Poster #S17

Establishing Clinical Benefit of HLD200, a Novel Delayed-Release and Extended-Release Formulation of Methylphenidate, Using a Model-Based Approach

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Abstract

Background: Several extended-release formulations of methylphenidate (MPH), usually characterized by a dual release process, have been developed for the treatment of attention-deficit/hyperactivity disorder (ADHD). HLD200 is the first and only evening-dosed delayed-release and extended-release formulation of MPH that utilizes a novel drug delivery system (DELEXIS®) designed to delay initial drug release by approximately 8-10 hours, targeting the onset of clinically meaningful treatment effect upon awakening and throughout the day. The purpose of this study was to develop pharmacokinetic (PK) and PK/pharmacodynamic (PD) models for HLD200 to establish its clinical response versus two currently available extended-release MPH (ie, OROS MPH and MPH CD). **Methods:** A population PK model was developed by using data collected from 25 sampling tests of a phase 1 PK study in 20 healthy adults receiving HLD200 (20 mg or 100 mg), and evaluating alternative *in vivo* release models. A PK/PD model was also developed by using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) scores over 9 sampling times in a randomized phase 3 trial of children with ADHD receiving either HLD200 (n = 64) or placebo (n = 53). An indirect response model described the trajectories of SKAMP scores following placebo administration and a maximum effect (E_{max}) model characterized the drug-related change from placebo. Clinical benefit of HLD200, based on changes from placebo, was compared with the published data of OROS MPH and MPH CD. **Results:** The best performing PK model was a one-compartment model with a time varying absorption rate described well by a single Weibull *in vivo* release function. Covariate analysis identified that volume of distribution was weight-dependent and gender affected the time of MPH release from HLD200. The placebo response model properly described SKAMP score trajectories, and the population PK/PD model established an exposure-response relationship, where a drug concentration of ~15 ng/mL is necessary to induce an improvement in clinical response by ~40%. Covariate analysis indicated an effect of gender on the half maximal effective concentration (EC_{50}). HLD200 (~65 mg) was found to provide a clinical benefit that is comparable with medium-to-high doses of OROS MPH and MPH CD, and produced a more constant and less fluctuating response throughout the day. Furthermore, HLD200 had a clinical response earlier in the day compared with OROS MPH and MPH CD, and a dose-dependent duration of clinical response that lasted into the evening hours. **Conclusions:** The population PK/PD model developed for HLD200 provided a reasonable estimate of its clinical benefit. When compared with OROS MPH and MPH CD, the model revealed that HLD200 produces a clinical response that occurs earlier in the day, remains constant with less fluctuation throughout the day, and has a dose-dependent duration of effect that lasts into the evening.

Introduction

- Several extended-release formulations of methylphenidate (ER MPH), usually characterized by a dual release process, have been developed for the treatment of attention-deficit/hyperactivity disorder (ADHD)
- HLD200 is the first evening-dosed delayed-release (DR) and extended-release (ER) formulation of methylphenidate (MPH) that utilizes a novel drug delivery system (DELEXIS®) designed to delay initial drug release to target the onset of clinically meaningful treatment effect upon awakening and lasting into the evening
- HLD200 capsules contain hundreds of uniform microbeads comprising two functional film coatings surrounding an MPH-loaded core
  - The outer DR layer was designed to provide a controlled time of release of MPH to target therapeutic effect upon awakening
  - The inner ER layer was designed to provide a controlled rate of release for therapeutic effect throughout the remainder of the day and into the evening
- Evening administration of HLD200 produces a pharmacokinetic (PK) profile characterized by an 8- to 10-hour delay in initial MPH release, followed by a period of extended, controlled release resulting in an ascending absorption profile[1]
- In a pivotal phase 3 trial, HLD200 demonstrated significant improvements in ADHD symptom control and reductions in at-home functioning during the early morning, late afternoon, and evening[2]
- However, the clinical response of HLD200 relative to other ER MPH products has not been established

Objective

- The aim of this study was to develop population PK and PK/pharmacodynamic (PD) models for HLD200 to determine its clinical response versus two currently available ER MPH (ie, osmotic release oral system methylphenidate [OROS MPH] and methylphenidate controlled release [MPH CD])

