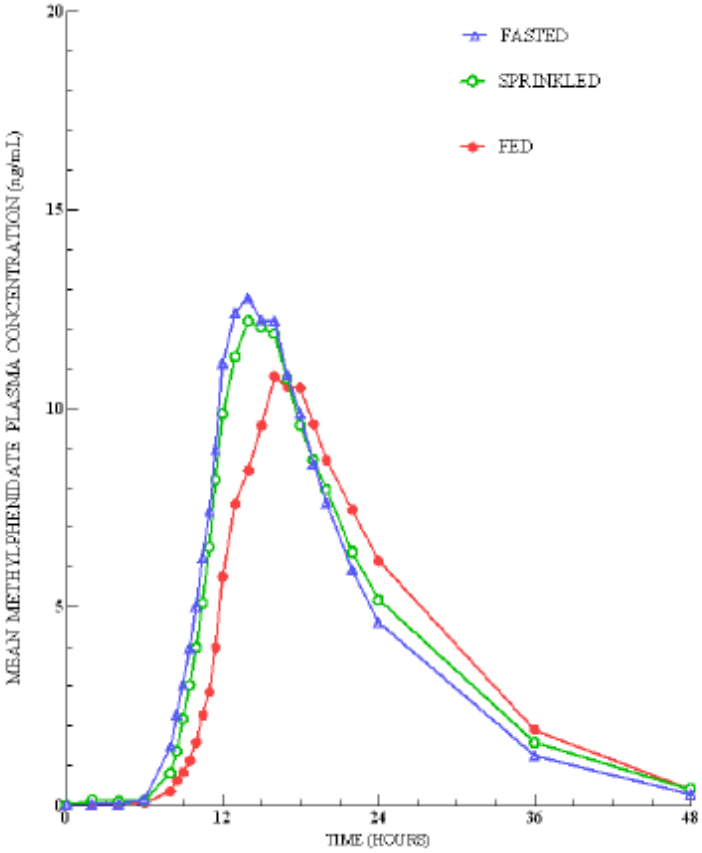


Table 2: MPH Pharmacokinetic Parameters after 100 mg HLD200 in Fed, Sprinkled, and Fasted State.

Parameter	HLD200 100 mg Treatment Group		
	A (Fed) N = 18	B (Sprinkled) N = 18	C (Fasted) N = 18
C_{max} (ng/mL), mean (CV%)	12.21 (41.3)	13.71 (39.5)	14.17 (46.5)
T_{max} (hours), median (range)	16.50 (13.00-20.00)	14.00 (11.50-20.02)	14.00 (11.50–18.05)
$T_{1/2}$ (hours), mean (CV%)	5.94 (23.5)	6.25 (27.2)	5.90 (41.6)
λ_z (1/hour), mean (CV%)	0.1216 (19.1)	0.1187 (27.0)	0.1307 (28.8)
AUC_{0-t} (ng•hr/mL), mean (CV%)	174.8 (41.9)	182.5 (39.6)	179.8 (44.7)
$AUC_{0-\infty}$ (ng•hr/mL), mean (CV%)	178.7 (43.4)	187.4 (40.0)	183.0 (44.3)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time; AUC_{0-t} = area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration; C_{max} = peak observed plasma concentration; CV = coefficient of variation; λ_z = terminal phase rate constant; $T_{1/2}$ = terminal phase half-life; T_{max} = time to teak observed plasma concentration.

Table below summarizes the bioequivalence analysis for the fed, sprinkled, and fasted state. The lower bounds of the Cmax confidence intervals for the fed state compared with both the fasted and sprinkled states were below the limit for bioequivalence. The comparison between sprinkled and fasted states based on Cmax met the criteria for bioequivalence. Total exposure (AUC0-t) was within the limits of bioequivalence for comparison between each of the dosing conditions.

Table 3: **Bioequivalence Analysis of 100 mg HLD200 in Fed, Sprinkled, and Fasted State**

	Geometric Least Squares Mean		Intrasubject CV%	*P* Value	Geometric Mean Ratio (90% CI)
FED (A) VS. FASTED (C)					
	FED (Test) N = 18	FASTED (Reference) N = 18			
AUC_{0-t} (ng•hr/mL)[a]	161.5	166.2	16.72	0.61	97.17 (88.48, 106.72)
C_{max} (ng/mL)	11.25	12.99	21.24	0.048	86.58 (76.89. 97.48)
SPRINKLED (B) VS. FASTED (C)					
	SPRINKLED (Test) N = 18	FASTED (Reference) N = 18			
AUC_{0-t} (ng•hr/mL)[a]	170.7	166.2	16.72	0.63	102.74 (93.55, 112.84)
C_{max} (ng/mL)[a]	12.71	12.99	21.24	0.76	97.84 (86.89. 110.16)

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Safety: The fed treatment condition was associated with a lower number of AEs, subjects with AEs, drug-related AEs, subjects with drug-related AEs, and subjects with the more common types of AEs compared to the 2 treatments (capsule and sprinkled) administered after fasting. The AE profile of HLD200 of the 3 treatments was consistent with the established side effect profile of MPH. No safety effects were noted in the laboratory, ECG, or suicidality data. Substantial elevations from Baseline in mean pulse rate were seen starting a few hours before T_{max} and lasting through 24 hours post-dose. The AEs and elevated pulse rate observed were consistent with the expected pharmacological results of the sympathomimetic mechanism of action of MPH.

Overall Sponsor Conslusions

Mean Cmax after the high-fat meal was 14% lower than after the fasted dose, and median Tmax after the high-fat meal was 2.5 hours longer than after the fasted dose. Mean Cmax and median Tmax after the sprinkled dose were similar to the results after the fasted dose. Mean Cmax after the high-fat meal was 11% lower than after the sprinkled dose, and median Tmax after the high-fat meal was 2.5 hours longer than after the sprinkled dose. Mean AUC and T1/2 were similar between the fed and fasted doses, between the sprinkled and fasted dose, and between the sprinkled and fed doses.

Bioequivalence was demonstrated for all 3 dosing conditions on the basis of total exposure (AUC0-t) and for the dosing conditions after fasting (whole capsule administration and sprinkled on food) on the basis of Cmax, but the lower bounds of the confidence intervals of Cmax for the fed state were below the limit for bioequivalence to both the fasted and sprinkled state.

These PK and safety data indicate that HLD200 capsules can be administered safely and effectively with or without food and that the contents of the capsules may be sprinkled on food.

Reviewer Comments

1. *Study Design:*

This study was a single-dose, 3-way, Latin square crossover Phase1 clinical trial. Each subject received all the 3 treatment arms (fed, fasted and sprinkled) and thus was an appropriate design. This is a night time food-effect study with the subjects getting the food (or fasted) at the time of administration of HLD200 capsule.

- *The study was conducted with the final to-be-marketed formulation of HLD200*
- *The study was conducted at the highest planned strength of 100 mg.*
- *A single-dose, cross-over study design with 3-treatment arms, 3-period and 6 sequences ensured that all subjects received all the 3 treatments and had no sequence effects.*
- *A high-fat, high-calorie food was given to be finished 5 min prior to dosing. No additional food was given up to next morning. The duration of fasting was at least 8 hours. A standard 240 mLs of water was given with the capsule.*
- *Adequate numbers (N=18) of healthy adult subjects were used.*
- *Healthy males and females between the ages of 18 and 55 years were included*
- *PK analysis using a validated method was performed for methylphenidate (D+L) and appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.*
- *The study excluded all prescription medicines, OTC's, good or herbal supplements.*
- *Therefore, the overall study design was acceptable.*

2. *Protocol deviation:*

No protocol deviations were reported in this study. This was acceptable.

