CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

STATISTICAL REVIEW(S)

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Statistical Review and Evaluation

NDA#:	21-284
Sponsor:	Novartis
Drug:	Ritalin — —— release capsule
Indication:	ADHD
Date Received at HFD-120:	November 30, 2000
Biometrics reviewer:	Kallappa M. Koti
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Contents

Figure 2.1: Evaluation Schedule

PHASE	Pre-randomization			Double-blind Treatment		Open-label Extension
PERIOD	Screening	Titration	Washout			
WEEKS	≤ 6 weeks	2-4 weeks	1 week	2 weeks		12 weeks
DOSING		Start Ritalin	Start Placebo	Start Double-blind treatment		Continue Ritalin
STUDY VISIT	Visit 1	Visit 2	Visit 3 / Baseline	Visit 4	Visit 5*	Extension Visit
Informed consent	X					
Background information	X					
Inclusion/Exclusion criteria	X					
Randomization			X			
Concomitant therapy	X	X	X	X	X	X
Adverse events		X	X	X	X	X
CGI-S	X	X	X	X	X	
CGI-I				X	X	
CADS-T & CADS-P		X	X	X	X	
Dispense study drug	X	X	X	X	X	
Study drug adm. (daily)	X	X	X	X	X	X
Dose adjustment		X		X	X	
Return unused medicine		X	X	X	X	X
Phase completion					X	X

* Study Phase Completion

Subjects were all male and female aged 6 to 12 years, meeting DSM-IV criteria for ADHD (any type). Subjects were functioning at age-appropriate levels and were attending school in a classroom setting, having the same teacher for the duration of the study. Subjects were either already treated with methylphenidate (MPH) or *de novo* subjects. Subjects with any chronic, progressive or severe somatic or psychiatric disorders requiring drug treatment other than MPH were excluded, as were patients judged by the investigator as likely to be non-compliant. The numbers are:

Table 2.1: Subjects randomized and analyzed

	Ritalin	**Placebo**	All
Number of subjects randomized	66	71	137
Intent-to-treat population- efficacy	63	71	134
All completed subjects- efficacy	60	69	129

Demographic and background characteristics of the randomized subjects in Protocol 07 are summarized in the following table.

Table 2.2: Subject demographics and baseline characteristics
(All randomized subjects)

Demographic Variable	Ritalin ~~—~~ N = 65	Placebo N = 71
Sex		
Male	52 (80.0%)	52 (73.2%)
Female	13 (20.0%)	19 (26.8%)
Race		
Caucasian	55 (84.6%)	62 (87.3%)
Black	3 (4.6%)	2 (2.8%)
Oriental	1 (1.5%)	1 (1.4%)
Other	6 (9.2%)	6 (8.5%)
Age (years)		
N	65	71
Mean	9.1	8.8
SD	1.7	1.9
Weight (kg)		
N	65	71
Mean	34.8	34.5
SD	11.0	11.1
Height (cm)		
N	65	71
Mean	137.4	137.1
SD	11.1	12.2
DISC DSM-IV diagnosis		
Inattentive	18 (27.7%)	8 (11.3%)
Hyperative-impulsive	2 (3.1%)	0 (0.0%)
Combined type	42 (64.6%)	60 (84.5%)
No DISC diagnosis	3 (4.6%)	3 (4.2%)

This table includes two subjects (randomized to Ritalin- ~~—~~) who had no post-baseline measurements on the primary efficacy variable (CADS-T) and were, therefore, not includes in the ITT population.

Ritalin ~~—~~ capsules were provided in four dose strengths: 10 mg, 20 mg, 30 mg and 40 mg. Ritalin-~~—~~ or matching placebo was administered orally, once daily in the morning between approximately 7:00 and 8:00 a.m. throughout all phases of the study.