Methods

PK Model Development

- Data collected from 25 sampling tests of a phase 1, single-center, single-dose, open-label PK study in 20 healthy adults receiving HLD200 were used for PK model development
  - Using a Latin square, two-sequence, two-period crossover design, a single evening dose of HLD200 (20 mg or 100 mg) was administered to healthy adults at 8:00 PM in a fasted state, who then received a medium-fat breakfast the following morning
- The PK model was developed by performing the following steps:
  1. **Base structural model:** An initial evaluation of the PK data indicated that the concentration-time profile exhibits a disposition/elimination shape consistent with a one-compartment PK model (**Figure 1**):

$$\frac{dC_p}{dt} = f(t) - kel \cdot C_p \quad \textbf{(Eq. 1)} \qquad f(t) = \frac{dr}{dt} \quad \textbf{(Eq. 2)}$$

where f(t) is the time varying *in vivo* release rate, kel is the elimination rate constant, and C_p is the MPH concentration

  - A convolution-based modeling approach was applied using a prescribed input function with two time varying *in vivo* absorption models (ie, single and double Weibull functions)[3]:

Methods (cont'd)

Figure 1. Schematic of the HLD200 PK Model

kel, elimination rate constant; C_p, methylphenidate concentration; MPH, methylphenidate; PK, pharmacokinetic

$$r1(t) = e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} \quad \textbf{(Eq. 3)} \qquad r2(t) = ff \cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} + (1 - ff) \cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)} \quad \textbf{(Eq. 4)}$$

where r(t) is the input function, ff is the fraction of the dose released in the first process, td is the time necessary to absorb 63.2% of the dose released in the first process, td1 is the time necessary to absorb 63.2% of the dose released in the second process, ss is the sigmoidicity factor for the first process, and ss1 is the sigmoidicity factor for the second process

  2. **Covariate analyses:**
     - The effect of weight and gender, both prospectively identified as covariates of interest, were evaluated by a forward inclusion and backward elimination process, using the likelihood ratio test with an alpha level of 0.05 set *a priori*
     - Simulations were performed to illustrate the effects of the retained covariates and their combinations on MPH exposure
  3. **Model evaluation:** Using a nonlinear mixed-effect modeling approach, the following population characteristics of PK parameters were estimated for the base and final models:
     - Fixed effect parameters: kel, volume of distribution (Vd), ss, and td
     - Random effect parameters: inter-individual variability (IIV) and inter-occasion variability (IOV) on fixed effect parameters
     - Residual error: additive and proportional model components
  4. **Model refinement:** Simulations, goodness-of-fit diagnostic plots, and visual predictive checks were conducted on base and final models to determine the concordance between the model-based simulated data and observed data

PK/PD Model Development

- A PK/PD model was developed by using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP) composite scores over 9 sampling times from a pivotal phase 3, multicenter, randomized, double-blind, placebo-controlled, forced-withdrawal, parallel group, analog classroom study (NCT02493777) of HLD200 (n = 64) versus placebo (n = 53) in children (6–12 years) with ADHD
  - The trial consisted of 3 phases: screening period of up to 4 weeks; 6-week, open-label, treatment optimization phase during which the optimal daily dosage and evening administration time were determined for HLD200; and 1-week, double-blind, placebo-controlled, analog classroom test phase
  - The primary efficacy endpoint was the model-adjusted average of all post-dose SKAMP composite scores measured on the laboratory classroom day following a week of double-blind, once-daily treatment with HLD200 (optimal dose and time) or placebo during a 12-hour time period from 8:00 AM to 8:00 PM
- A sequential PK/PD modeling approach was applied consisting of the following steps:
  1. **Estimated PK exposure:** As MPH concentrations were not obtained in this trial, MPH exposure of each subject treated with HLD200 was determined by using the population PK model derived from demographic data (weight and gender) and HLD200 dosing histories
  2. **Placebo model:** A placebo-response model was developed by using SKAMP measurements from subjects treated with placebo, and an indirect response model was used to describe the trajectories of SKAMP scores following placebo administration
     - R(t) is the placebo response defined by:

$$\frac{dR}{dt} = k_{in} \cdot (1 + p(t)) - k_{out}R \quad \textbf{(Eq. 5)} \qquad p(t) = AA \cdot e^{-t \cdot P1} \quad \textbf{(Eq. 6)}$$

where k_{in} is the zero-order rate constant for the response (R), k_{out} is the first-order rate constant for the loss of response, AA is the amplitude of the placebo effect, and P_1 is the rate of change in the placebo effect

