U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209311
Supplement #:	NA
Drug Name:	(b) (4)™ (Methylphenidate Hydrochloride) Capsule 20, 40, 60, 80, or 100 mg/day
Indication(s):	1. Treatment of ADHD. (b) (4)
Applicant:	Ironshore Pharmaceuticals and Development Inc.
Date(s):	Initial submission date: September 30, 2016 PDUFA due date: July 30, 2017
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1 EXECUTIVE SUMMARY

This review describes statistical findings about Sponsor's studies (pivotal trials HLD200-107 and HLD200-108, supporting trial HLD200-106), supporting the request for approval of [redacted]™ for the indication of treatment of Attention Deficit Hyperactivity Disorder (ADHD) [redacted] The Sponsor submits HLD200-106 which used a different formulation as a supporting trial.

The review confirms Sponsor's findings from HLD200-107 that prior evening treatment with HLD200 at doses ranging from 20 to 100 mg/day is effective in improving control of ADHD symptoms from 9 AM to 4 PM in children aged 6-12 years old with ADHD. The primary efficacy endpoint, the average of all post-dose Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale combined scores (SKAMP CS) measured on the laboratory classroom day (Visit 9) during the 12-hour time period from 8:00 am to 8:00 pm, was met (LS means [SE]: 14.8 [1.03] HLD200 versus 18.4 [1.07] placebo, p = 0.010). The key secondary endpoint, the rating of morning behavior based on Parent Rating of Evening and Morning Behavior – Revised (PREMB-R) morning subscale (PREMB-R AM), was also met (LS means [SE]: 0.7 [0.25] HLD200 versus 3.3 [0.25] placebo, p <0.001). However, FDA expressed concerns on the acceptability of PREMB-R AM as a key secondary endpoint at the end of Phase 2 (EOP2) meeting and the pre-NDA meeting. The decision on the acceptability of PREMB-R AM is deferred to the Clinical Outcomes Assessments (COA) team.

This review also confirms Sponsor's finding from the pediatric study HLD200-108 that there is a statistically significant improvement in the ADHD Rating Scale based on criteria from the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (ADHD-RS-IV) total score at Visit 5 (Week 3) in the HLD200-treated group at doses ranging from 40 mg/day to 80 mg/day compared with the placebo-treated group (p = 0.002). The key secondary endpoints evaluated at Visit 5 and based on Before-School Functioning Questionnaire (BSFQ) total score (evaluated approximately from 6:00 am to 9:00 am) also showed a statistically significant improvement in the HLD200-treated group compared with the placebo-treated group (p <0.001). [redacted]

2 INTRODUCTION

2.1 Overview

Methylphenidate Hydrochloride (HCl) Modified Release (MR) Capsules (HLD200) is an evening-dosed, delayed-release and extended-release (DR/ER) formulation of

methylphenidate hydrochloride that was specifically designed to control ADHD symptoms and functional impairments in the early morning and throughout the day.

The Sponsor submits this New Drug Application (NDA) seeking approval of HLD200. The indication sought for HLD200 is the treatment of ADHD (b) (4) . This submission is based on two phase 3 pivotal studies, HLD200-107 and HLD200-108, along with a supporting study HLD200-106. Study HLD200-106 used a different formulation of HLD200.

Table 1: List of All Studies Included in Analyses

Protocol Number	Phase and Design	Treatment Period	Follow-up Period	# of randomized Subjects	Study Population
HLD200-107	Phase 3, double blind, placebo-controlled, parallel, randomized forced-withdrawal study, conducted at 7 centers in the US	6 week open label and 1 week double blind treatment	none	Placebo 72 HLD200 83	Children 6-12 years old with ADHD
HLD200-108	Phase 3 double blind, placebo-controlled, parallel, randomized study, conducted at 21 centers in the US	3 week double blind treatment	none	Placebo 81 HLD200 82	Children 6-12 years old with ADHD
HLD200-106	Phase 3, double blind, placebo-controlled, parallel, randomized forced-withdrawal study, conducted at 4 centers in the US	6 week open label and 1 week double blind treatment	none	Placebo 21 HLD200 22	Children 6-12 years old with ADHD

2.2 Data Sources

The Sponsor submitted study reports, analysis datasets, raw datasets, and programs for all three studies. The analysis datasets and raw datasets are located in the following directories of the CDER electronic document room (EDR):
\\CDSESUB1\evsprod\NDA209311\0000\m5 and
\\CDSESUB1\evsprod\NDA209311\0005\m5.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor submitted a protocol amendment (SDN 38) acknowledging an error in randomization of 15 subjects out of 17 enrolled in Cohort 2 at Site 15 (Turnbow). The amendment can be found in (\\Cdsesub4\nonectd\IND118074\5997311). The Sponsor contracted (b) (4) to evaluate the clinical data quality and data variability of Trial HLD200-107. (b) (4) found that there was sufficient evidence of serious data integrity issue at Site #10, which randomized 36 subjects. The randomization was stratified by site. FDA clinical inspector agrees that the Site 10 data lacks the data integrity to be included in the Trial HLD200-107 analyses. The reviewer finds the quality and integrity of the remaining submitted data satisfactory and acceptable for the review analysis.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 HLD200-107

This was a Phase 3, multicenter, open-label treatment-optimized, double-blind, randomized, placebo-controlled, forced-withdrawal, parallel group study to evaluate the safety and efficacy of evening dosed HLD200 in children aged 6-12 years old with ADHD in a Laboratory Classroom Setting. The study was conducted at 7 centers in the United States.

This study had 3 phases:

- Screening/ADHD medication withdrawal phase (up to 4 weeks with a minimum 5-day washout)
- Open label treatment-optimization phase (6 weeks): At the start of this phase (Visit 2), subjects began daily evening (8:00 pm ±30 minutes) treatment with 20 or 40 mg/day HLD200 (based on prior treatment history) for a period of 1 week and then had up to 4 additional weekly visits (Visits 3 to 6) for treatment adjustments to achieve both a) an optimal daily dose and b) an optimal treatment time prior to the next phase. During Visits 3, 4, 5, and 6, investigators were permitted to titrate the dose of study drug (up or down) in 20 to 40 mg/day increments until either achieving the "optimal" daily dose or reaching a maximum daily dose of 100 mg/day and/or a maximum dose not exceeding 3.7 mg/kg (based on Visit 2 [baseline] weight), whichever occurred first.
- Double-blind placebo-controlled test phase (1 week)

A total of 161 subjects were enrolled, of whom 155 (96.3%) were randomized and 154 completed the study. There is one subject (in the placebo group) discontinued from the study after randomization due to loss of follow-up.

The primary endpoint was the model-adjusted average of all post-dose SKAMP combined scores from 8:00 am to 8:00 pm measured on the laboratory classroom day (Visit 9). The key secondary endpoint is PREMB-R AM at Visit 9.

The design of the study is appropriate for the objectives of the study. The choice of primary endpoint is appropriate for the study design. FDA informed the Sponsor during the EOP2 and pre-NDA meeting "The determination on the acceptability of the PREMB-R AM will depend on the adequacy of submitted data and will be a matter for review."

3.2.1.2 HLD200-108

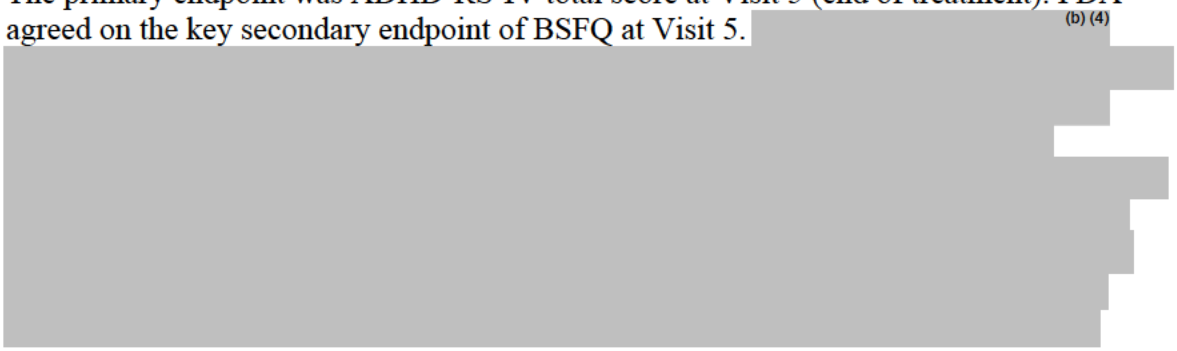
This was a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel group study to evaluate the safety and efficacy of evening-dosed HLD200, on post-waking, early morning function in children aged 6 to 12 years old with ADHD. The study was conducted at 21 centers in the United States.

This study has two phases:

- Screening/washout phase (up to 2 weeks with a minimum 72 hours washout)
- Randomized, placebo-controlled test phase (3 weeks). At the start of this phase (Visit 2), subjects were randomized to receive either HLD200 or placebo in a 1:1 ratio. Subjects were instructed to begin dosing at 40 mg/day each evening (8:00 pm ±30 minutes) for 1 week, with scheduled titration, as medically indicated and tolerated, over the subsequent 2 weeks to 60 mg/day (Visit 3) and 80 mg/day (Visit 4) and/or a dose not to exceed 3.7 mg/kg (based on Visit 2 [baseline] weight). Following dose escalation above 40 mg/day, subjects were permitted to reduce the dose by 1 step (from 60 mg/day to 40 mg/day or 80 mg/day to 60 mg/day) if necessary for tolerability. Subjects who are unable to tolerate a dose of at least 40 mg/day during the final (third) week of treatment, from Visit 4 to Visit 5 were discontinued.

A total of 163 subjects were enrolled and randomized in the study, of whom 138 (84.7%) completed the study.

The primary endpoint was ADHD-RS-IV total score at Visit 5 (end of treatment). FDA agreed on the key secondary endpoint of BSFQ at Visit 5. (b) (4)



[redacted] (b) (4)

The design of the study is appropriate for the objectives of the study. The primary endpoint and one of the key secondary endpoint (BSFQ) are appropriate for the study design.

3.2.1.3 HLD200-106

This multicenter study utilized a 6-week, open-label, treatment-optimization phase followed by a double-blind, placebo-controlled, 1-week, randomized, parallel-group test period designed to assess the safety and efficacy of HLD200 treatment in pediatric subjects with ADHD. The study was conducted at 4 centers in the United States.

The study consisted of three phases:

- Screening/Washout Phase (up to 4 weeks);
- Open-label, Treatment-optimization Phase (Open-label Phase) (6 weeks); and
- Double-blind, Placebo-controlled Test Phase (Double-blind Phase) (1 week).

A total of 43 subjects were enrolled, randomized in the study. All of them completed the study. There were no discontinuations.

The primary endpoint was SKAMP CS obtained from 8:00 am through 4:00 pm at the final double-blind visit (Visit 9/Day 50). The key secondary endpoints were the BSFQ and the SKAMP CS at both 6:00 and 8:00 pm (21 and 23 ± 2.0 hours post dose) at Visit 9. FDA informed the Sponsor in an advice letter dated April 9, 2014 that "*A positive outcome on the primary variable (SKAMP combined score) must rely on statistically significant differences between drug and placebo on the SKAMP at a number of time points, tested in a pre-specified sequence and, to support an extended duration claim, spanning a time interval of at least 8 hours.*".

The design of the study is appropriate for the objectives of the study. The primary endpoint and one of the key secondary endpoints, BSFQ, are appropriate for the study design.