The primary efficacy measure is based on the Conners ADHD/DSM-IV Scale for Teachers (CADS-T). The CADS-T includes the DSM-IV total sub-scale (18 items), which is divided into the DSM-IV Inattentive sub-scale (9 items), and the DSM-IV Hyperactive-Impulsive sub-scale (9 items). Items are rated on a 0 to 3 scale (0=not true at all, 3=very much true); in this study these ratings were based on the child's behavior in school during the past week. Note that the CADS-T DSM-IV total sub-scale score can range from 0 to 54. The protocol defined **Primary efficacy variable** is the change from baseline (Visit 3) (end of Placebo-Washout Period) to the final (Visit 5) rating in the Conners ADHD/DSM-IV Scale for Teachers (CADS-T). That is,

Change = Baseline (CADS-T) - Final visit (CADS-T).

Higher CADS-T DSM-IV total scores are associated with a greater degree of ADHD symptomatology. Thus, a positive value for the change from baseline implies that the subject improved over time.

The CGI-Improvement scale (CGI-I) is a single-item investigator's assessment of the subjects' global improvement from the baseline visit at the end of the Placebo-Washout Period (Visit 3) to the end of the Double blind Treatment Phase. A rating of '1' indicates that the subject's condition was very much improved, a rating of '4' that the condition was unchanged, and a rating of '7' that the condition was very much worse. The final CGI-I ratings were also summarized by collapsing the ordinal responses into two categories: "improvement" (includes categories: very much, much, or minimally improved) and "no improvement" (includes categories: no change, worse, much or very munch worse). Clinical Global Impressions-Improvement (CGI-I) scores- evaluated at Visit 5 was a secondary efficacy measure.

Evaluation of the primary efficacy variable was performed using an analysis of covariance (ANCOVA). Treatment group, center and the baseline score of the CADS-IV total sub-scale were included in the model as explanatory variables. Secondary CADS variables were analyzed using a similar model. The final rating of the CGI-I was analyzed by an extended Cochran-Mantel-Haenszel test, stratified by center, and by Fisher's exact test.

A statistically significant treatment effect in favor of Ritalin — was observed for the primary and all secondary efficacy variables as measured by teachers (CADS-Teacher) and investigators (CGI-I). The sponsor's results for the CADS variables are shown below in Table 2.3 and Table 2.4.

Table 2.3

CADS-T DSM-IV total sub-scale score / Change from baseline by treatment / Last observation carried forward / Intent-to-treat population

		Ritalin	Placebo	
Visit 3 (Baseline)	N	62	70	
	Mean	27.2	28.3	
	SD	15.45	15.83	
Visit 5 / Final Visit	N	63	71	
	Mean	16.3	31.3	
	SD	12.12	15.37	
Change from baseline	N	62	70	
	Mean	10.7	-2.8	
	SD	15.68	10.59	
	p-value			<0.0001

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Table 2.3: **Efficacy results**

Efficacy variables	Mean change from baseline (LOCF, ITT)		
	Ritalin-—	Placebo	p-value
CADS-Teacher total sub-scale	10.7	-2.8	<0.0001
CADS-Teacher inattentive sub-scale	5.3	-1.5	<0.0001
CADS-Teacher hyperactive-impulsive sub-scale	5.4	-1.3	<0.0001
CADS-Parent total sub-scale	6.3	0.5	0.0043
CADS-Parent inattentive sub-scale	2.8	0.2	0.0213
CADS-Parent hyperactive-impulsive sub-scale	3.5	0.3	0.0015

ANCOVA with treatment, center, and baseline score as explanatory variables.

At the final assessment, the LOCF, ITT data show that 70% of the Ritalin— group were rated (by CGI-I) at the final visit as having improved from baseline, versus 40% of the placebo group (p = 0.0009, LOCF).

The results of this study of children with ADHD evaluated during their normal routine at school and at home, demonstrate that Ritalin- — a modified-release oral dosage form of Ritalin, was safe and effective relative to placebo in controlling symptoms of ADHD when administered once-daily at individually titrated doses ranging from 10 to 40 mg per day.

3. Protocol 02

This was a double blind, randomized, five-treatment crossover study of four formulation/dose variances of Ritalin- — versus placebo in outpatient children with ADHD. The five treatments are:

1. Ritalin- — Form 1, — mg cap
2. Ritalin- — Form 1, 20 mg cap
3. Ritalin- — Form 1 — mg cap
4. Ritalin- — Form 2, 20 mg cap
5. Placebo capsule

This study was conducted in a laboratory classroom setting, designed specifically to collect both pharmacokinetic and behavioral data. Total study duration for individual subjects was 75 calendar days. There were being three study phases: Screening; Baseline; and the Treatment Phase. The study design is illustrated in Table 3.1 below.