     - Since the system was assumed to be stationary, R begins at a predetermined baseline value (Bas) that changes with time and returns back to Bas

$$R(t = 0) = Bas = \frac{k_{in}}{k_{out}} \quad \textbf{(Eq. 7)}$$

  3. **PK/PD modeling:** SKAMP scores of subjects treated with HLD200 were analyzed by fixing the placebo and PK exposure parameter estimates
     - The effect of HLD200 was described by a change from placebo in SKAMP scores using an E_{max} model:

$$SKAMP(t) = R(t) \cdot \left(1 - \frac{Emax \cdot C_p{}^g}{EC_{50}{}^g + C_p{}^g}\right) \quad \textbf{(Eq. 8)}$$

where E_{max} is the MPH concentration associated with maximal effect, EC_{50} is the MPH concentration associated with half maximal response, and g is the shape of the exposure-response relationship

     - The percent change from placebo is defined by:

$$\text{Change from placebo (\%)} = \frac{Emax \cdot C_p{}^g}{EC_{50}{}^g + C_p{}^g} \quad \textbf{(Eq. 9)}$$

  4. **Covariate analysis:** Graphical and statistical approaches along with consideration of underlying scientific rationale were used to identify covariates of the PK/PD model; weight, gender, and age were prospectively identified as covariates of interest
  5. **Model evaluation:** Nonlinear mixed effects modeling was used to describe the exposure-response relationship of HLD200, specifically between MPH concentrations and the primary efficacy measure, SKAMP scores
  6. **Model validation:** Using simulations, goodness-of-fit diagnostic plots, and visual predictive checks, the concordance between the model-based simulated data and observed data were determined for both the placebo and final PK/PD model

Clinical Response of HLD200 vs. OROS MPH and MPH CD

- Clinical benefit was defined as the cumulative (area under the curve [AUEC]) change from placebo in SKAMP scores estimated over a 12-hour period (8:00 AM to 8:00 PM)
- Using simulations of the PK/PD model for HLD200, the following was evaluated:
  - Impact of different *in vivo* release rates (varied td from 8–16 hours and ss from 4.5–8.5) and dosing times (varied from 4–14 hours before the start of the morning classroom session at 8:00 AM) on the expected clinical benefit
  - Clinical response (trajectories of SKAMP scores) of HLD200 at doses of 60 mg, 80 mg, and 100 mg
- Clinical responses of OROS MPH and MPH CD were compared with HLD200 using:
  - Previously determined PK time courses of OROS MPH and MPH CD, which were best described by a convolution-based model using a double Weibull function (**Eq. 4**)[3]
  - SKAMP data extracted from the previously published COMACS study, a multicenter, double-blind crossover study of OROS MPH (18 mg, 36 mg, 54 mg), MPH CD (20 mg, 40 mg, 60 mg) and placebo with each treatment administered for 1 week[4]
- Clinical response and variability in response were evaluated using the average change from placebo in SKAMP scores (CHP) (**Eq. 8 and 9**) and the fluctuation index (FI), respectively:

$$FI = \frac{[\max(CHP) - \min(CHP)]}{average(CHP)} \quad \textbf{(Eq. 10)}$$

Software

- All data preparation, summary statistics, and graphical display presentation were performed using SAS (version 9.3) and R (version 3.2.5); SAS and R scripts were used for final analyses
- Population PK and PK/PD modeling and simulations were performed using NONMEM® (version 7.3), and the R-based package, Xpose (version 4.3), was used as a model building aid
- SAS (version 9.3) was also used to perform statistical evaluations of simulated clinical trial outcomes

Results

PK Model for HLD200

- A total of 960 plasma MPH concentration measurements were available from 20 subjects for PK model development; the demographic data are provided in **Table 1**

Table 1. Demographics of the Subjects Included in the PK Population

Population, n (%)		Body Weight (kg)			
		Mean	Median	Minimum	Maximum
Total	20 (100%)	67.59	65.65	51.80	90.10
Female	14 (70%)	63.36	60.90	51.80	79.20
Male	6 (30%)	77.45	77.05	64.80	90.10

PK, pharmacokinetics

- The best performing PK model was a one-compartment model with the time varying absorption rate described by a single Weibull *in vivo* release function
  - The presence of IOV parameters in the model significantly improved its performance (*P*<0.001)
  - Covariate analysis revealed that the best performing model was one that included the effect of weight on Vd and gender on td
    - Vd increased with weight and td was ~20% longer in females vs. males
- The estimated parameters of the final PK model are presented in **Table 2** and the outcomes of the PK model are illustrated in **Figure 2**