3. *Data Analysis (i.e., any outliers etc.):*

No outliers were observed and no subjects were left out from data analysis. Though 24 subjects were initially enrolled in the study, 6 subjects withdrew (either voluntarily or due to AE-related discontinuations). However, all 6 subjects who withdrew received only 1 of the treatment arm (i.e., either fed, sprinkled or fasted) and did not receive the 3 treatment arms for any PK comparison between the treatments. Therefore, results from all the 18 subjects (i.e., 3 subjects within each of the treatment sequence) who received all 3 treatment arms were included in the PK analysis, without leaving out any legitimate subject. This was acceptable.

4. *Bioanalytical Method:*

A validated analytical methodology was used which was acceptable.

5. *Pharmacokinetic findings:*

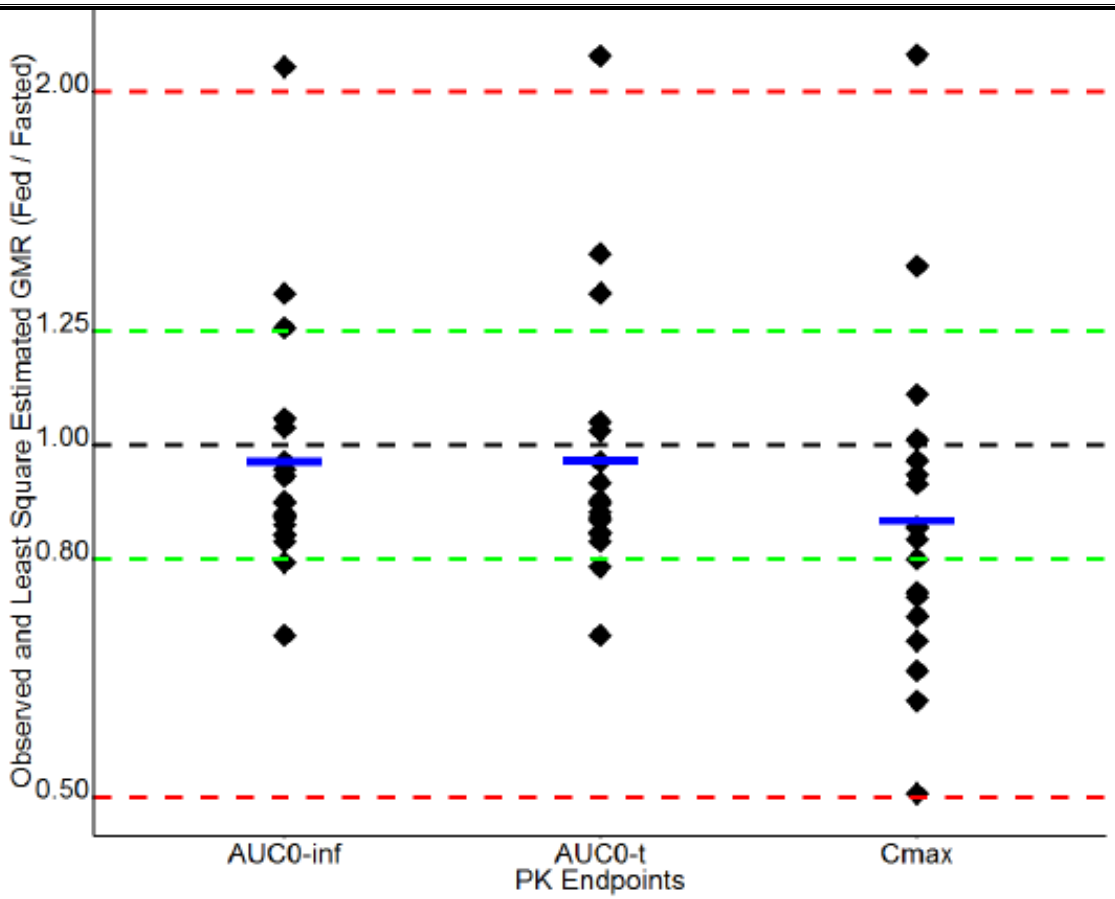
- *We agree with the PK data analysis provided by the sponsor.*
- *For getting a true sense on the intra-subject variability in this food effect study, in addition to the mean data, we also looked at the individual subject data. Since this study was a 3-way cross-over study, each subject had been dosed with 100 mg HLD200 under the 3 condition (i.e., high fat fed, fasted, or sprinkled on applesauce). The variability of exposure (i.e., Cmax and AUC) within a subject was analyzed. Based on the Table and Figure below, a majority of the subjects had AUC ratio's within 80% to 125% with generally an equivalent percentage of subjects having the AUC ratio <80% or greater than 125%. Thus, the individual subject data did not demonstrate any subject with unreasonably high change in exposure due to the presence of food, suggesting it's suitability to be administered without regards to food in the clinic.*

Table 4: Distribution of Individual Subject Ratios for Study HLD200-109 by Food Effect (Reference = Fasted, N = 18).

Ratio of PK Parameters[1]	<50%	< 80%	80%-125%	>125%	>200%
Fed vs. Fasted					
C_{max}	0 (0%)	7 (38.9%)	9 (50.0%)	2 (11.1%)	1 (5.56%)
AUC_{0-t}	0 (0%)	2 (11.1%)	13 (72.2%)	3 (17.7%)	1 (5.56%)
AUC_{0-inf}	0 (0%)	2 (11.1%)	13 (72.2%)	3 (17.7%)	1 (5.56%)
Sprinkled vs. Fasted					
C_{max}	0 (0%)	6 (33.3%)	9 (50.0%)	3 (16.7%)	1 (5.56%)
AUC_{0-t}	0 (0%)	1 (5.56%)	16 (88.9%)	1 (5.56%)	1 (5.56%)
AUC_{0-inf}	0 (0%)	1 (5.56%)	16 (88.9%)	1 (5.56%)	1 (5.56%)

AUC = area under the curve; C = concentration; PK = pharmacokinetic
[1]Data are presented as number of subjects followed by the % of subjects in ( )

Figure 2: Scatter Plot of the Individual Subject Ratios and the Geometric Least Square Mean Ratio (Fed vs Fasted) for the PK parameters for Study HLD200-109 (N = 18)



Reviewer's Overall Conclusion: **Based on the review of the results provided in this study report:**

- **We agree that HLD200 can be dosed with or without food. Though a high fat meal can delay the Tmax and lead to a marginal (~14%) decrease in Cmax, the overall exposure (i.e., AUC) remains the same to fasted state. Similarly, the sprinkled food did not change the Cmax, AUC or the Tmax. Therefore, we agree, that HLD200 can be administered without regards to food in the clinic. However, to ensure consistent response, the patients should be instructed to either take the product consistently with meals or consistently without meals each evening.**

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report # HLD200-104	**Study Period:** 05-June-2015 to 27-July-201
NDA 209311	
Title	A Phase I, Single Center, Single-Dose, Open-Label Study in Two Parts: Part 1: 2-Way Crossover Dose Proportionality Study of HLD200 Methylphenidate HCl Modified Release Capsules in Healthy Volunteers with Subjects Receiving HLD200 (20 or 100 mg). Part 2: Study of the Bioavailability following Administration of HLD200 (100 mg) in the Evening with a Lowfat/ Low-calorie Breakfast in the Morning to the Subjects from Part 1.
Objectives:	**Primary:** • To determine pharmacokinetic (PK) dose proportionality of HLD200 in healthy adult volunteers by investigating the relationship between PK exposures and dose administered (20 or 100 mg). • To investigate the bioavailability of HLD200 (100 mg) with a low-fat/low-calorie breakfast provided the morning after dosing. **Secondary:** • To determine safety and tolerability in healthy adult volunteers