Table 3.1: **Tabular description of study design**

Phase:	**Screening**	**Baseline**	
Period:	Evaluation	Run-in	Evaluation
# of Study days	-14	6	1
Visit #	1	-	2

Table 3.1 continued ...

Phase:	**Treatment**									
Period:		Trtment Evaluation **A**		Trtment Evaluation **B**		Trtment Evaluation **C**		Trtment Evaluation **D**		Trtment Evaluation **E**
# of study days	=13		=13		=13		=13		=13	
Visit #										
		← Randomization								

During the one-day Baseline Evaluation Period (Visit 2), all pharmacodynamic and pharmacokinetic measures were completed to establish the baseline profile for each child on standard Ritalin, dosed at 10mg, bid. At the conclusion of the Baseline Phase, subjects entered the Treatment Phase.

The four Treatment Evaluation Periods (Visits 3-6) were conducted in the laboratory classroom according to a fixed schedule of events. Subjects were required to come to the study center on four separate days, from approximately 7:00 am until 6:30 p.m. (11.5 hours total). Assignment of a randomization number was documented in the CRF prior to the start of Visit 3. The test treatments were administered to subjects according to a randomly assigned sequence. One capsule was administered to each subject during each Treatment Evaluation Period, according to the sequence indicated on the labels of the double-blind study medication assigned to that subject.
The **fifth and final** Treatment Evaluation Period followed the same procedure as described above for Visits 3-6. In addition, at the conclusion of the final evaluation, whenever it occurred at Visit 7 or at the time of premature discontinuation from the study, the investigator conducted a brief interview with the subject and completed the Study Completion CRF, noting the final status and reason for premature discontinuation (if applicable).

A total of 49 subjects were screened for the study. Of these, 40 subjects were eligible for enrollment into the Baseline Phase. Six subjects discontinued prematurely during the Baseline Phase, primarily due to withdrawal of consent. The remaining 34 subjects were randomized to the Treatment Phase, and all completed the study. The demographics of the randomized subjects are shown in Table 3.2 below.

Table 3.2: Demographics of the randomized subjects

Age (Years)	
N	34
Mean	9.59
SD	1.46
Sex (%)	
Male	26 (76.5)
Female	8 (23.5)
Race (%)	
White	26 (76.5)
Black	2 (5.9)
Asian/Oriental	1 (2.9)
Other	5 (14.7)
Weight (kg)	
N	33
Mean	38.5
SD	14.96
Full scale IQ #	
N	34
Mean	103.16
SD	18.23

The **primary efficacy** variable was the area under the curve (AUC) for the Attention factor scores of the Swanson, Kotkin, Agler, F-Flynn & Pelham (SKAMP) Rating Scale, obtained over the entire evaluation period (i.e., 0-9 hours post-dose).

The SKAMP-Attention score is the average of six, seven-point scales. The items contributing to the Attention factor/sub-scale include: difficulty getting started on class assignment, difficulty staying on task for a class period, problems completing assignments, problems performing accurate work, difficulty attending to an activity or discussion in class, and difficulty in stopping and making transition to the next period.

Secondary efficacy variables include: (1) the AUC for SKAMP-Attention scores obtained over the second half of the evaluation period, only (i.e. 12:00 - 5:00 pm), (2) the AUC for SKAMP-Deportment scores obtained over the entire evaluation period and also the second half of the evaluation period, alone, (3) the AUC for Math Test scores.

AUC was computed using the trapezoidal rule. The primary efficacy variable was analyzed using an analysis of variance (ANOVA) model with treatment, period, classroom, subject-nested-in-classroom, and a period-by-classroom interaction term as factors. The results of the analyses of the primary and secondary efficacy variables (mean

AUC values) for each of the four formulation/dose variants of Ritalin — and placebo are summarized in Table below.