3.2.2 Statistical Methodologies

3.2.2.1 HLD200-107

The intent-to-treat (ITT) population was the basis for the primary and secondary efficacy analyses. The ITT population consisted of all randomized subjects who received at least 1 dose of double-blind study drug and had at least 1 post-baseline evaluation of the primary efficacy variable. Efficacy data were analyzed according to the treatment the subject was randomized to receive.

During study conduct, it was learned that up to 15 of the 17 subjects enrolled in Cohort 2 at Site 15 were assigned multiple randomization. In all ITT analyses, these subjects were analyzed according to the treatment associated with the randomization number ultimately used. All decisions related to the subjects in Cohort 2 at Site 15 were finalized prior to database unblinding and final database lock.

Both the Sponsor and FDA clinical inspector agree that the Site 10 data lacks the data integrity to be included in the Trial HLD200-107 analyses. It was included in the Sponsor's analysis. FDA reviewer performed analysis including and excluding Site 10.

A mixed model repeated-measure (MMRM) analysis was used to analyze the primary endpoint. The model included treatment, study center, time point, and time point-by-treatment interaction as fixed effects and subjects as a random effect. An unstructured correlation matrix was used to model the within-patient errors, and restricted maximum likelihood estimation was used. The Kenwood-Roger method was used for the denominator degrees of freedom. If the model failed to converge with an unstructured covariance matrix, first-order heterogeneous autoregressive, heterogeneous compound symmetric, and compound symmetric were to be tested. The average treatment difference over all post-dose time points was estimated using least squares (LS) means from the MMRM. The treatment comparison was conducted as a 2-sided test at the 5% level of significance. The standard error (SE) and 95% CI for the treatment difference were provided.

When the primary efficacy outcome was statistically significant ($p < 0.05$), an assessment of onset and duration of efficacy (i.e., clinical effect) of HLD200 versus placebo was performed, as described in the statistical analysis plan. Onset and duration of efficacy were evaluated using the same MMRM analysis as for the primary efficacy variable. Testing was conducted on each time point (8:00 am, 9:00 am, 10:00 am, 12:00 pm, 2:00 pm, 4:00 pm, 6:00 pm, 7:00 pm, and 8:00 pm) individually using a model-based t-test. Onset time of efficacy action was to be claimed at the earliest post-dose time point at which the difference between the 2 treatments was statistically significant ($p < 0.05$). Duration of efficacy was the difference between the onset time and the latest consecutive time point at which the difference between the 2 treatments was still statistically significant ($p < 0.05$).

The primary analysis was repeated on the ITT population with the exclusion of the 17 subjects in Cohort 2 at Site 15, and on the PP population using the MMRM analysis.

If the primary efficacy outcome was statistically significant ($p < 0.05$), the PREMB-R AM at Visit 9 would be assessed using an analysis of covariance (ANCOVA) model with treatment as the main effect and study center and baseline score at Visit 2 as the covariates. The key secondary analysis was repeated on the ITT population with the exclusion of the 17 subjects in Cohort 2 at Site 15.

Two sensitivity analyses of the primary analysis were pre-specified in SAP: a pattern mixture model analysis (PMM) and a repeat of the primary analysis with missing data

imputed via a last observation carried forward (LOCF) approach. FDA commented that the sensitivity analysis based on LOCF was not proper. Because of the laboratory classroom trial design, only 1 of the 155 randomized patients discontinued. Therefore, no pre-specified sensitivity analysis was performed.

3.2.2.1 HLD200-108

The ITT population was the basis for analyses of the primary and secondary efficacy endpoints. The ITT population consisted of all randomized subjects who received at least 1 dose of study drug and had at least 1 post-baseline evaluation of the primary efficacy variable.

An MMRM analysis was used to analyze the primary endpoint. The model included treatment, study center, visit, and visit-by-treatment interaction as fixed effects, subjects as a random effect, and baseline ADHD-RS-IV as a covariate. An unstructured correlation matrix was used to model the within-patient errors, and restricted maximum likelihood estimation was used. The Kenwood-Roger method was used for the denominator degrees of freedom. If the model failed to converge with an unstructured covariance matrix, first-order heterogeneous autoregressive, heterogeneous compound symmetric, and compound symmetric were to be tested. The treatment difference at Visit 5 was estimated using least squares means from the mixed effects repeated measures model. The treatment comparison was conducted as a 2-sided test at the 5% level of significance. The standard error and 95% confidence interval for the treatment difference was provided. The primary analysis will be repeated on the PP population using the MMRM analysis.

The BSFQ was analyzed using the mixed model repeated measures methods described for the primary efficacy variable with treatment, study center, visit, and visit by treatment interaction as main effects, BSFQ score at Baseline (Visit 2) as a covariate, and subject intercept as a random effect.

(b) (4)

A fixed-sequence testing procedure was used in this study to control the overall familywise error rate for the primary and key secondary endpoints. Hypothesis testing will be conducted in the following order:
1. ADHD-RS-IV total score at Visit 5
2. BSFQ at Visit 5

(b) (4)

Two sensitivity analyses of the primary analysis were pre-specified in SAP: a pattern mixture model analysis (PMM) and a repeat of the primary analysis with missing data

imputed via a last observation carried forward (LOCF) approach. FDA commented that the sensitivity analysis based on LOCF was not proper. The PMM analysis method assumes: intermittent missing data prior to discontinuation are MAR; the missing values for subjects withdrawing for lack of efficacy would be similar to the responses reported among placebo subjects at the time the subject withdrew; The missing values for subjects withdrawing for adverse events and/or tolerability issues would be similar to the ADHD-RS-IV total scores/BSFQ score reported at baseline. One hundred imputed datasets were generated for analysis.

3.2.2.3 HLD200-106

The ITT population was defined as all subjects who were randomized and had at least one SKAMP combined score post randomization available. The ITT population was the primary population for efficacy evaluation in this study.

The treatment difference between HLD200 and placebo from 8:00 am through 4:00 pm was estimated using LS means from an MMRM with treatment, session, and treatment-by-session interaction as fixed effects and subject as a random effect. Session was considered a classification variable. An unstructured correlation matrix was used to model the within-patient errors. Least squares mean differences between HLD200 and placebo were also calculated at each session (8:00 am, 9:00 am, 10:00 am, 12:00 pm, 2:00 pm, and 4:00 pm) using the same MMRM analysis applied in the primary analysis.

There were two key secondary efficacy analyses. BSFQ assessments at Visit 9/Day 50 were analyzed using an analysis of covariance (ANCOVA) model with treatment group as a fixed effect and the pre-randomization BSFQ score (i.e., Visit 8/Day 43) as the covariate. The second key secondary efficacy analysis examined the SKAMP combined score individually at 6:00 pm and 8:00 pm on Visit 9/Day 50. The analysis was performed using the same MMRM methods used in the primary analysis. LS mean differences and model-based t-tests (2-sided) were calculated for the 6:00 pm and 8:00 pm sessions.

FDA informed the Sponsor in an advice letter dated April 9, 2014 that "*A positive outcome on the primary variable (SKAMP combined score) must rely on statistically significant differences between drug and placebo on the SKAMP at a number of time points, tested in a pre-specified sequence and, to support an extended duration claim, spanning a time interval of at least 8 hours*." A pre-specified fixed-sequence testing procedure was applied to control the familywise Type I error rate in the primary and key secondary analyses and to determine the onset and duration of the treatment effect. The order of the fixed testing sequence was as follows: SKAMP combined score at 8 AM, 9 AM, 10AM, 12 PM, 2 PM, and 4 PM, BSFQ, SKAMP combined score at 6 PM and 8 PM.

No sensitivity analysis was performed because there is no discontinuation during double blind treatment phase.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 HLD200-107

A total of 161 subjects enrolled in the study, of whom 155 (96.3%) were randomized. One hundred fifty-four subjects (95.7% of enrolled subjects) completed the study (i.e., completed the phone call). Of the 7 subjects who discontinued prematurely from the study, 6 did so prior to randomization. The subject who discontinued from the study after randomization (Subject (b) (6) in the placebo group) was lost to follow-up. A summary of subject disposition of all enrolled subjects is presented in Table 2.

Table 2: Subject Disposition (All Enrolled Subjects) – HLD200-107

Disposition	Not Randomized N = 6 n (%)	HLD200 N = 83 n (%)	Placebo N = 72 n (%)	Total N = 161 n (%)
Enrolled	6 (100.0)	83 (100.0)	72 (100.0)	161 (100.0)
Randomized		83 (100.0)	72 (100.0)	155 (100.0)
Study completion				
Completed [1]		83 (100.0)	71 (98.6)	154 (95.7)
Discontinued	6 (100.0)	0	1 (1.4)	7 (4.3)
Reason for premature discontinuation				
Investigator decision	0	0	0	0
Subject or parent/guardian request	1 (16.7)	0	0	1 (14.3)
Adverse event	3 (50.0)	0	0	3 (42.9)
Failure to continue to meet inclusion/exclusion criteria	1 (16.7)	0	0	1 (14.3)
Lost to follow-up	0	0	1 (100.0)	1 (14.3)
Pregnancy	0	0	0	0
Other	1 (16.7)	0	0	1 (14.3)

The enrolled population was defined as all subjects who completed the Baseline Visit.
The reason for discontinuation denominator is the total number of subjects who discontinued from the study.
1 Completed the follow-up phone call.

Source: Sponsor's Table 3 on Page 47 of Clinical Study Report HLD200-107.

The ITT population consisted of 153 subjects (95.0% of enrolled subjects). Two randomized subjects were not included in the ITT population; they were Subjects (b) (6), who were randomized to HLD200 and placebo, respectively, but did not attend the laboratory classroom day (Visit 9).

Summary of the demographic and baseline physical characteristics is presented in Table 3 and Table 4. Over half the population was male (63.4%), white (66.7%), and non-Hispanic/Latino (66.0%). The median age was 10.0 years (range 6 to 12 years), and the median weight at the Baseline Visit was 32.40 kg (range 20.4 to 79.9 kg). Over half of the ITT population (56.9%) was in the age category of 8 to 10 years. The most common

ADHD subtype overall was combined, accounting for 88.9% of subjects. No subject was categorized as predominantly hyperactive-impulsive. The predominant CGI-S categories at baseline were moderately ill (32.0%) and markedly ill (42.5%). The median CGI-P total score was 23.0 (range 11 to 30) at baseline. The median ADHD-RS-IV total score was 42.0 (range 26 to 54) at baseline.

The demographic and baseline characteristics of the HLD200 and placebo groups of the ITT population were generally comparable with a few exceptions. Compared with the placebo group, the HLD200 group had a higher percentage of subjects aged 11 to 12 years (37.8% versus 23.9%) and subjects categorized as severely ill on the CGI-S (30.5% versus 18.3%). The HLD200 group also had a lower percentage of subjects with predominantly inattentive ADHD than the placebo group (6.1% versus 16.9%).