Study Design:

This study was a crossover clinical trial of modified-release (MR) methylphenidate hydrochloride (MPH) capsules. Healthy volunteers between 18 and 55 years of age were screened within 28 days of randomization. Twenty subjects who met all eligibility criteria were randomized in a 1:1 ratio to 1 of the following 2 treatment sequences of a single dose of MPH MR capsules (HLD200) in the fasted state (for a minimum of 8 hours) in Part 1:

Treatment Sequence	Treatment Period 1	Treatment Period 2
AB	100 mg	20 mg
BA	20 mg	100 mg

In each Treatment Period in Part 1, subjects were admitted to the clinical research unit (CRU) on the day before dosing, and eligible subjects were dosed at approximately 8 pm on Days 0 and 7. An evening snack was provided approximately 2 hours post-dose. All subjects received a standard low to moderate-fat/high-calorie meal breakfast the next morning (not specified in the protocol but information on file at the Sponsor). Subjects remained in the CRU for 48 hours after the dose for PK sampling and safety assessments (reporting of adverse events [AEs], clinical laboratory evaluations, vital signs, physical examinations, and electrocardiogram [ECGs]). There was a 7-day (± 1 day) Washout Period between the Treatment Periods. Subjects returned to the CRU on Day 13 (± 1 day) for safety assessments. The Columbia Suicide Severity Rating Scale (C-SSRS) was administered at Screening, before each dose, and at Follow-up on Day 13.

In Part 2, 13 subjects who had received both treatments in Part 1 were administered 100 mg HLD200 in the fasted state (for a minimum of 8 hours) at approximately 8 pm followed by a standard low-fat/low-calorie meal at approximately 8 am the next day. Subjects were admitted to the CRU on the day before dosing and remained in the CRU for 48 hours after the dose for PK sampling and safety assessments. Subjects returned to the CRU on Day 6 (± 1 day) for safety assessments. The C-SSRS was administered at Screening and at Follow-up on Day 6.

Thus, the study had 2 parts:

- Part 1 = Dose proportionality (20 mg vs. 100 mg)
- Part 2 = Food effect study

Test Product, Dose/Strength/Concentration, Mode of Administration, and Batch Number:

MPH MR (HLD200) 100 mg capsules, oral, batch number: 3125683

MPH MR (HLD200) 20 mg capsules, oral – manufactured at the investigational site using material from 100 mg capsules

Duration of Treatment: 3 doses 7 days apart (approximately 15 days)

Route of Administration	Oral
Sampling Times	PK sample collection times: Pre-dose and at 2, 4, 6, 8, 8.5, 9, 9.5 10, 10.5, 11, 11.5, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 36, and 48 hours post-dose
PK and safety Parameters	**Pharmacokinetics:** • C_{max}: peak observed plasma concentration • T_{max}: time to peak observed plasma concentration • λ_z: terminal phase rate constant • $T_{1/2}$: terminal phase half-life • AUC_{0-t}: area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration • $AUC_{0-\infty}$: area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time **Safety:** AEs, clinical laboratory results, vital signs, ECG results, C-SSRS findings
PK Moieties	Methylphenidate (D+L)
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	

PK data analysis and the statistical analysis of bioequivalence were performed using the computer program Phoenix WinNonlin version 6.4. A mixed effects model analysis based on the US Food and Drug Administration Guidance for Industry: Statistical Approaches to Establishing Bioequivalence was performed on the logarithmic transformation of determined dose-normalized primary PK exposure metrics C_{max} and AUC_{0-t}. The 100 mg dose was regarded as the reference state for the statistical comparisons with 20 mg dose. The 100 mg doses in Part 1 and Part 2 were also compared to each other.

AEs were coded using the Medical Dictionary for Regulatory Affairs and summarized by treatment for frequency and severity. Clinical laboratory results were summarized by mean, median, standard deviation (SD), and range. Laboratory abnormalities were analyzed by summarizing frequency, severity, and changes from baseline. Shift tables were also created for hematology and chemistry results. Vital signs were listed with the clinically significant values denoted; data were summarized by treatment using raw data and change from Baseline values by treatment by mean, median, SD, and range. Abnormal ECG results were listed. C-SSRS findings were displayed in subject listings.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Methylphenidate (D+L)		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population

Number of Subjects: Planned: 20 Analyzed: 20

Main Criteria for Inclusion: Healthy males and females aged 18 to 55, inclusive

Table 1: Summary of demographics

Characteristic	Part 1 A-B N = 10	Part 1 B-A N = 10	Part 2 C N = 13
Sex, n (%)			
Male	3 (30.0)	3 (30.0)	6 (46.2)
Female	7 (70.0)	7 (70.0)	7 (53.8)
Age (years)			
Mean (SD)	25.3 (6.25)	27.9 (5.67)	26.5 (6.63)
Range: minimum, maximum	18, 39	22, 38	18, 39
Race, n (%)			
White	8 (80.0)	8 (80.0)	10 (76.9)
Black or African-American	1 (10.0)	1 (10.0)	2 (15.4)
Asian	1 (10.0)	1 (10.0)	1 (7.7)
Ethnicity, n (%)			
Not Hispanic/Latino	10 (100.0)	10 (100.0)	13 (100.0)
Hispanic/Latino	0	0	0
Weight (kg)			
Mean (SD)	65.8 (9.64)	69.4 (12.29)	69.0 (11.68)
Range: minimum, maximum	52, 78	54, 90	52, 90
Body mass index (kg/m^2)			
Mean (SD)	22.730 (1.7607)	23.800 (2.3777)	23.069 (1.9610)
Range: minimum, maximum	19.30, 24.90	18.50, 26.50	19.30, 25.90

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast; B = 20 mg followed by a low to moderate-fat/high-calorie breakfast; C = 100 mg followed by a low-fat/low-calorie breakfast.
Abbreviations: SD = standard deviation.

Results

Pharmacokinetic Results

The table summarizes the MPH PK parameters for the treatments A, B, and C.

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast;
B = 20 mg followed by a low to moderate-fat/high-calorie breakfast;
C = 100 mg followed by a low-fat/low-calorie breakfast.

Table 2: MPH Pharmacokinetic Parameters after 20 and 100 mg HLD200.

Parameter	HLD200 Treatment Group		
	A N = 20	B N = 20	C N = 13
C_{max} (ng/mL), mean (CV%)	12.31 (36.5)	2.56 (34.4)	13.05 (31.8)
T_{max} (hours), median (range)	14.00 (13.00–20.00)	14.00 (13.00–19.00)	14.00 (13.00–17.00)
$T_{1/2}$ (hours), mean (CV%)	6.40 (34.5)	6.51 (32.3)	5.35 (36.1)
λ_z (1/hour), mean (CV%)	0.1192 (29.3)	0.1166 (29.4)	0.1394 (22.1)
AUC_{0-t} (ng•hr/mL), mean (CV%)	171.4 (33.0)	33.4 (38.9)	170.7 (34.5)
$AUC_{0-\infty}$ (ng•hr/mL), mean (CV%)	176.7 (34.0)	34.7 (40.5)	173.7 (36.3)

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast;
B = 20 mg followed by a low to moderate-fat/high-calorie breakfast;
C = 100 mg followed by a low-fat/low-calorie breakfast.