Table 3.3: **SKAMP and Math Test scores / Summary of mean AUC values and between-treatment analyses / ITT population**

AUC Variable	Ritalin - — Form 1 17.5mg	Ritalin- — Form 1 20mg	Ritalin — Form1 25mg	Ritalin- Form 2 20mg	Placebo
SKAMP-Attention (0-9)	16.8	16.7	15.7	16.7	19.8
SKAMP-Attention (0-4)	6.6	6.7	6.6	6.3	8.2
SKAMP-Attention (4-9)	10.2	10.1	9.2	10.4	11.6
SKAMP-Deportment (0-9)	16.6	16.0	13.8	15.9	22.8
SKAMP-Deportment (0-4)	5.8	5.9	5.4	6.1	9.5
SKAMP-Deportment (4-9)	10.8	10.1	8.4	9.8	13.4
Math Test-attempted (0-9)	1172.4	1200.1	1183.7	1147.4	808.3
Math Test – correct (0-9)	1134.6	1171.5	1150.3	1101.1	777.6

There was a statistically significant treatment effect ($p < 0.0001$) in favor of Ritalin — on the primary efficacy variable for all formulation/dose variants. The two 20-mg formulation/dose variants of the primary analysis were still statistically significant different from placebo when the Hochberg procedure was applied.

4. Sponsor's summary of findings

The results of *Protocol 07*, conducted in children with ADHD who were evaluated in their normal routine at school and at home, demonstrated that Ritalin- — administered once-daily at individually titrated doses in the range 10-40 mg/day was effective relative to placebo in controlling symptoms of ADHD. The efficacy of Ritalin- was consistently reflected in the assessments of teachers, parents, and investigators.

The results of *Protocol 02*, conducted in a laboratory classroom setting in children with ADHD, demonstrated that single doses of Ritalin- at 17.5, 20, and 25 mg were effective relative to placebo in improving classroom behavior and cognitive responses. The improvement relative to placebo was statistically significant during both the morning and the afternoon.

5. Reviewer's Analyses and comments

5.1 Study 07

Most of the subjects enrolled in this study were Caucasian males of an average age of 65-71 years. For majority of the subjects the DISC DSM-IV diagnosis was of "combined type." The details are shown in Table 2.2 on page 4.

The change from baseline to the final rating in the Conners ADHD DSM-IV Scale (CADS)-Teacher DSM-IV total sub-scale is the protocol defined **primary efficacy variable** for this study. Treatment wise descriptive statistics for the hyperactive-impulse

score, the inattentive score and for their total at Visit 3 and Visit 5 are presented below in Table 5.1.1 and Table 5.1.2, respectively.

Table 5.1.1
Descriptive statistics by Treatment at Visit 3 (Baseline)

TREAT	Efficacy Variable	n	Mean	Std Dev	Min	Max
Placebo	Teachers hyperactive-impulse score	70	13.4	8.83		
	Teachers inattentive score	70	14.9	7.94		
	Teachers total score	**70**	**28.3**	**15.83**		
Ritalin	Teachers hyperactive-impulse score	62	12.31	8.06		
	Teachers inattentive score	62	14.85	8.38		
	Teachers total score	**62**	**27.16**	**15.45**		

As seen from the above table, baseline (Visit 3) mean CADS-Teacher DSM-IV total sub-scores under placebo and Ritalin were 28.3 and 27.16, respectively. One-way analysis of variance indicated that the two treatment groups were not significantly different (p-value = 0.6772).

Table 5.1.2
Descriptive statistics by Treatment at Visit 5

TREAT	Efficacy Variable	n	Mean	Std Dev	Min	Max
Placebo	Teachers hyperactive-impulse score	68	15.25	8.39		
	Teachers inattentive score	68	16.99	7.73		
	Teachers total score	**68**	**32.24**	**14.96**		
Ritalin	Teachers hyperactive-impulse score	54	6.56	5.87		
	Teachers inattentive score	54	9.44	6.67		
	Teachers total score	**54**	**16.0**	**11.61**		

Descriptive statistics on the protocol defined primary efficacy variable are shown below in Table 5.1.3. These are in agreement with those of the sponsor shown in Table 2.4 above.