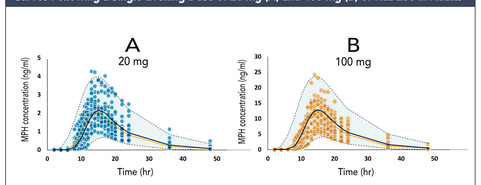
Table 2. Final Population PK Model Parameter Estimates for HLD200

Parameter	Estimated value	SE	RSE (%)	CV (%)
Fixed effect				
td in males (hr)	10.90	0.34	3.10	NA
td of females (hr)	13.20	0.39	3.00	NA
Vd (L)	4000.00	282.00	7.00	NA
ss	7.52	0.39	5.20	NA
kel (hr^{-1})	0.11	0.01	6.10	NA
Residual variability				
Additive error	0.04	0.01	22.50	NA
Proportional error	0.17	0.02	10.00	NA
Interindividual variability				
td (hr)	0.005	0.0026	55.50	6.86
Vd (L)	0.094	0.0281	29.90	30.66
ss	0.040	0.0240	60.30	19.95
kel (hr^{-1})	0.067	0.0185	27.70	25.83
Interoccasion variability				
td (hr)	0.009	0.0032	35.00	9.59
Vd (L)	0.008	0.0039	46.50	9.17
ss	0.016	0.0085	51.90	12.77
kel (hr^{-1})[a]	NA	NA	NA	NA

[a] Assumed that kel did not change from one occasion to another
CV, coefficient of variation; kel, elimination rate constant; NA, not available; PK, pharmacokinetics; RSE, root mean square error; SE, standard error; ss, sigmoidicity factor; td, time necessary to absorb 63.2% of the dose released; Vd, volume of distribution

Results (cont'd)

Figure 2. Median Predicted and Median Observed Methylphenidate Concentration-Time Curves Following a Single Evening Dose of 20 mg (A) and 100 mg (B) of HLD200 in Adults[a]



[a]The dark blue solid lines represent the median predicted concentrations (light blue circles); the gold solid lines represent the median observed concentration, and the shaded gray area represents the 90% prediction interval
MPH, methylphenidate

PK/PD Model for HLD200

- For PK/PD model development, a total of 557 SKAMP measurements were available from 64 subjects treated with HLD200 and 470 SKAMP measurements from 53 subjects treated with placebo; the demographic data are provided in **Table 3**

Table 3. Demographics of Subjects Included in the PK/PD Population

	HLD200 (n = 64)	Placebo (n = 53)
Gender, n (%)		
Male	42 (65.63)	38 (71.70)
Female	22 (34.38)	15 (28.30)
Age (y)		
Mean (SD)	9.58 (1.58)	9.28 (1.68)
Median (min, max)	10.00 (6.00, 12.00)	9.00 (6.00, 12.00)
Height (cm) at screening		
Mean (SD)	136.49 (10.73)	137.03 (12.47)
Median (min, max)	136.10 (114.60, 169.00)	137.00 (114.30, 163.80)
Weight (kg) at screening		
Mean (SD)	32.68 (8.88)	32.76 (8.16)
Median (min, max)	30.85 (19.80, 56.10)	31.50 (20.90, 50.10)

PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation

- The final mean optimized dose of HLD200 was approximately 65 mg (males: 64.9 mg; females: 66.0 mg)
- The placebo model adequately described the shape of SKAMP score trajectories in subjects treated with placebo, and the final PK/PD model provided a reasonable estimate of HLD200 effect
  - Covariate analysis revealed that the best performing model was one that included the effect of gender on the EC_{50}
    - EC_{50} was ~2-fold higher in males vs. females (*P*=0.0005)
- The estimated parameters of the final PK/PD model are presented in **Table 4**

Table 4. Final PK/PD Model Parameter Estimates for HLD200

Parameter	Estimated value	SE	RSE (%)	CV (%)
Fixed effect				
EC_{50} in males (ng/mL)	8.400	0.572	6.80	NA
EC_{50} in females (ng/mL)	3.720	0.536	14.40	NA
E_{max}	0.402	0.035	8.70	NA
g	12.600	6.260	49.70	NA
Residual variability				
Additive error	2.270	0.350	15.40	NA
Proportional error	0.298	0.031	10.30	NA
Interindividual variability				
EC_{50} (ng/mL)	0.0437	0.0188	43.00	20.90
E_{max}	0.0712	0.0218	30.60	26.68