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time; AUC_{0-t} = area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration; C_{max} = peak observed plasma concentration; CV = coefficient of variation; λ_z = terminal phase rate constant; $T_{1/2}$ = terminal phase half-life; T_{max} = time to teak observed plasma concentration.

Figure 1 illustrates the concentration-time curves for the treatments at 20 mg vs. 100 mg. The overlapping profiles obtained by the 100 mg arm vs. the 20 mg arm (normalized to 100 mg) clearly demonstrated dose proportionality between the 20 and 100 mg doses.

Figure 1: MPH Plasma Concentration after 20 and 100 mg HLD200

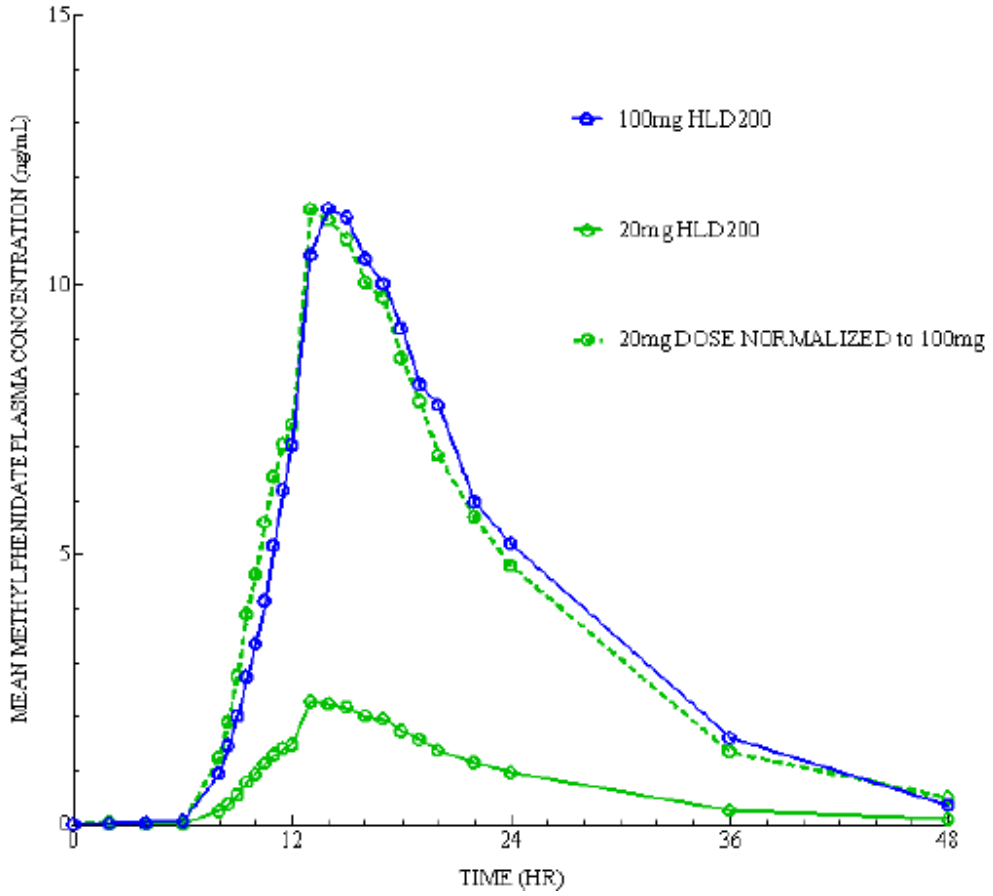


Table 3: **Bioequivalence Analysis of Dose-Normalized PK Parameters for 20 mg of HLD 200 (treated as Test) and 100 mg of HLD200 (treated as Reference).**

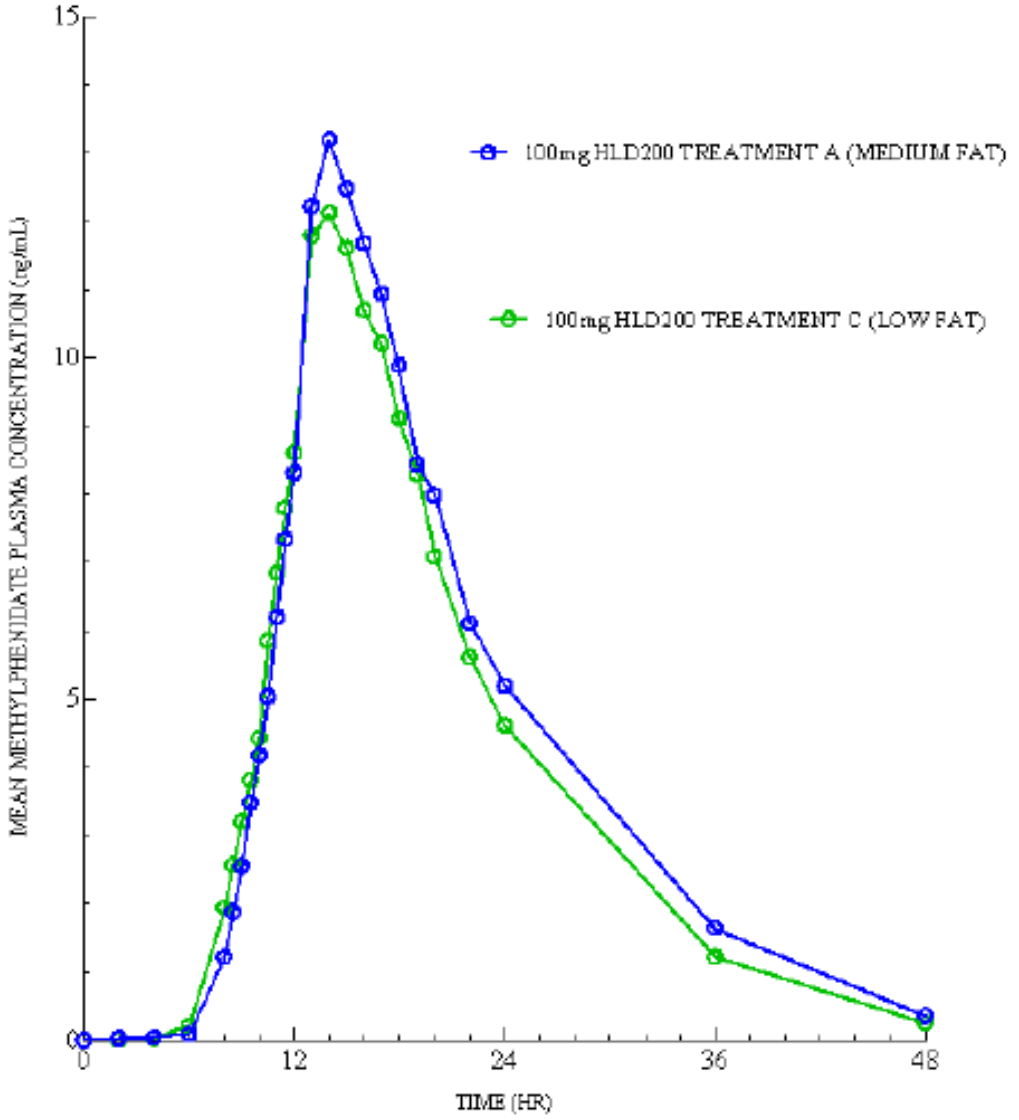
	Geometric Least Squares Mean				
	20 mg (B) (Test) N = 20	100 mg (A) (Reference) N = 20	Intrasubject CV%	*P* Value	Geometric Mean Ratio (90% CI)
DN AUC_{0-t} (ng•hr/mL)[a]	1.57	1.63	12.42	0.36	96.37 (90.04, 103.13)
DN C_{max} (ng/mL)[a]	0.12	0.12	20.06	0.52	104.18 (93.43, 116.17)

[a] Within the 0.80 to 1.25 limits of bioequivalence

Abbreviations: AUC_{0-t} = area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration; C_{max} = peak observed plasma concentration; CV = coefficient of variation; DN = dose-normalized.