Table 5.1.3
Change from baseline in the Visit 5 CADS-T DSM-IV total sub-scale score*
Descriptive statistics by Treatment / LOCF / Intent-to-treat population

Treatment	N	Mean	Std Dev	Minimum	Maximum
Placebo	70	**-2.77**	10.58		
Ritalin	62	**10.73**	15.68		

*** Primary efficacy variable: Change = Baseline (CADS-T) – Visit 5 (CADS-T).**

The protocol defined primary analysis is analysis of covariance (ANCOVA). Treatment group, center and the baseline CADS-Teacher DSM-IV total sub-scale are included in the model as explanatory variables. SAS output of this model is as follows.

General Linear Models Procedure
Dependent Variable: CADSTCH

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	16	13687.324670	855.457792	6.54	0.0001
Error	115	15035.061693	130.739667		
Corrected Total	131	28722.386364			

R-Square	C.V.	Root MSE	CADSTCH Mean
0.476539	320.4474	11.434145	3.5681818

Source	DF	Type III SS	Mean Square	F Value	Pr > F
CADSTBAS	1	5992.5943301	5992.5943301	45.84	0.0001
CENTER	14	950.2342172	67.8738727	0.52	0.9178
TREAT	1	6326.0796712	6326.0796712	48.39	0.0001

General Linear Models Procedure
Least Squares Means

TREAT	CADSTCH LSMEAN	Pr > |T| HO: LSMEAN1=LSMEAN2
0	-2.9708085	0.0001
1	11.1077083	

However, as shown in Table 5.1.3 above, the standard deviations for placebo and Ritalin groups are 10.58 and 15.68, respectively. The F-test indicates that the "equality of variances" assumption is not valid (p-value = 0.0008).

The Wilcoxon rank-sum test on the change from baseline (Visit 3) in the final visit (5) CADS-T DSM-IV total sub-scale scores indicated that the two treatment groups are significantly different (p-value = 0.0001).

CGI-Improvement scale at Visit 5 is a **secondary efficacy variable.** The frequency distribution of CGI-I by treatment is shown below.

Table 5.1.4
CGI-I at Visit 5 by Treatment

CGI-I	Placebo		Ritalin	
	Frequency	Percentage	Frequency	Percentage
1	5	7.2	6	10.0
2	9	13.0	21	35.0
3	14	20.3	17	28.3
4	24	34.8	16	26.7
5	12	17.4	0	0
6	3	4.3	0	0
7	2	2.9	0	0
Total	69		60	

A rating of either '1' or '2' or '3' indicates that the subject's condition is improved. Thus, the number of subjects in the "improvement" categories under placebo and Ritalin are 28 and 44, respectively. The chi-squared test indicates that the proportion (73%) of "improved" subjects under Ritalin is significantly higher than the proportion (41%) of "improved" subjects under placebo (p-value = 0.001).

5.2 Study 02 - Reviewer's comments

This reviewer has reviewed Protocol 02. The details are shown in Section 3. This was a crossover study conducted in a laboratory classroom setting, designed specifically to collect both pharmacokinetic and behavioral data. The area under the curve (AUC) for the Attention factor scores is the efficacy measure. Analysis of covariance with treatment, period, classroom, subjects-nested-in-classroom, and period-by-classroom interaction term as factors was the protocol defined primary analysis.

The data collected from the crossover trial are not independent. Individual patients contribute observations to each test period. The generalized linear model (GLM) specified in the protocol is not appropriate for this type of data. On the other hand, the sponsor has made no attempt to use the clinical data in supporting their labeling claim of rapid onset. This reviewer could not see how to use the efficacy data to support such a claim. Therefore, no further attempt to reanalyze these data was made by this reviewer.

6. Reviewer's overall conclusions

- The efficacy data from Study 07 indicate that the reduction in Visit-5 CADS-T DSM-IV total sub-scale scores under Ritalin — is significantly larger than that of placebo. In fact, there was no reduction in the Visit-5 CADS-T DSM-IV score under placebo. That is, Ritalin- ~ is likely to be effective relative to placebo in controlling symptoms of ADHD. The data on CGI-I support the above conclusion.

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