Table 3: Summary of Demographic Characteristics (ITT) – HLD200-107

Characteristic Category or Statistic	HLD200 N = 82	Placebo N = 71	Total N = 153
Gender – n (%)			
Male	55 (67.1)	42 (59.2)	97 (63.4)
Female	27 (32.9)	29 (40.8)	56 (36.6)
Age (years)			
N	82	71	153
Mean	9.7	9.3	9.5
SD	1.66	1.63	1.65
Median	10.0	9.0	10.0
Range (min, max)	(6, 12)	(6, 12)	(6, 12)
Age category – n (%)			
6-7 years	8 (9.8)	10 (14.1)	18 (11.8)
8-10 years	43 (52.4)	44 (62.0)	87 (56.9)
11-12 years	31 (37.8)	17 (23.9)	48 (31.4)
Race – n (%)			
White	54 (65.9)	48 (67.6)	102 (66.7)
Black/African American	22 (26.8)	19 (26.8)	41 (26.8)
Asian	0	0	0
Native Hawaiian/Pacific Islander	2 (2.4)	0	2 (1.3)
American Indian/Alaska Native	0	0	0
Other	4 (4.9)	4 (5.6)	8 (5.2)
Ethnicity – n (%)			
Hispanic/Latino	29 (35.4)	23 (32.4)	52 (34.0)
Non-Hispanic/Latino	53 (64.6)	48 (67.6)	101 (66.0)
Height at Visit 1/Screening (cm)			
N	82	71	153
Mean	138.25	138.36	138.30
SD	12.386	12.617	12.453
Median	137.05	137.20	137.10
Range (min, max)	(114.6, 181.0)	(114.3, 177.0)	(114.3, 181.0)
Weight at Visit 1/Screening (kg)			
N	82	71	153
Mean	34.42	33.69	34.08
SD	10.313	8.813	9.622
Median	31.70	32.00	31.80
Range (min, max)	(19.1, 78.4)	(21.1, 57.0)	(19.1, 78.4)

Source: Extracted from Sponsor's Table 5 on Page 51 of Clinical Study Report HLD200-107.

Table 4: Summary of Selected Characteristics (ITT) – HLD200-107

Characteristic Category or Statistic	HLD200 N = 82	Placebo N = 71	Total N = 153
ADHD type – n (%)			
Predominantly inattentive	5 (6.1)	12 (16.9)	17 (11.1)
Predominantly hyperactive-impulsive	0	0	0
Combined	77 (93.9)	59 (83.1)	136 (88.9)
CGI-S at Visit 2/Day 1/Baseline – n (%)			
Normal/not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	0	0
Moderately ill	23 (28.0)	26 (36.6)	49 (32.0)
Markedly ill	33 (40.2)	32 (45.1)	65 (42.5)
Severely ill	25 (30.5)	13 (18.3)	38 (24.8)
CGI-P (total score) at Visit 2/Day 1/Baseline			
N	82	71	153
Mean	23.2	21.4	22.4
SD	5.13	4.83	5.06
Median	24.5	22.0	23.0
Range (min, max)	(11, 30)	(12, 30)	(11, 30)
ADHD-RS-IV (total score) at Visit 2/Day 1/Baseline			
N	82	71	153
Mean	43.5	41.8	42.7
SD	6.58	5.85	6.29
Median	43.5	42.0	42.0
Range (min, max)	(26, 54)	(27, 54)	(26, 54)

Source: Extracted from Sponsor's Table 5 on Page 51 of Clinical Study Report HLD200-107.

3.2.3.2 HLD200-108

A total of 163 subjects enrolled in the study (completed the Baseline Visit). All 163 subjects were randomized to treatment with either HLD200 (82 subjects) or placebo (81 subjects). A summary of subject disposition of all enrolled subjects is presented in Table 5.

Table 5: Subject Disposition (All Enrolled Subjects) – HLD200-108

	HLD200 (N = 82) n (%)	Placebo (N = 81) n (%)	Total (N = 163) n (%)
Enrolled	82 (100.0)	81 (100.0)	163 (100.0)
Randomized	82 (100.0)	81 (100.0)	163 (100.0)
Analysis populations			
Safety	81 (98.8)	80 (98.8)	161 (98.8)
Intent-to-treat	81 (98.8)	80 (98.8)	161 (98.8)
Per protocol	67 (81.7)	67 (82.7)	134 (82.2)
Study completion			
Completed	73 (89.0)	65 (80.2)	138 (84.7)
Discontinued	9 (11.0)	16 (19.8)	25 (15.3)
Reason for premature discontinuation			
Pregnancy	0	0	0
Investigator decision	1 (11.1)	0	1 (4.0)
Subject or parent/guardian request	0	6 (37.5)	6 (24.0)
Adverse event	1 (11.1)	4 (25.0)	5 (20.0)
Failure to continue to meet inclusion/exclusion criteria	0	0	0
Lost to follow-up	3 (33.3)	2 (12.5)	5 (20.0)
Other	4 (44.4)	4 (25.0)	8 (32.0)

Source: Sponsor's Table 2 on Page 46 of the Clinical Study Report HLD200-108.

Among the 163 randomized subjects, Subjects (b) (6) from the placebo arm and (b) (6) from the HLD200 arm did not receive at least 1 dose of study drug. Therefore, they were excluded from the ITT population. The ITT population was composed of 161 subjects.

Summary of the demographic and baseline physical characteristics is presented in Table 6 and **Table 7**. The majority of subjects in the ITT population were male (70.2%), white (65.2%), and non-Hispanic/non-Latino (78.3%). The median age was 9.0 years (range 6 to 12 years), and almost half of all subjects (48.4%) were included in the age category of 8 to 10 years. The median height at the Screening Visit was 140.30 cm (range 114.0 to 170.5 cm), and the median weight at the Screening Visit was 34.00 kg (range 20.1 to 98.5 kg).

The proportion of subjects who were white was larger in the HLD200 group than in the placebo group (71.6% versus 58.8%), whereas the proportion who were black/African American was larger in the placebo group than in the HLD200 group (32.5% versus 23.5%). Subjects aged 11 to 12 years were more common in the HLD200 group than in the placebo group (38.3% versus 25.0%), whereas subjects aged 6 to 7 years were more common in the placebo group than in the HLD200 group (26.3% versus 13.6%). Demographic characteristics were otherwise comparable between the 2 treatment groups.

With respect to baseline disease characteristics, most subjects (90.1% overall) were categorized as having combined ADHD, with no subjects being categorized as having the predominantly hyperactive-Impulsive subtype. At the Baseline Visits, the majority of all subjects were assessed as markedly ill by CGI-S (65.8% at Baseline). The mean (SD) overall CGI-P total scores was 22.3 (4.83), respectively, and the mean ADHD-RS-IV scores was 43.3 (7.07), respectively. The HLD200 and placebo groups were comparable with respect to baseline disease characteristics.

Table 6: Summary of Demographic Characteristics (ITT) – HLD200-108

Characteristics / Statistic	HLD200 (N = 81)	Placebo (N = 80)	Total (N = 161)
Gender - n (%)			
Male	55 (67.9)	58 (72.5)	113 (70.2)
Female	26 (32.1)	22 (27.5)	48 (29.8)
Age (years)			
n	81	80	161
Mean	9.6	9.0	9.3
SD	1.79	1.73	1.79
Median	10.0	9.0	9.0
Range (min, max)	(6, 12)	(6, 12)	(6, 12)
Age categories - n (%)			
6-7 years	11 (13.6)	21 (26.3)	32 (19.9)
8-10 years	39 (48.1)	39 (48.8)	78 (48.4)
11-12 years	31 (38.3)	20 (25.0)	51 (31.7)
Race - n (%)			
White	58 (71.6)	47 (58.8)	105 (65.2)
Black/African American	19 (23.5)	26 (32.5)	45 (28.0)
Asian	1 (1.2)	0	1 (0.6)
Native Hawaiian/Pacific islander	0	0	0
American Indian/Alaska native	0	1 (1.3)	1 (0.6)
Other	3 (3.7)	6 (7.5)	9 (5.6)
Ethnicity - n (%)			
Hispanic/Latino	17 (21.0)	17 (21.3)	34 (21.1)
Non-Hispanic/Latino	63 (77.8)	63 (78.8)	126 (78.3)
Missing	1 (1.2)	0	1 (0.6)
Height at Visit 1/Screening (cm)			
n	81	80	161
Mean	141.31	138.27	139.80
SD	12.558	11.257	11.990
Median	143.50	137.70	140.30
Range (min, max)	(114.0, 170.5)	(114.3, 163.0)	(114.0, 170.5)
Weight at Visit 1/Screening (kg)			
n	81	80	161
Mean	37.67	35.97	36.82
SD	13.770	11.918	12.871
Median	34.00	32.85	34.00
Range (min, max)	(20.1, 98.5)	(20.4, 69.9)	(20.1, 98.5)

Source: Extracted from Sponsor's Table 4 on Page 49 of the Clinical Study Report HLD200-108.

Table 7: Summary of Selected Other Characteristics (ITT) – HLD200-108

Characteristics / Statistic	HLD200 (N = 81)	Placebo (N = 80)	Total (N = 161)
ADHD type - n (%)			
Predominantly Inattentive	6 (7.4)	10 (12.5)	16 (9.9)
Predominantly Hyperactive-Impulsive	0	0	0
Combined	75 (92.6)	70 (87.5)	145 (90.1)
CGI-S at Visit 2/Day 1/Baseline – n (%)			
Normal/not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	0	0
Moderately ill	18 (22.2)	11 (13.8)	29 (18.0)
Markedly ill	51 (63.0)	55 (68.8)	106 (65.8)
Severely ill	12 (14.8)	13 (16.3)	25 (15.5)
Amongst the most extremely ill subjects	0	1 (1.3)	1 (0.6)
CGI-P (total score) at Visit 2/Day 1/Baseline			
n	81	80	161
Mean	22.8	21.8	22.3
SD	4.84	4.79	4.83
Median	23.0	23.0	23.0
Range (min, max)	(11, 30)	(11, 30)	(11, 30)
ADHD-RS-IV (total score) at Visit 2/Day 1/Baseline			
n	81	80	161
Mean	43.1	43.5	43.3
SD	7.33	6.84	7.07
Median	44.0	43.0	44.0
Range (min, max)	(26, 54)	(26, 54)	(26, 54)

Source: Extracted from Sponsor's Table 4 on Page 49 of the Clinical Study Report HLD200-108.

3.2.3.3 HLD200-106

A total of 43 subjects were enrolled in the study, all of whom were randomized (22 HLD200, 21 placebo) and included in the ITT populations. All 43 subjects completed the entire study; there were no discontinuations.

Demographic and baseline characteristics of the ITT population are summarized in Table 8 and are comparable between the 2 treatment groups. There were slightly more male than female subjects enrolled in the study (53.5% male, 46.5% female). The median age is 10

years old. Most subjects were white (79.1%) and no Hispanic/Latino (74.4%). Most subjects were ADHD type of Combined (74.4%).

Table 8: Summary of Demographic Characteristics (ITT) – HLD200-106

	HLD200 (N = 22)	Placebo (N = 21)	Total (N = 43)
Gender			
Male	11 (50.0%)	12 (57.1%)	23 (53.5%)
Female	11 (50.0%)	9 (42.9%)	20 (46.5%)
Age (years)			
Median	10	10	10
Min, Max	7, 12	6, 12	6, 12
Age group (years)			
Age <8	3 (13.6%)	4 (19.0%)	7 (16.3%)
8≤ Age ≤10	11 (50.0%)	11 (52.4%)	22 (51.2%)
Age >10	8 (36.4%)	6 (28.6%)	14 (32.6%)
Race			
Native Aboriginal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	2 (9.1%)	0 (0.0%)	2 (4.7%)
White	18 (81.8%)	16 (76.2%)	34 (79.1%)
Black	1 (4.5%)	3 (14.3%)	4 (9.3%)
Asian and Black	1 (4.5%)	0 (0.0%)	1 (2.3%)
White and Black	0 (0.0%)	1 (4.8%)	1 (2.3%)
Other	0 (0.0%)	1 (4.8%)	1 (2.3%)
Ethnicity: Hispanic/Latino			
Yes	7 (31.8%)	4 (19.0%)	11 (25.6%)
No	15 (68.2%)	17 (81.0%)	32 (74.4%)
ADHD subtype			
Hyperactive-Impulsive	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inattentive	5 (22.7%)	6 (28.6%)	11 (25.6%)
Combined	17 (77.3%)	15 (71.4%)	32 (74.4%)

Source: Sponsor's Table 4 on Page 46 of the Clinical Study Report of HLD200-106.