Figure 2 illustrates the concentration-time curves for the 100 mg treatments (A [followed by a low to moderate-fat/high-calorie breakfast] and C [followed by low-fat/low-calorie breakfast]). PK parameters and the concentration-time curves in the 2 groups administered 100 mg doses were similar.

Figure 2: MPH Plasma Concentration after 100 mg (Medium fat breakfast vs. Low fat breakfast)



Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast;
C = 100 mg followed by a low-fat/low-calorie breakfast.

Table 4: Bioequivalence Analysis of 100 mg HLD200 (A= Medium fat breakfast vs. C= Low fat breakfast)

	Geometric Least Squares Mean			
	100 mg (C) (Test) N = 13	**100 mg (A) (Reference) N = 13**	***P* Value**	**Geometric Mean Ratio (90% CI)**
AUC_{0-t} (ng•hr/mL)	161.4	174.80	0.56	92.33 (73.25, 116.40)
C_{max} (ng/mL)	12.45	12.83	0.82	96.99 (77.33, 121.65)

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast;
C = 100 mg followed by a low-fat/low-calorie breakfast.
Abbreviations: AUC_{0-t} = area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration; C_{max} = peak observed plasma concentration; CV = coefficient of variation.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Table 5: Overall Summary of Adverse Events by Treatment Group

Category	HLD200 Treatment Group		
	Treatment A N = 20	Treatment B N = 20	Treatment C N = 13
Subjects with AEs, n (%)	6 (30.0)	6 (30.0)	2 (15.4)
Number of AEs	8	6	6
Subjects with SAEs, n (%)	0	0	0
Number of SAEs	0	0	0
Subjects with drug-related, n (%)	5 (25.0)	1 (5.0)	2 (15.4)
Number of drug-related AEs	6	1	5
Subjects with at least 1 severe AE, n (%)	0	0	0
Subjects withdrawn due to AEs, n (%)	0	0	0
Deaths, n (%)	0	0	0
Subjects with at least 1 AE of severity no greater than moderate, n (%)	6 (30.0)	6 (30.0)	2 (15.4)
Subjects with at least 1 AE of severity no greater than mild, n (%)	5 (25.0)	5 (25.0)	2 (15.4)

Treatments: A = 100 mg followed by a low to moderate-fat/high-calorie breakfast; B = 20 mg followed by a low to moderate-fat/high-calorie breakfast; C = 100 mg followed by a low-fat/low-calorie breakfast.
Abbreviations: AE = adverse event; SAE = serious adverse event.

Overall Sponsor Conslusions:

Pharmacokinetic Results: Mean PK parameters, concentration-time curves, and bioequivalence analysis demonstrated dose proportionality for the 20 and 100 mg doses of HLD200.

Mean PK parameters and concentration-time curves showed little difference between the 100 mg HLD200 doses with different post-dose feeding conditions (followed by a low to moderate-fat/high-calorie breakfast or by a low fat/ low-calorie breakfast) although the lower bound of the 90% confidence interval was below 80% for both Cmax and AUC0-t in the bioequivalence analysis.

Safety Results: No differences in safety profiles were noted among the 3 treatments. The AE profile of HLD200 of the 3 treatments was consistent with the established side effect profile of MPH. No safety effects were noted in the laboratory, ECG, or suicidality data. Across all treatments increased mean pulse rate (by as much as 24.4 bpm higher than the Baseline value) was seen starting a 2 to 3 hours before Tmax and lasting through 24 hours post-dose. The AEs and elevated pulse rate observed were consistent with the expected pharmacological results of the sympathomimetic mechanism of action of MPH.

Conclusions: The PK exposure between the lowest (20 mg) and highest dose (100 mg) to be marketed was proportional to dose administered. The PK and safety data obtained in this study indicate that HLD200 can be administered safely and effectively at doses between 20 and 100 mg and that safety and efficacy are not affected by the type of meal eaten approximately 12 hours post-dose.

Reviewer Comments

1. *Study Design:*

This study was a Phase 1 cross-over study with adequate numbers of healthy adult subjects. Appropriate PK parameters were assessed. The overall study design was acceptable.

- *The study was conducted with the final to-be-marketed formulation of HLD200*
- *The study was conducted using both the lowest planned strength of 20 mg as well as the highest planned strength of 100 mg.*
- *A single-dose, cross-over study design with 2-treatment arms, 2-period and 2 sequences ensured that all subjects received both the treatments (i.e., 20 mg and 100 mg) and had no sequence effects.*
- *The study was done under the standard fasting condition (duration of fasting was at least 8 hours and a standard 240 mLs of water was given with the capsule) which minimized any food-related effects on PK.*
- *Adequate numbers (N=20) of healthy adult subjects were used.*
- *Healthy males and females between the ages of 18 and 55 years were included*
- *PK analysis using a validated method was performed for methylphenidate (D+L) and appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.*
- *The study excluded all prescription medicines, OTC's, good or herbal supplements.*
- *Therefore, the overall study design was acceptable.*

2. *Protocol deviation:*

No protocol deviations were reported in this study. This was acceptable.

3. *Data Analysis (i.e., any outliers etc.):*

No outliers were observed and no subjects were left out from data analysis. This was acceptable.

4. *Bioanalytical Method:*

A validated analytical methodology was used which was acceptable.