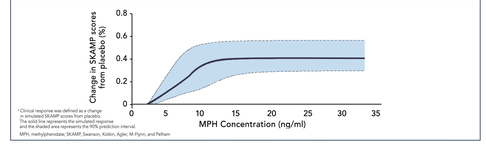
CV, coefficient of variation; E_{50}, half maximal effective concentration; E_{max}, maximum effect; g, shape of the exposure-response relationship; PD, pharmacodynamic; PK, pharmacokinetics; RSE, root mean square error; SE, standard error

- The simulated exposure-response relationship for HLD200 revealed that a drug concentration of approximately 15 ng/mL was necessary to induce an improvement in clinical response by approximately 40% (**Figure 3**)

Clinical Response of HLD200 vs. OROS MPH and MPH CD

- Comparisons of PK/PD model simulations using different in vivo release rates and dosing times revealed that:
  - The current HLD200 formulation provides an optimal clinical benefit (AUEC: 193.47) and that only a marginal improvement is expected with any modifications in *in vivo* release rates (AUEC range: 150.17–193.92)
  - Clinical benefit of HLD200 in a laboratory classroom setting is strongly dependent on evening dosing time, with the optimal dosing time estimated at 12 hours prior to morning classroom start (AUEC: 196 at 12 hr post-dose vs. 193 at 10 hr, 173 at 8 hr, 167 at 14 h, 143 at 6 hr, and 111 at 4 hr)

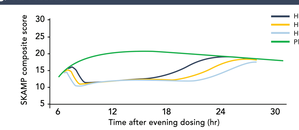
Figure 3. Relationship Between MPH Exposure and Predicted Clinical Response[a] for HLD200



[a] Clinical response was defined as a change in simulated SKAMP scores from placebo. The solid line represents the simulated response and the shaded area represents the 90% prediction interval.
MPH, methylphenidate; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham

- Simulations of clinical response (ie, SKAMP composite score trajectories) indicated that higher doses of HLD200 provide an extended duration of clinical response that occurs earlier in the day, remains constant throughout the day, and last longer into the evening (**Figure 4**)

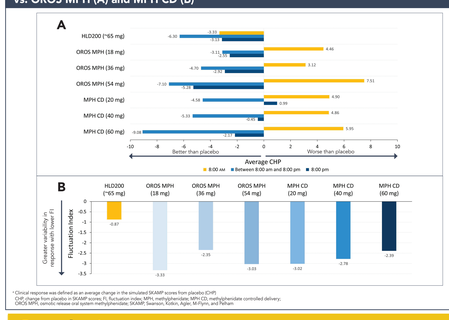
Figure 4. Predicted Clinical Response[a] of HLD200 at Varying Doses (60 mg, 80 mg, and 100 mg) vs. Placebo



[a] Clinical response was represented by the simulated SKAMP composite score trajectories
SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham

- Comparisons of model-predicted SKAMP composite score trajectories of HLD200 (~65 mg) to those of OROS MPH (18 mg, 36 mg, 54 mg) and MPH CD (20 mg, 40 mg, 60 mg) revealed that HLD200 provides a clinical response that is (**Figure 5**):
  - Comparable with medium-to-high doses of OROS MPH and MPH CD
  - Occurs earlier in the day compared with OROS MPH and MPH CD
  - More constant and less fluctuating throughout the day (FI is ≥2.7-fold lower, indicating less variability in the clinical response)

Figure 5. Comparisons of Clinical Response[a] and Fluctuation Indices of HLD200 (~65 mg) vs. OROS MPH (A) and MPH CD (B)



[a] Clinical response was defined as an average change in the simulated SKAMP scores from placebo (CHP).
CHP, change from placebo in SKAMP scores; FI, fluctuation index; MPH, methylphenidate; MPH CD, methylphenidate controlled delivery; OROS MPH, osmotic release oral system methylphenidate; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham

Conclusions

- The PK of HLD200 was best characterized by a one-compartment PK model with the time varying absorption rate described by a single Weibull *in vivo* release function
- The PK/PD model developed for HLD200 provided a reasonable estimate of its mean clinical response
- When compared with OROS MPH and MPH CD, HLD200 produces a clinical response that occurs earlier in the day, remains constant with less fluctuation throughout the day, and has a dose-dependent duration of effect that lasts into the evening
- Given that the estimated mean clinical response of HLD200 was dependent on the dosage strength and timing of evening administration, treatment may be individualized based on the needs of the patient

Disclosures

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Bev Incledon, PhD: Employee – Ironshore Pharmaceuticals & Development, Inc.

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