3.2.4 Results and Conclusions

3.2.4.1 HLD200-107

Sponsor's Results and Conclusions:

Based on the primary analysis results (Table 9) for the pre-specified primary endpoint, the Sponsor concluded that the difference between treatment groups for average SKAMP CS during the 12 hours period from 8:00 am to 8:00 pm was statistically significant, favoring

HLE200 (p = 0.010). The onset of the primary efficacy is 9:00 am (p = 0.009). The duration is from 9:00 am to 4:00 pm. Figure 1 and Figure 2 graphically depict the LS mean values and LS mean treatment group differences, respectively, for SKAMP CS over time at Visit 9. The key secondary endpoint, the rating of morning behavior based on PREMB-R AM was also met (p < 0.001). The primary analysis result for the key secondary endpoint is summarized in Table 10.

Table 9: Summary of SKAMP CS Results – HLD200-107

Visit 9 - Day 50 (Double-blind Test) Time Point/Endpoint	HLD200 LS Mean (SE)	Placebo LS Mean (SE)	Treatment Difference (HLD200 - Placebo) LS Mean (SE)	P-value
Average over all post-dose time points[1]	14.8 (1.03)	18.4 (1.07)	-3.6 (1.40)	0.010
8:00 am	11.0 (1.03)	12.1 (1.07)	-1.1 (1.40)	0.433
9:00 am	12.0 (1.13)	16.1 (1.18)	-4.1 (1.55)	0.009
10:00 am	12.5 (1.16)	17.8 (1.21)	-5.3 (1.60)	0.001
12:00 pm	11.8 (1.16)	17.2 (1.21)	-5.5 (1.61)	<0.001
2:00 pm	13.6 (1.20)	19.3 (1.25)	-5.6 (1.66)	<0.001
4:00 pm	15.4 (1.19)	20.6 (1.24)	-5.1 (1.64)	0.002
6:00 pm	19.1 (1.27)	21.5 (1.34)	-2.3 (1.78)	0.190
7:00 pm	18.3 (1.31)	21.0 (1.38)	-2.8 (1.83)	0.133
8:00 pm	19.1 (1.33)	20.1 (1.40)	-0.9 (1.87)	0.624

ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP CS = Swanson, Kotkin, Agler, M-Flynn, and Pelham combined score

1 The primary efficacy outcome was the model-adjusted average of all post-dose SKAMP CS values from 8:00 am to 8:00 pm as measured on the laboratory classroom day (Visit 9). The SKAMP CS was obtained by summing items 1-13, in which each item was rated on a 7-point scale (0 = normal to 6 = maximal impairment).

Least squares means, SEs, and p-values were generated using a mixed model repeated-measures analysis, with treatment (HLD200/placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect, with change from predose SKAMP CS as the dependent variable.

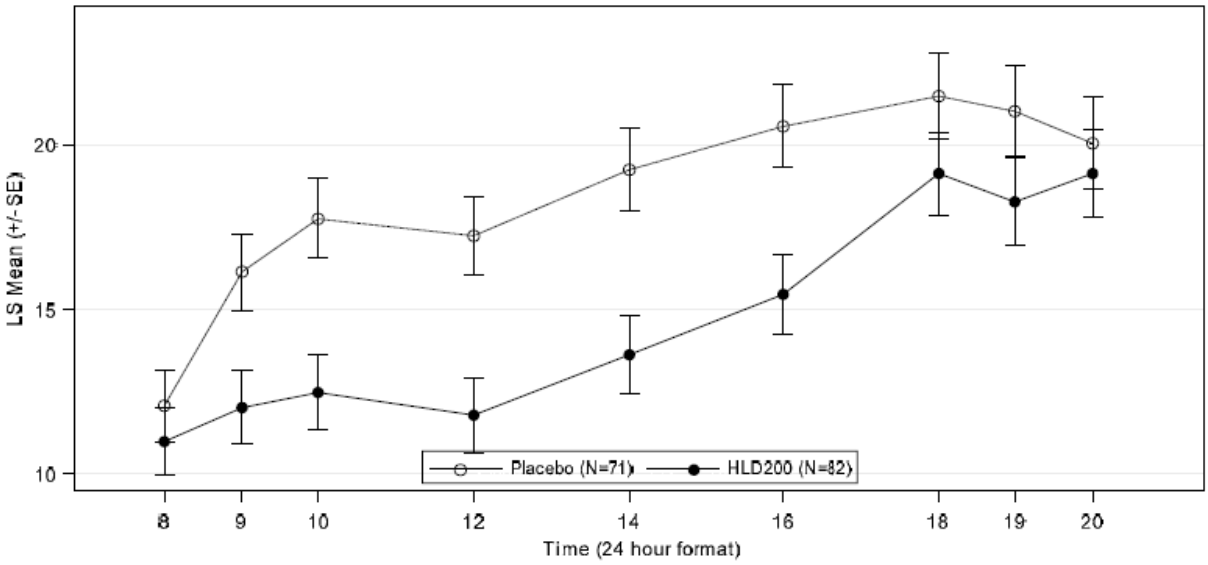
Source: Sponsor's Table 9 on Page 62 of Clinical Study Report HLD200-107.

Table 10: Summary of PREMB-R AM Results – HLD200-107

Visit Statistic	HLD200 N = 82 n (%)	Placebo N = 71 n (%)	Treatment Difference (HLD200 – Placebo)
Visit 9 - Day 50 (Double-blind Test)			
N	82	71	
Mean	0.9	3.5	
SD	1.29	2.76	
Median	0.0	3.0	
Range (min, max)	(0, 5)	(0, 9)	
LS mean (SE)	0.7 (0.25)	3.3 (0.25)	-2.6 (0.33)
95% CI	(0.2, 1.2)	(2.8, 3.8)	(-3.2, -1.9)
P-value			<0.001

Source: Sponsor's Table 8 on Page 59 of the Clinical Study Report HLD200-107.

Figure 1: LS Mean SKAMP CS over Time at Visit 9 – HLD200-107



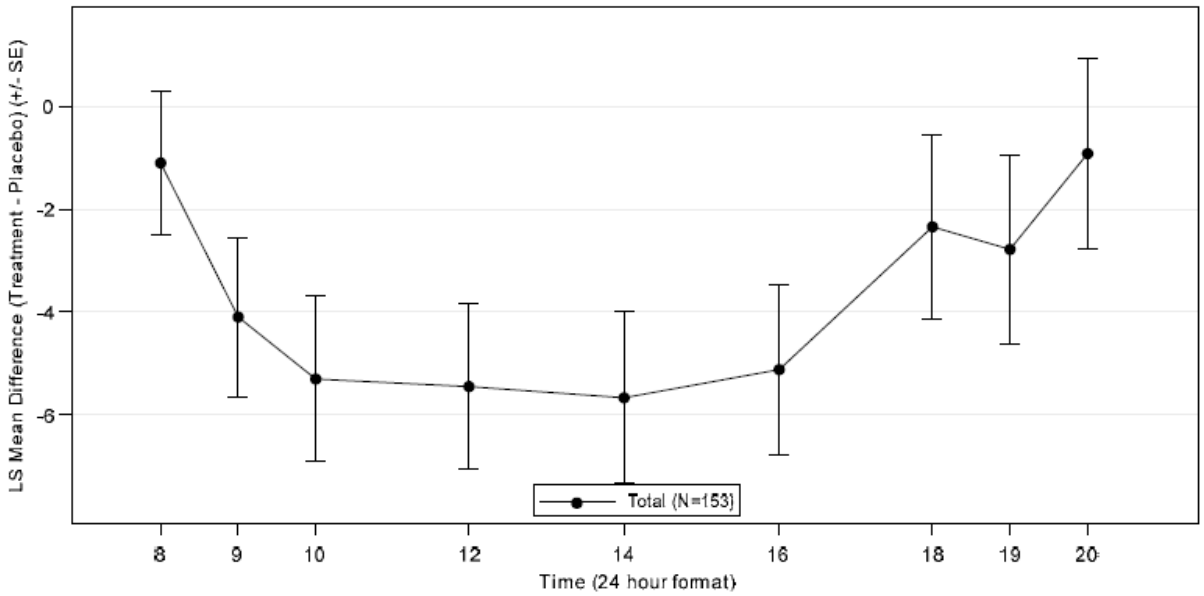
ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP CS = Swanson, Kotkin, Agler, M-Flynn, and Pelham combined score

The SKAMP CS was obtained by summing items 1-13, with each item being rated on a 7-point scale (0 = normal to 6 = maximal impairment).

Treatment comparisons were assessed using a mixed model repeated-measures analysis, with treatment (HLD200/placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect.

Source: Sponsor's Figure 1 on Page 61 of the Clinical Study Report HLD200-107.

Figure 2: LS Mean Difference in SKAMP CS over Time at Visit 9 – HLD200-107



ITT = intent-to-treat; LS = least squares; SE = standard error; SKAMP CS = Swanson, Kotkin, Agler, M-Flynn, and Pelham combined score

The SKAMP CS was obtained by summing items 1-13, with each item being rated on a 7-point scale (0 = normal to 6 = maximal impairment).

Treatment comparisons were assessed using a mixed model repeated-measures analysis, with treatment (HLD200/placebo), study center, time point, and time point-by-treatment interaction as main effects, and subject intercept as a random effect.

Source: Sponsor's Figure 2 on Page 61 of the Clinical Study Report HLD200-107.

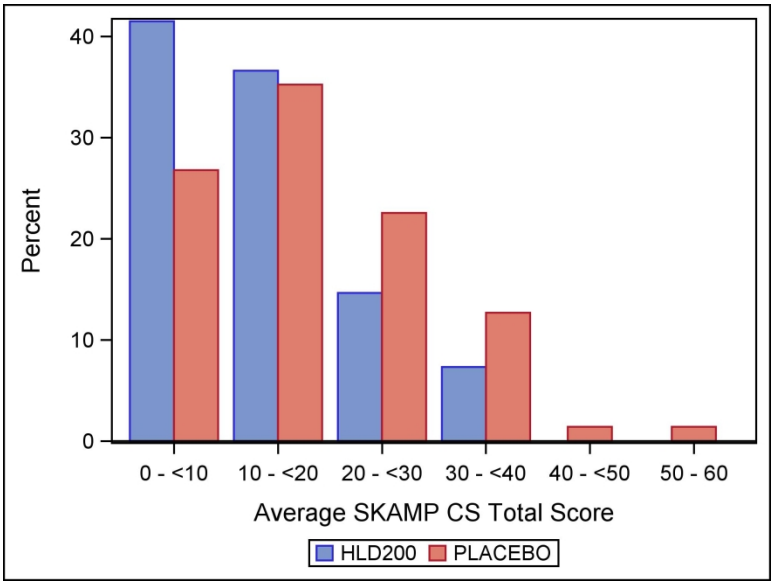
Only 1 of the 155 randomized patients discontinued due to loss of follow up. Therefore, no pre-specified sensitivity analysis was performed. During study conduct, it was learned that up to 15 of the 17 subjects enrolled in Cohort 2 at Site 15 were assigned multiple randomization numbers. Sensitivity analyses of the primary efficacy endpoint and the key secondary endpoint excluding Cohort 2 at Site 15 from the ITT population were performed. The primary efficacy endpoint and the key secondary endpoint were met for the sensitivity analyses. A statistically significant improvement in the overall SKAMP CS from 8:00 am through 8:00 pm at Visit 9 was observed in the HLD200 group relative to the placebo group (LS means [SE]: 14.6 [1.11] HLD200 versus 18.6 [1.09] placebo, $p = 0.008$). The improvement in the PREMB-R AM total score at Visit 9 for the HLD200 group relative to the placebo group was also statistically significant ($p < 0.001$).