5. *Pharmacokinetic findings:*

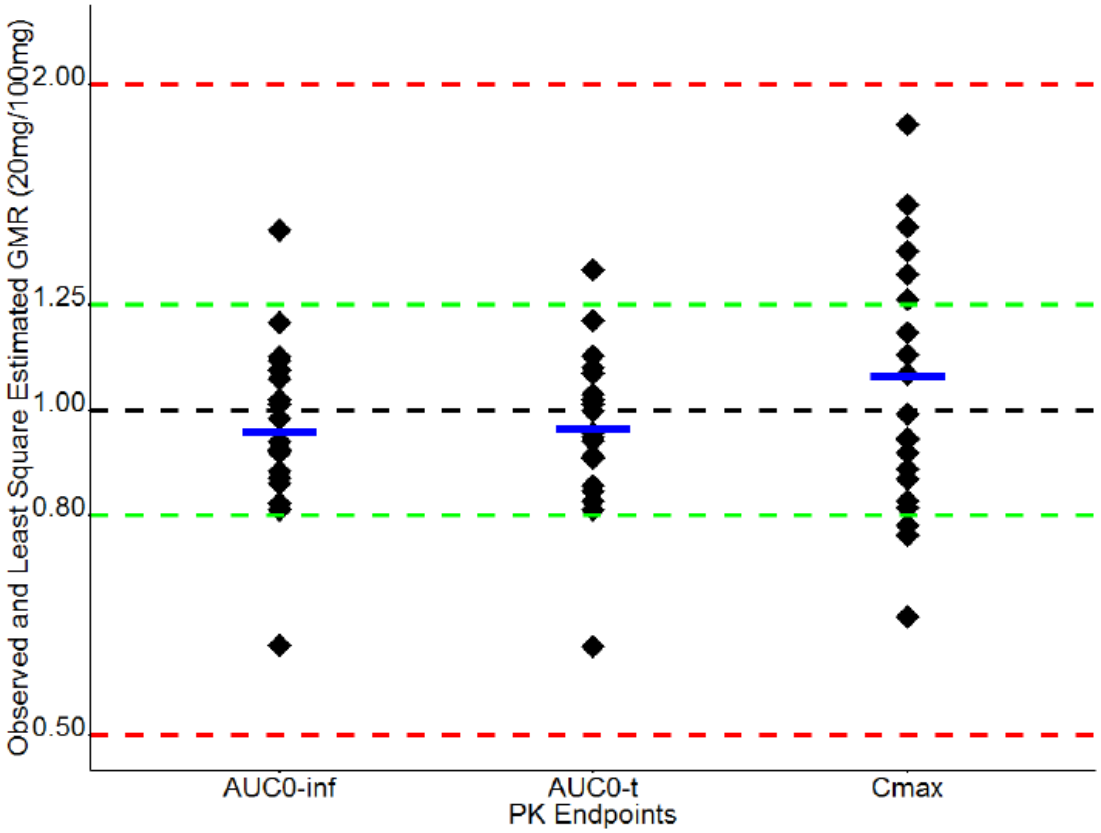
- *We agree with the PK data analysis provided by the sponsor. The overlapping profiles obtained by the 100 mg arm vs. the 20 mg arm (normalized to 100 mg) clearly demonstrate dose proportionality between the 20 and 100 mg doses.*
- *For getting a true sense on the intra-subject variability, in addition to the mean data, we also looked at the individual subject data. Since each subject was dosed both 20 mg and 100 mg in a cross-over fashion, variability within a subject was assessed by comparing the "dose-normalized" exposures (i.e., Cmax and AUC) after the 2 treatments. Based on the Table and Figure below, it is clear, that in addition to the mean data, an analysis of the individual subject data demonstrated that 90% of the subjects had AUC ratio's within the 80% to 125% limit, suggesting a strong dose-proportionality of the product. Additionally, not even a single subject (out of N=20) had their Cmax or AUC ratio vary by more than 2X- margin, suggesting a lack of any extreme variability and general dose-proportionality in all individual subject in this study.*

Table 6: Distribution of Individual Subject Ratios for Study HLD200-104 (Reference = 100 mg, N = 20)

PK Parameters[1]	<50%	< 80%	80%-125%	>125%	>200%
C_{max}	0 (0%)	3 (15%)	11 (55%)	6 (30%)	0 (0%)
AUC_{0-t}	0 (0%)	1 (5%)	18 (90%)	1 (5%)	0 (0%)
AUC_{0-inf}	0 (0%)	1 (5%)	18 (90%)	1 (5%)	0 (0%)

AUC = area under the curve; C = concentration; PK = pharmacokinetic
[1]Data are presented as number of subjects followed by the % of subjects in ( )
Data Source: HLD200-104 PK Report Table 8 and Table 9

Figure 3: Scatter Plot of the Individual Subject Ratios and the Geometric Least Square Mean Ratio (20 mg vs 100 mg) for the Dose Adjusted PK Parameters for Study HLD200-104 (N = 20)



Reviewer's Overall Conclusion: **Based on the review of the results provided in this study report:**

- **We agree that PK is dose-proportional for HD200 from 20 mg to 100 mg dose level. The overlapping profiles obtained by the 100 mg arm vs. the 20 mg arm (normalized to 100 mg) clearly demonstrate dose proportionality between the 20 and 100 mg doses.**

- **Part 2 of the study which is presented as a "food-effect" study cannot be accepted as a typical food-effect study. The 2 treatment arm compare a "low fat breakfast" vs. "medium fat breakfast" and thus lacks a true comparison to a fasted arm. Additionally, this study addresses the effect of food in the morning (i.e., only 10 or so hours after the dosing in the night). Though the results are helpful they in no way would predict the overall magnitude of a true effect of food. An additional study done by the sponsor (HLD200-109) will be used to assess the true food-effect.**

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Report # HLD200-102	**Study Period:** 06-Aug-2013 to 6-Oct-2013
NDA 209311	
Title	A Phase I/II, Single Center, Single-Treatment, Open-Label, Adaptive Clinical Trial Design Examining the Pharmacokinetic Effects of up to Two Separate HLD200 Modified Release Formulations of Methylphenidate in Adolescent and Pediatric Subjects with Attention-Deficit Hyperactivity Disorder
Objectives	**Primary:** - To determine the rate and extent of absorption (i.e., pharmacokinetics [PK]) of MPH following single treatment with up to 2 HLD200 (54 mg) modified-release (MR) formulations (B and C, in separate cohorts) in adolescents (Stage 1) and children (Stage 2) with Attention-Deficit Hyperactivity Disorder (ADHD). **Secondary:** - To determine safety and tolerability of up to 2 formulations of HLD200 in adolescents and children with ADHD - To determine to explore the pharmacodynamics (PD) effects on ADHD symptomatology following single treatment of up to 2 HLD200 formulations in children only

Study Design:

Methodology:

This study was an open-label, single dose, PK study of 2 formulations of HLD200 MR in adolescents and children with ADHD. Up to 36 subjects per HLD200 formulation (B and C) were planned to be enrolled: 18 adolescents (ages 13-17 years) and 18 children (6-12 years). The study was conducted in 2 separate stages, firstly in adolescents (Stage 1) and then in children (Stage 2).

Note: The C-HLD200 formulation was never tested in this study as the B-HLD200 formulation resulted in an acceptable PK profile.

Following consent/assent and screening procedures, eligible subjects were required to wash-out of all ADHD medications for 5 days prior to dosing. Subjects then were admitted to the Clinical Research Unit (CRU) in the afternoon and fitted with a catheter for repeated plasma sampling. A pre-dose PK sample (t=0) was obtained within 15 minutes prior to dosing. A single oral dose was administered at ~9pm, followed by PK sampling at 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 36 and 48 hours after dosing. To explore a PD affect, children also underwent math testing using the pen-and-paper Permanent Product Measure of Performance (PERMP) 1 hour prior to dosing and at 9, 10, 11, 12, 13, 14, 16, 18, 20, 22 and 24 hour after dosing.

Safety was assessed by incidences of adverse events (AEs), clinical laboratory parameters, vital signs, electrocardiograms (ECGs), and physical examinations. The Columbia-Suicide Severity Rating Scale (C-SSRS) for adolescents and pediatrics were administered at Screening and during the study. Subjects were released from the CRU 24 hours after dosing and completed the study after the 48 hour PK sample and safety assessments.

Formulation: Though it was initially planned to use 2 different formulations, only 1 formulation i.e., batch B= N450137 was eventually used for the study. Additionally, though this formulation was not exactly the same as "to-be-marketed" (it lacked the [redacted] (b) (4)), this formulation is acceptable as "to-be-marketed" formulation since the changes were within the SUPAC limits and it had similar dissolution profile to the "to-be-marketed" formulation.

Name of Sponsor Company: Ironshore Pharmaceuticals & Development, Inc.
Name of Test Product: HLD200 (Formulation B - MPH00400)
Name of Active Ingredient: Methylphenidate hydrochloride (MPH)

Oral dose = 54 mg of HLD200

Duration of Treatment:
1 dose, followed by PK, PD (children) sampling, and safety assessments for 48 hours after dosing.

Reference Therapy, Dose/Strength/Concentration, Mode of Administration, and Batch Number:
None.

Treatments Administered
Subjects were required to eat dinner before 5:00 pm and then fasted for a minimum of 4 hours prior to dosing. Water was allowed *ad libitum*. HLD200, 54 mg, was administered orally with 240 mL of water at 9:00 pm ±30 minutes.