Reviewer's Results and Conclusions:

Figure 3 and Figure 4 display the histogram of the primary endpoint and the key secondary endpoint by treatment, respectively. Figure 5 and Figure 6 display the cumulative

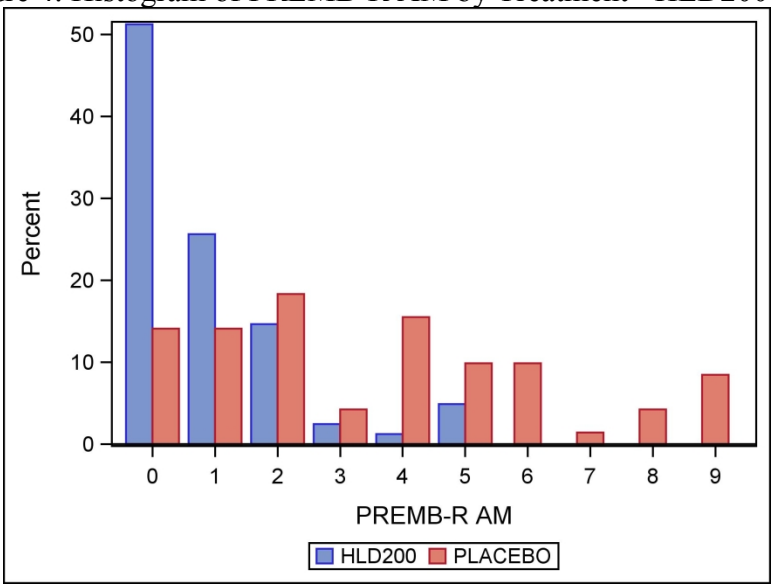
distribution function (CDF) of the primary endpoint and the key secondary endpoint by treatment, respectively.

Figure 3: Histogram of Average SKAMP CS Total Score by Treatment - HLD200-107



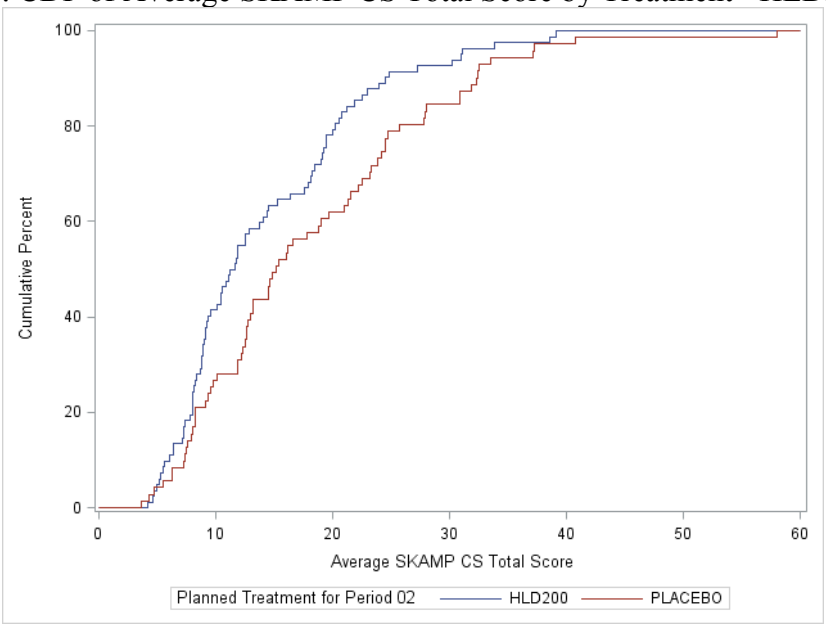
Source: This reviewer.
Note: One patient from the Placebo group with missing data due to loss of follow up is excluded.

Figure 4: Histogram of PREMB-R AM by Treatment - HLD200-107



Source: This reviewer.
Note: One patient from the Placebo group with missing data due to loss of follow up is excluded.

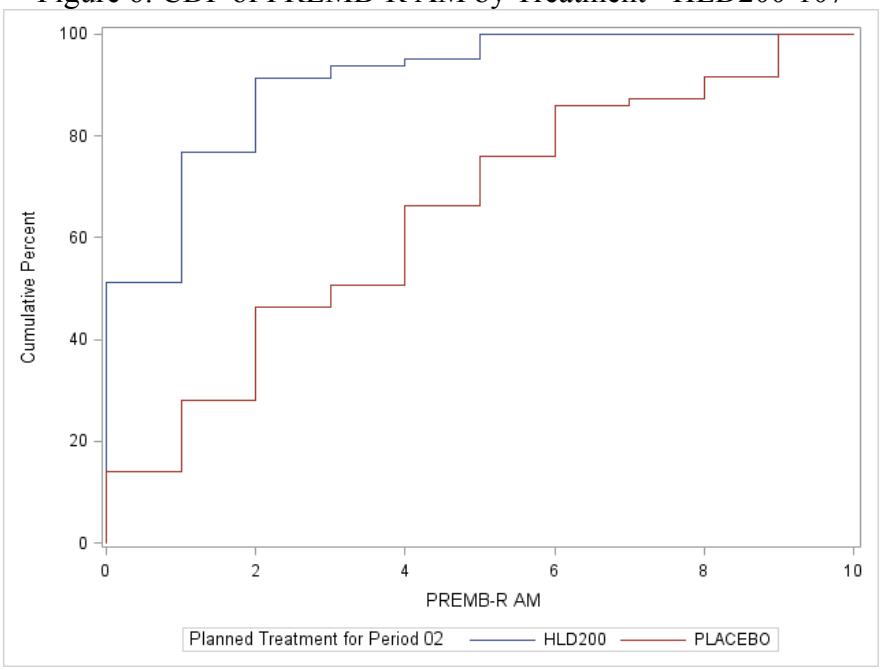
Figure 5: CDF of Average SKAMP CS Total Score by Treatment - HLD200-107



Source: This reviewer.

Note: One patient from the Placebo group with missing data due to loss of follow up is excluded.

Figure 6: CDF of PREMB-R AM by Treatment - HLD200-107

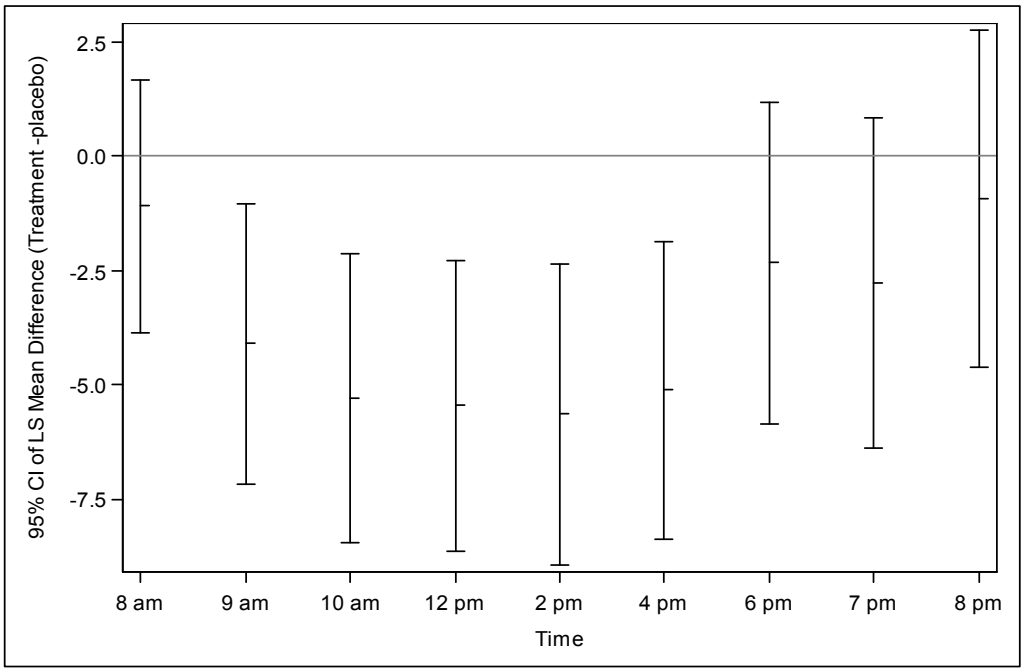


Source: This reviewer.

Note: One patient from the Placebo group with missing data due to loss of follow up is excluded.

The reviewer repeated the primary analysis and obtained the same results as the Sponsor (p= 0.001). That is, HLD200 is statistically significantly better than the placebo in terms of average SKAMP CS during the 12 hour period from 8:00 am to 8:00 pm. Figure 7 graphically depicts the 95% CI of LS mean of treatment group differences in SKAMP CS during the 12 hour period of Visit 9. From Figure 7, the onset is 9:00 am and the duration is from 9:00 am to 4:00 pm. The key secondary endpoint, the rating of morning behavior based on PREMB-R AM was also met ($p < 0.001$).

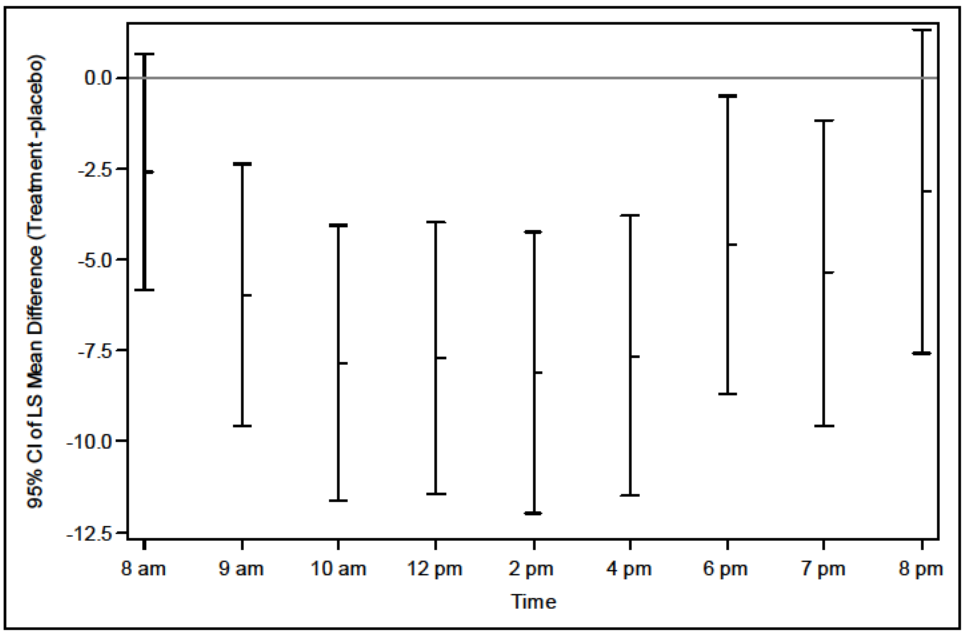
Figure 7: 95% CI of LS Mean Treatment Difference in SKAMP CS Over Time at Visit 9 – HLD200-107



Source: This reviewer. This figure plots 95% CI while Figure 2 plots 1 SE around the LS mean.

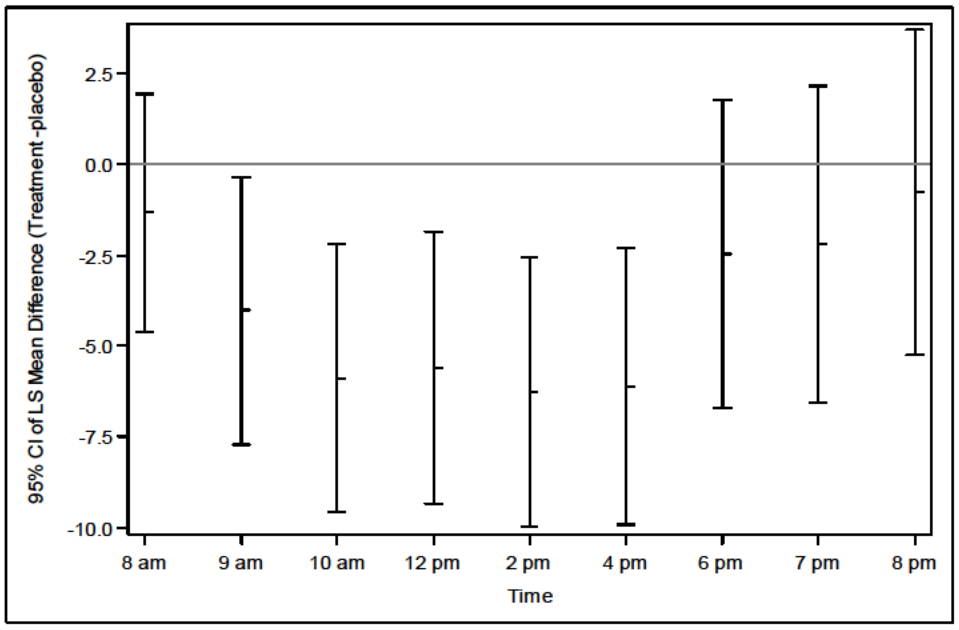
This reviewer agreed that no pre-specified sensitivity analysis was needed since only 1 of 155 randomized subjects discontinued. This reviewer repeated the primary analysis on the primary efficacy endpoint and the key secondary endpoint excluding Site 10, or Site 15, or Sites 10 and 15 from the ITT population. The results on the primary endpoint are summarized in Figure 8 to Figure 10. Excluding Site 15 does not change any results. However, excluding Site 10 only will increase the duration of the effect from 7 hours (9 AM to 4 PM) to 10 hours (9 AM to 7 PM). Excluding both Sites 10 and 15 will increase the duration of effect from 7 hours to 9 hours (9AM to 6 PM). For the key secondary endpoint, excluding either of the Sites or both sites yields the similar results with $p < 0.0001$.

Figure 8: 95% CI of LS Mean Treatment Difference in SKAMP CS Over Time at Visit 9 – HLD200-107 (Excluding Site 10)



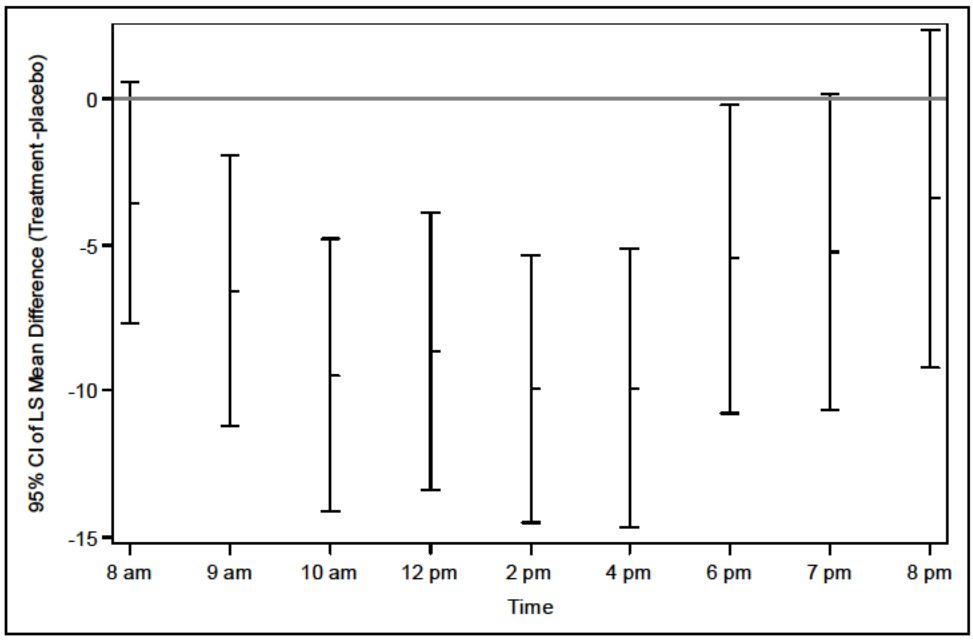
Source: This reviewer.

Figure 9: 95% CI of LS Mean Treatment Difference in SKAMP CS Over Time at Visit 9 – HLD200-107 (Excluding Site 15)



Source: This reviewer.

Figure 10: 95% CI of LS Mean Treatment Difference in SKAMP CS Over Time at Visit 9 – HLD200-107 (Excluding Sites 10 and 15)



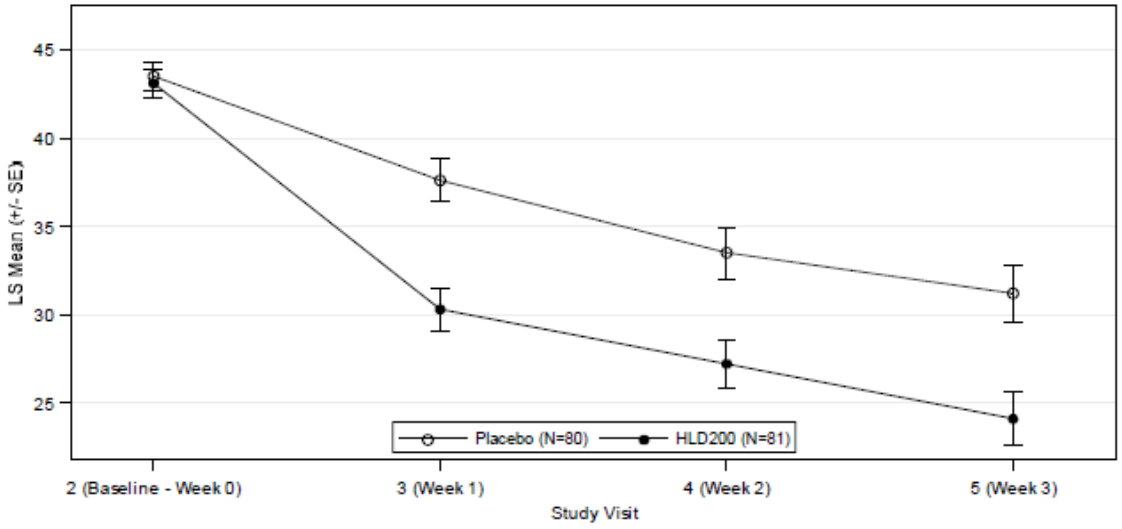
Source: This reviewer.

3.2.4.2 HLD200-108

Sponsor's Results and Conclusions:

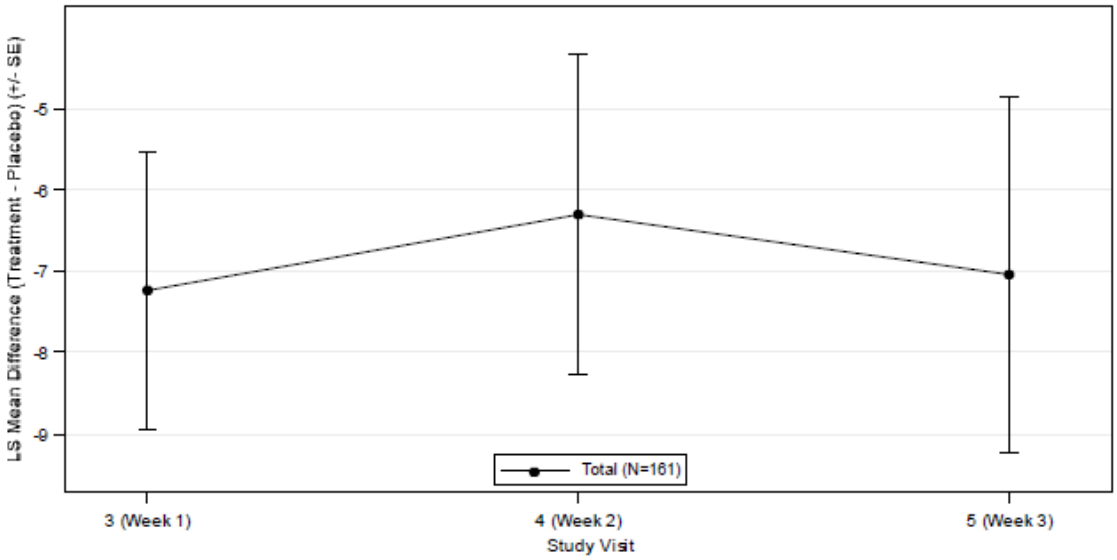
The primary efficacy endpoint was met. At Visit 5 (Week 3), the LS mean (SE) ADHD-RS-IV total score in the HLD200 group was 24.1 (1.50) compared with 31.2 (1.60) in the placebo group. The LS mean (SE) treatment group difference, -7.0 (2.19), was statistically significant (95% CI -11.4, -2.7; p = 0.002). Figure 11 and Figure 12 graphically depict the LS mean values and LS mean treatment group differences, respectively, for ADHD-RS-IV during the double blind treatment phase.

Figure 11: LS Mean ADHD-RS-IV Total Score over Time – HLD200-108



Source: Sponsor's Figure 1 on Page 56 of the Clinical Study Report HLD200-108.

Figure 12: LS Mean Treatment Difference in ADHD-RS-IV Total Score over Time – HLD200-108



Source: Sponsor's Figure 2 on Page 57 of the Clinical Study Report HLD200-108.

FDA only agreed on one of the key secondary efficacy endpoint, the BSFQ total score. Despite of FDA's disapproval of the other two key secondary endpoints, the Sponsor presented analysis results on these two endpoints as key secondary endpoints.