Route of Administration	Oral
Sampling Times	<u>PK sample collection times</u> A pre-dose PK sample was obtained within 15 minutes prior to dosing. A single oral dose was administered at ~9 pm, followed by PK sampling at 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 36 and 48 hours after dosing. Samples were collected in a sodium fluoride/potassium oxalate tube. The tubes were centrifuged at 3000 rpm and 4°C for 10 minutes within 30 minutes of collection. The resulting plasma was stored as 2 aliquots in polypropylene tubes at ≤70°C prior to shipment to the analysis laboratory on dry ice. MPH concentration was measured in each sample by high performance liquid chromatography with tandem mass spectrometry. To explore a PD affect, children also underwent math testing using the pen-and-paper Permanent Product Measure of Performance (PERMP) 1 hour prior to dosing and at 9, 10, 11, 12, 13, 14, 16, 18, 20, 22 and 24 hour after dosing.

PK and safety Parameters	**Pharmacokinetics:** - AUC_{0-tz}: area under the plasma concentration curve to the time point with the last measurable drug concentration - $AUC_{0-\infty}$: area under the plasma concentration time curve to infinity - C_{max}: maximum plasma concentration - T_{max}: time to maximum plasma concentration - Absorption lag time: difference in time between drug administration and last time point where drug concentration was below the limit of assay quantitation - λz: terminal elimination rate constant - $t_{1/2elim}$: half-life of elimination **Safety:** - AEs - Clinical laboratory tests - Vital signs - ECGs - Physical exam - C-SSRS **Pharmacodynamics:** - PERMP
PK Moieties	Methylphenidate (D+L)
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	PK analyses was performed using WinNonlin. Primary exposure parameters AUC and C_{max} values were normalized for dose and body weight in terms of [mg/kg] so the units for these normalized parameters were ng·hr/mL[mg/kg] and ng/mL[mg/kg], respectively. The PK analyses are described in this clinical study report and in the PK report (dated March 22, 2016). Statistical analyses of safety data were descriptive. Summary statistics for quantitative variables include: number (n), mean, standard deviation (SD), minimum, median, and maximum. Qualitative results are provided in listings. The analyses are further described in this clinical study report and are detailed in the Statistical Analysis Plan.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Methylphenidate (D+L)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Study Population

- **Male and female, children (6-12 years) and adolescents (13-17 years) with ADHD**

Number of Subjects: **Planned**: Up to 72
Analyzed: 29: 18 adolescents, 11 children

Diagnosis and Main Criteria for Inclusion:
Previous diagnosis of ADHD, confirmed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). All subjects were required to be on an ADHD medication and have symptoms controlled. Additionally, subjects were either to be controlled on an MPH containing ADHD regimen at screening or have a history of being controlled on an MPH containing regimen.

9.3.1 Inclusion Criteria

Subjects had to meet all the following criteria to be eligible for the study:

1. Male and female adolescents (13-17 years; Stage 1) and children (6-12 years; Stage 2)
2. Previous diagnosis of ADHD and confirmation using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
3. ADHD symptoms controlled on a stable dose of ADHD medication; subjects should be on MPH or have previous history of symptom control during treatment with MPH
4. Physical examination free of clinically significant findings, unless deemed not clinically significant by the Investigator and Medical Monitor
5. Able to swallow treatment capsules
6. Available for entire study period

Table 1: Demography of subjects by age group

Variable	Adolescents (N=18)	Children (N=11)
Age (years)		
Mean (SD)	15.4 (1.24)	10.5 (1.37)
Minimum, Maximum	13, 17	8, 12
Sex, n (%)		
Male	14 (77.8%)	6 (54.5%)
Female	4 (22.2%)	5 (45.5%)
Race, n (%) [a]		
Asian	0 (0.0%)	1 (9.1%)
Black	4 (22.2%)	3 (27.3%)
Other	1 (5.6%)	2 (18.2%)
White	15 (83.3%)	9 (81.8%)
Ethnicity, n (%)		
Hispanic or Latino	3 (16.7%)	2 (18.2%)
Not Hispanic or Latino	15 (83.3%)	9 (81.8%)
Weight (kg)		
Mean (SD)	67.71 (14.588)	36.08 (7.950)
Minimum, Maximum	51.7, 103.4	25.9, 54.0
Body Mass Index (kg/m^2) [b]		
Mean (SD)	23.50 (4.525)	17.45 (2.789)
Minimum, Maximum	17.2, 35.2	13.9, 23.7

Subject disposition by age group:

All subjects enrolled into the study completed the study. One child signed assent but withdrew from participation prior to dosing and is not included in the table below or any of the analyses.

Variable	Adolescents (N=18)	Children (N=11)
Subject completed all study activities	18 (100.0%)	11 (100.0%)
Subject did not complete all study activities	0 (0.0%)	0 (0.0%)

Protocol Deviations:

No major or minor protocol deviations were reported and all subjects met the eligibility criteria for the study.

Results

Pharmacokinetic Results

A summary of the primary PK parameters from the adolescents, children, and adults is shown in the Table 2. The dose body weight normalization of the mean AUC0-t and Cmax parameters showed that the 3 groups are similar but the mean dose body weight normalized Cmax for the children was lower than the adolescents by 16% and lower than the adults by 18.5%. However, the corresponding values for the dose body weight normalized AUC0-t were almost the same for the 3 groups.

Table 2: **Comparison of Mean/Median Pharmacokinetic Parameters by Age Group**

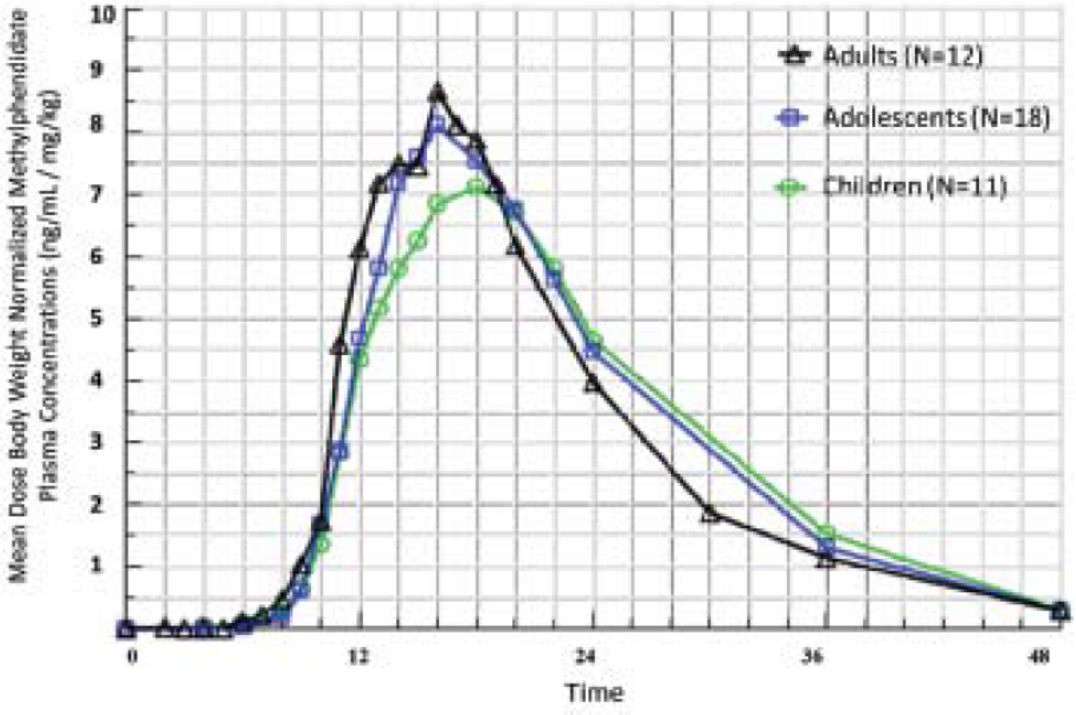
Parameter	Adolescents (N=18)	Children (N=11)	Adults (N=12)
Mean C_{max} (ng/mL) ± CV (%)	7.17 ± 23.7	11.64 ± 36.3	5.99 ± 24.0
Median T_{max} (range)	16.3 (13.9-22.1)	18.2 (12.4-22.0)	16.0 (13-18)
Mean AUC_{0-t} (ng·hr/mL) ± CV (%)	105.5 ± 30.0	205.5 ± 39.1	83.4 ± 27.1
Mean AUC_{0-inf} ±CV (%)	109.6 ± 30.8	210.1 ± 38.5	NA
Dose Body Weight Normalized Parameters			
Mean C_{max} (ng/mL)/[mg/kg] ± CV (%)	8.84 ± 34.5	7.44 ± 30.1	9.13 ± 35.2
Mean AUC_{0-t} (ng/mL)/[mg/kg] ± CV (%)	129.4 ± 34.8	129.7 ± 27.3	126.5 ± 35.5