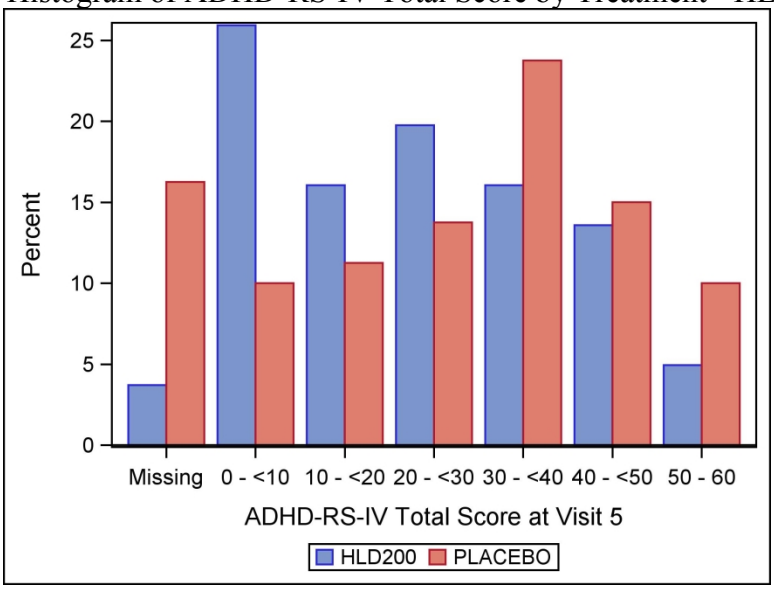
(b) (4)

(b) (4)

Reviewer's Results and Conclusions:

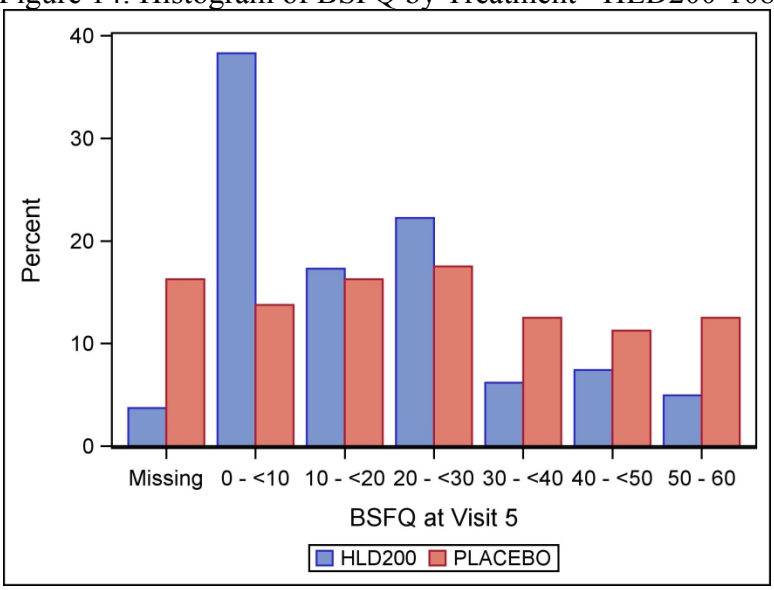
Figure 13 to Figure 16 display the histograms of the primary endpoint and the key secondary endpoints by treatment, respectively.

Figure 13: Histogram of ADHD-RS-IV Total Score by Treatment - HLD200-108



Source: This reviewer.

Figure 14: Histogram of BSFQ by Treatment - HLD200-108



Source: This reviewer.

(b) (4)

The reviewer repeated the primary analysis obtained the same results as the Sponsor (LS mean treatment group difference = -7.0 with p= 0.002). Subjects in HLD200 group have statistically significantly better ADHD-RS-IV total score than those in the placebo group. (b) (4) met statistical significance: p<0.001 for BSFQ (b) (4) Both pre-specified sensitivity analyses of the primary endpoint show HLD200 is statistically significantly better than placebo.

To assess the impact of the dropouts on the primary analysis results, this reviewer conducted sensitivity analyses using two different imputing methods on those discontinued in treatment period: 1). missing data are imputed by the worst observed score at Visit 5. 2). missing data are imputed by the mean score at Visit 5 from the placebo arm. Both imputations give the similar results as the primary analysis. The results are summarized in Table 11.

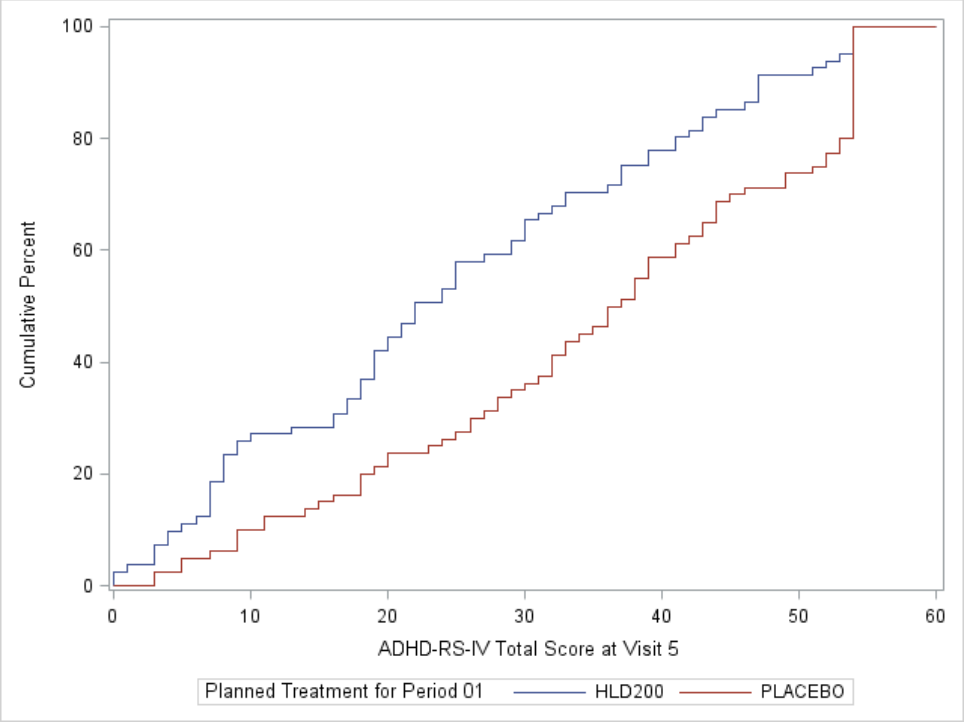
Table 11: Summary of Sensitivity Analysis Results Based on Imputing by the Worst Score or the Placebo Mean - HLD200-108

		HLD200 LS Mean (SE)	Placebo LS Mean (SE)	LS Mean Diff (SE) (HLD200-Placebo)
Imputed by the Worst Score	ADHD-RS-V	24.9 (1.63)	34.8 (1.64)	-9.9(2.31) (p<0.0001)
	BSFQ	20.2 (1.94)	33.9 (1.95)	-13.6 (2.74) (p<0.0001)
	PREMB-R AM	2.1 (0.27)	3.6 (0.27)	-1.5 (0.38) (p=0.0001)
	PREMB-R PM	9.4 (0.64)	12.2 (0.66)	-2.8 (0.91) (p=0.002)
Imputed by Placebo Mean	ADHD-RS-V	24.0 (1.42)	31.1 (1.43)	-7.0 (2.01) (p=0.0006)
	BSFQ	19.0 (1.59)	28.7 (1.60)	-9.7 (2.24) (p<0.0001)
	PREMB-R AM	2.1 (0.27)	3.6 (0.27)	-1.5 (0.38) (p=0.0001)
	PREMB-R PM	9.4 (0.64)	12.2 (0.66)	-2.8 (0.91) (p=0.002)

Source: This reviewer.

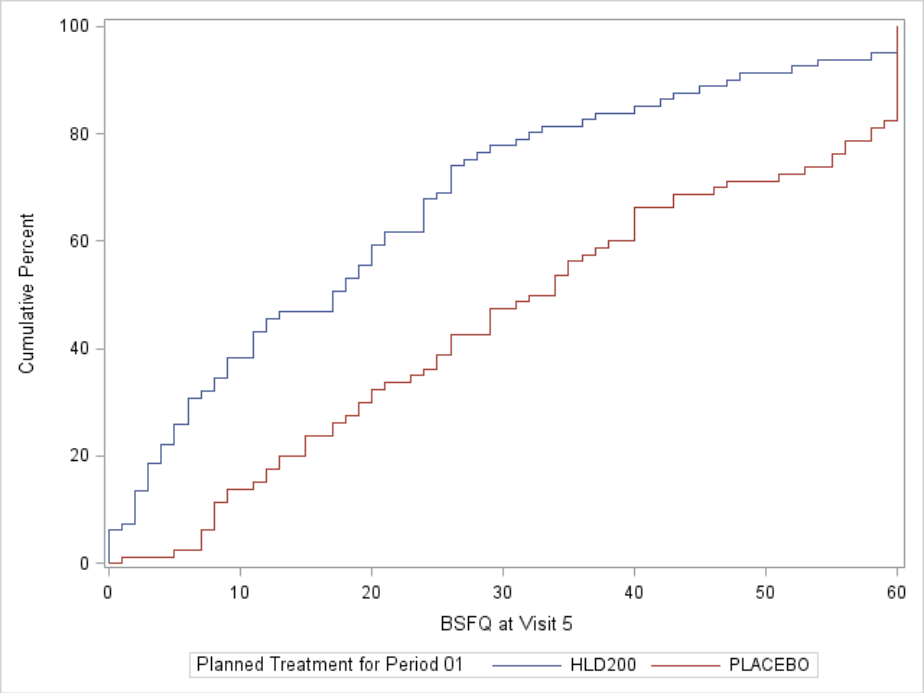
This reviewer also plotted the CDF of the primary endpoint and key secondary endpoints with the above two imputation methods in Figure 17 to Figure 24.

Figure 17: CDF of ADHD-RS-IV Total Score by Treatment (Imputed by the Worst Score) – HLD200-108



Source: This reviewer.

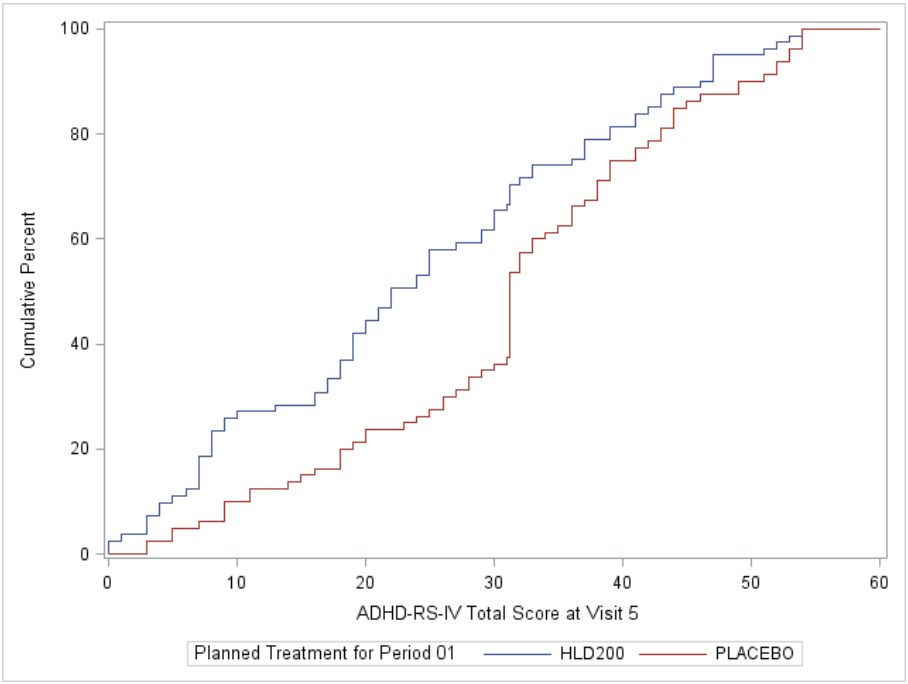
Figure 18: CDF of BSFQ by Treatment (Imputed by the Worst Score)- HLD200-108



Source: This reviewer.