The 90% confidence intervals (CIs) for the comparisons of ratios of least squares (LS) means normalized dose body weight Cmax and AUC0-t means of the groups is shown below in Table 3.

Table 3: LS Means Ratios and CIs for Dose Body Weight Normalized Primary Exposure Metrics

	Geometric LS Means		p Value	Ratio (mean)	CI	
					Lower	Upper
Adolescents v Children	Adolescents	Children				
AUC_{0-t} (ng/mL)/[mg/kg]	123.5	125.8	0.85 (NS)	0.98	0.79	1.22
C_{max} (ng/mL)/[mg/kg]	8.41	7.15	0.19 (NS)	1.18	0.96	1.45
Adults v Children	Adults	Children				
AUC_{0-t} (ng/mL)/[mg/kg]	119.1	125.8	0.71(NS)	0.95	0.75	1.20
C_{max} (ng/mL)/[mg/kg]	8.63	7.15	0.17(NS)	1.21	0.96	1.51
Adults v Adolescents	Adults	Adolescents				
AUC_{0-t} (ng/mL)/[mg/kg]	119.1	123.5	0.82(NS)	0.96	0.78	1.20
C_{max} (ng/mL)/[mg/kg] [a]	8.63	8.41	0.83 (NS)	1.03	0.84	1.25

Figure 1: Mean Body Weight Dose Normalized Methylphenidate Plasma Concentrations for Adolescents, Children, and Adult (54 mg HLD200)



Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

No clinically significant safety findings were observed in AEs, clinical laboratories, vital signs, ECGs, physical exam, or in suicidality as measured by C-SSRS. No serious AEs (SAEs) were reported in this trial. There were no differences in safety findings among adolescents and children.

Table 4 below summarizes reported AEs by category and age group. In the adolescent group, 10 (55.6%) subjects experienced AEs; 9 mild and 1 moderate (upper respiratory tract infection). In the children group, 6 (54.5%) subjects experienced 6 mild AEs. Overall there is no difference in the percent of AEs by age group, but 5 adolescents had AEs thought by the Investigator to be related to the study drug: flatulence (1), vomiting (1), headache (1), and abdominal pain upper (2). All events were mild and resolved prior to completing the study.

Table 4: **Overall Summary Table of Adverse Events by Age Group**

Category	Adolescents (N=18)	Children (N=11)
Number of Subjects with AEs	10 (55.6%)	6 (54.5%)
Total Number of AEs	11	6
Number of Subjects Withdrawn due to AEs	0 (0.0%)	0 (0.0%)
Number of Subjects with at least one AE severity ≤Mild	9 (50.0%)	6 (54.5%)
Number of Subjects with at least one AE severity ≤Moderate	10 (55.6%)	6 (54.5%)
Total Number of Serious AEs	0	0
Total Number of Drug-Related AEs	5	0
Number of Subjects with Drug-Related AEs	5 (27.8%)	0 (0.0%)

Overall Sponsor Conslusions

The PK results from adolescents and children with ADHD constituted proof of the formulation development concept: evening dosing of the MR formulation (HLD200) to adolescents and children, after a lag time in significant drug release of approximately 8 hours, resulted in a PK profile that allows for control of clinical ADHD symptoms in the post-waking morning period, and throughout the day.

Comparisons between the adolescent and child data, corrected for differences in body weight and dose, indicate close similarity in the PK of HLD200. Similarly, when analogous data from a prior adult study was included in the comparison, the PK of all 3 populations exhibited close similarity to each other.

Overall, a single dose of B-HLD200, 54 mg, was generally well-tolerated under fasting conditions in both adolescents and children.

Reviewer Comments

1. *Study Design:*

This was a typical open-label, single dose study designed to assess the PK of HLD200 in children and adolescents following its evening administration. The study design (single-dose), dose level (54 mg of HLD200), study subjects (children and adolescents with ADHD), bioanalytical method, PK and statistical method for data analysis were all acceptable for the primary objective of the study.

- *The study was an open-label, single dose, PK study in children and adolescents with ADHD*
- *The study was conducted using 54 mg of HLD200 which was safe and well tolerated in the younger subjects*
- *The study was done under fasting condition (duration of fasting was at least 4 hours and a standard 240 mLs of water was given with the capsule) which minimized any food-related effects on PK.*
- *Adequate numbers (N=29; adolescents=18 and children= 11) of subjects were used.*
- *The study included a full spectrum of age strata (e.g., 6-9, 10-12, 13-15, 16-17) with adequate distribution of patients in each age strata.*
- *PK analysis using a validated method was performed for methylphenidate (D+L) and appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.*
- *The study excluded all prescription medicines, OTC's, good or herbal supplements.*
- *Therefore, the overall study design was acceptable.*

2. *Protocol deviation:*

No major or minor protocol deviations were reported and all subjects met the eligibility criteria for the study. This was acceptable

3. *Data Analysis (i.e., any outliers etc.):*

All subjects enrolled into the study completed the study. The data for all study subjects was included in the analysis. This was acceptable.

4. *Bioanalytical Method:*

A validated bio-analytical methodology was used which was acceptable.

5. *Pharmacokinetic findings:*

- *The comparison of mean PK data (normalized for body weight and dose) demonstrated that PK characteristics were similar across children, adolescents and adults.*
- *A detailed visual assessment of the PK data for all the individual subjects (children and adolescents) clearly demonstrated that the PK profiles in pediatric subjects was similar in shape to the profile seen in adults. All the pediatric subjects demonstrated a delayed release of the drug with plasma exposures beginning to rise only at 6-8 hours similar to what was observed in adults. Similarly, the Tmax observed in pediatric subjects (16.3 hour in adolescents and 18.2 hour in children) was in line with the Tmax of around 16 hour observed in adults.*

Overall Reviewer Conslusions:

Based on this study result we agree that the mean PK data (i.e., the shape of the PK profile as well as the key PK characteristics) are similar across all age groups (i.e., children, adolescents and adults) after normalizing for body-weight.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRAVEEN BALIMANE
07/25/2017

XIAOFENG WANG
07/25/2017

KEVIN M KRUDYS
07/25/2017

HAO ZHU
07/25/2017