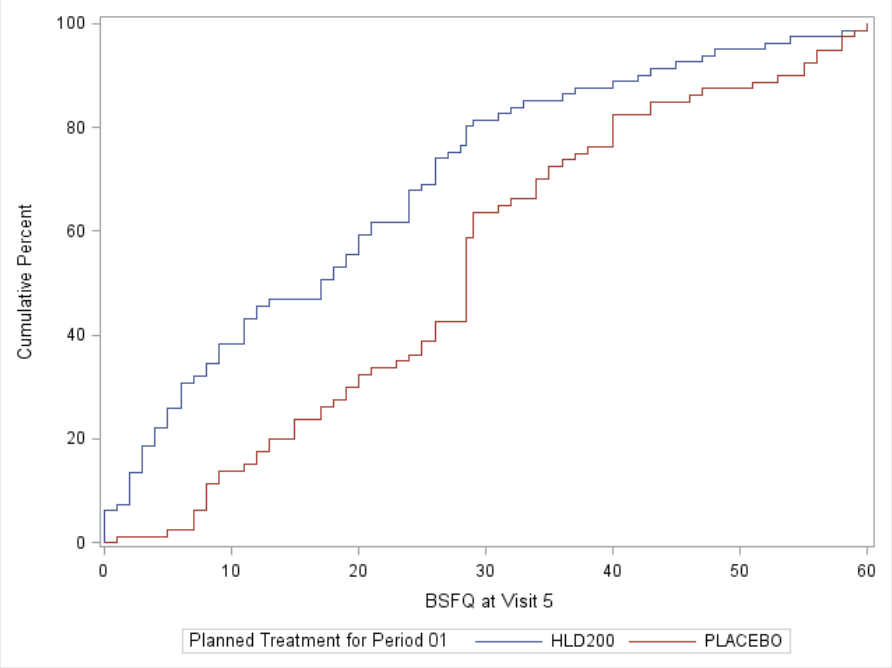
(b) (4)

Figure 21: CDF of ADHD-RS-IV Total Score by Treatment (Imputed by Placebo Mean) – HLD200-108



Source: This reviewer.

Figure 22: CDF of BSFQ by Treatment (Imputed by Placebo Mean) – HLD200-108



Source: This reviewer.

(b) (4)

3.2.4.3 HLD200-106

Sponsor's Results and Conclusions:

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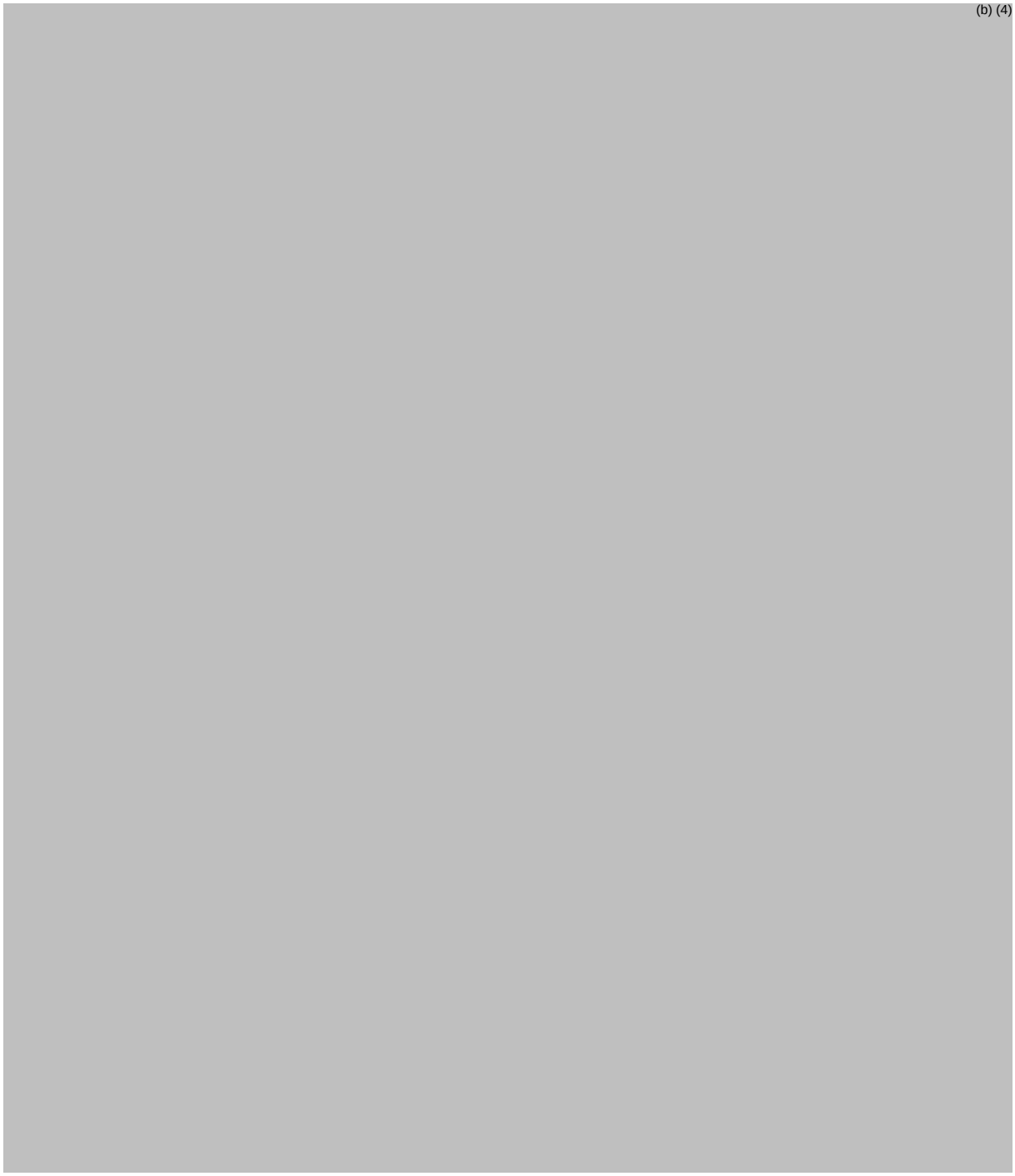

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS OF STUDY

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses,

those p-values are not presented here. Trial HLD200-106 [redacted] (b) (4) no subgroup analyses were performed.

4.1 Gender, Race, Age Group and Region

For all the studies, the patients age range from 6 to 12 years old. All the studies centers are in the US. Therefore, no subgroup analysis was performed on age group and region. Most of the patients are white. The other races were combined into one race "Non-White" for the subgroup analysis on race. The results are presented in Table 13 to Table 18. The Non-White group, which has about 33% of the subjects, has a different treatment direction (3.2) from that of the White group (-6.7) on the primary endpoint of Trial HLD 200-107. However, across two trials and 5 other primary and key secondary endpoints, the Non-White group has consistent results with the White group. Therefore, the one inconsistent result of Non-White may be due to chance.

HLD200-107

Table 13: Subgroup Analysis Results on Average SKAMP CS Total Score- HLD200-107

	Subgroup	HLD200 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
Overall		14.8 (1.03) (82)	18.4 (1.07) (71)	-3.6 (1.40) (p=0.01)
Gender	Female	11.4 (1.40) (27)	15.6 (1.37) (29)	-4.2 (1.88)
	Male	16.9 (1.32) (55)	20.3 (1.44) (42)	-3.4 (1.88)
Race	White	12.7 (1.25) (54)	19.5 (1.21) (48)	-6.7 (1.63)
	Non-White	19.0 (1.99) (28)	15.8 (2.28) (23)	3.2 (2.74)

Source: This reviewer.

Table 14: Subgroup Analysis Results on PREMB-R AM - HLD200-107

	Subgroup	HLD200 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
Overall		0.7 (0.25) (82)	3.3 (0.25) (71)	-2.6 (0.33) (p<0.0001)
Gender	Female	0.2 (0.49) (27)	3.8 (0.49) (29)	-3.5 (0.64)
	Male	1.0 (0.28) (55)	2.8 (0.30) (42)	-1.7 (0.39)
Race	White	0.7 (0.29) (54)	2.7 (0.28) (48)	-1.9 (0.38)
	Non-White	0.7 (0.48) (28)	4.6 (0.56) (23)	-3.9 (0.64)

Source: This reviewer.

HLD200-108

Table 15: Subgroup Analysis Results ADHD-RS-IV Total Score - HLD200-108

	Subgroups	HLD200 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
Overall		24.1 (1.50) (81)	31.2 (1.60) (80)	-7.0 (2.19) (p=0.0016)
Gender	Female	23.2 (3.01) (26)	30.7 (3.29) (22)	-7.6 (4.42)
	Male	25.6 (1.85) (55)	31.1 (1.87) (58)	-5.5 (2.62)
Race	White	23.2 (1.73) (58)	31.7 (2.04) (47)	-8.5 (2.62)
	Non-White	28.5 (3.39) (23)	31.5 (2.82) (33)	-3.0 (4.09)

Source: This reviewer.

Table 16: Subgroup Analysis Results on BSFQ - HLD200-108

	Subgroups	HLD200 LS Mean (SE) (n)	Placebo LS Mean (SE) (n)	LS Mean Diff (SE) (HLD200-Placebo)
Overall		18.7 (1.63) (81)	28.4 (1.73) (80)	-9.7 (2.37) (p<0.0001)
Gender	Female	16.0 (2.84) (26)	26.3 (2.95) (22)	-10.3 (4.06)
	Male	20.9 (2.12) (55)	29.3 (2.13) (58)	-8.4 (3.00)
Race	White	17.5 (1.90)	28.9 (2.24)	-11.4 (2.87)
	Non-White	25.4 (3.63)	29.9 (2.96)	-4.5 (4.23)

Source: This reviewer.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The duration of the effect of HLD 200 is demonstrated from 9 AM to 4 PM, which is 7 hours. We would like to defer to the clinical team to decide if the 7 hour duration is adequate.

5.2 Collective Evidence

The primary efficacy objective of Trial HLD 200-107 and Trial HLD 200-108 were met. Based on results from HLD 200-107, HLD200 is statistically significantly better than the placebo in terms of average SKAMP CS on the classroom day (from 8:00 am to 8:00 pm). The onset of effect is 9:00 am and the duration is from 9:00 am to 4:00 pm. The key secondary endpoint, the rating of morning behavior based on PREMB-R AM was also met ($p < 0.001$). Based on results from HLD 200-108, Subjects in HLD200 group have statistically significantly better ADHD-RS-IV total score than those in the placebo group. (b) (4) met statistical significance: BSFQ, (b) (4) (b) (4) expressed the concern about the acceptability of PREMB-R AM as a key secondary endpoint for Trial HLD200-107.

5.3 Conclusions and Recommendations

This reviewer concludes, based on statistical evidence found in the efficacy data of Trial HLD 200-107 (doses ranging from 20 to 100 mg/day) and HLD 200-108 (doses ranging from 40 to 80 mg/day) that prior evening treatment with HLD200 at doses ranging from 20 to 100 mg/day is effective in improving control of ADHD symptoms from 9 AM to 4 PM in children aged 6-12 years old with ADHD. There is a statistically significant improvement in the ADHD Rating Scale based on ADHD-RS-IV.

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

/s/

JINGLIN ZHONG
06/08/2017

PEILING YANG
06/13/2017

SUE JANE WANG
06/13/2017
concur with review