CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA: 21-121
Name of Drug : OROS (methylphenidate HCl)
Indication : Attention Deficit Hyperactivity Disorder (ADHD)
Sponsor : ALZA
Medical Reviewer : Mosholder, Andrew, M.D. (HFD-120)

APR 7 2000

BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder in children. The childhood disorder is characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity and includes three subtypes: combined, predominantly inattentive or predominantly hyperactive-impulsive. Methylphenidate (Ritalin® and generic equivalents) is the most commonly used agent to treat children with ADHD. The immediate release form of methylphenidate, Ritalin®, and its equivalents are widely used. However, the half-life of methylphenidate is only 2 to 3 hours. So the immediate-release formulation needs to be administered multiple times a day, preferably three times a day, to maintain the efficacy. The sustained released methylphenidate, Ritalin-SR®, is available and claims sustaining the action for up to 8 hours. However, Ritalin-SR® is less effective than immediate release Ritalin® due to the alternation of the formulation.

To address the clinical need, ALZA develop a once daily, controlled-release oral dosage form OROS® (methylphenidate HCl) using ALZA's Push-Pull® controlled release technology for drug delivery to the gastrointestinal tract. OROS® is intended to provide longer efficacy and to have a safety profile comparable to Ritalin ® tid.

ALZA submitted three controlled studies to support their claims of the efficacy and safety of OROS® on ADHD in 6 to 12 year old children. The three trials will be presented in this review.

Note: a note was attached in the end of this document for table and figure numbering scheme.

PROTOCOL C-98-003

Design and Objectives

This was a single-center, double-blind, three periods, three-treatment, six-sequence, crossover study comparing the following treatments

- Treatment O : OROS® (methylphenidate HCl) administered once per day at 0730.

- Treatment R : IR Ritalin ® administered three times a day at 0730, 1130 and 1530.

- Treatment P : Placebo.

During the study, patients received all three treatments and were assigned to one of the three dose levels based on their pre-study methylphenidate dose and regimen. The three dosage levels were 18, 36 and 54 mg given qd for OROS® and 5 mg, 10 mg and 15 mg given tid for Ritalin® .

Within the dose levels, patients were randomized into one of the six treatment sequences:

- Sequence 1: Treatments O, R, P
- Sequence 2: Treatments O, P, R
- Sequence 3: Treatments R, O, P
- Sequence 4: Treatments R, P, O
- Sequence 5: Treatments P, O, R
- Sequence 6: Treatments P, R, O.

Patients were dosed for 7 days during each of the treatment period for a total of 21 days. Due to the short half-life of methylphenidate, the sponsor indicated that the carry-over effect is not possible, so the wash-out period was not included in the design.

This studies consist of one practice day before randomization, three six-week community school days and three one-day laboratory school days which occurred at the seventh day following the community school days.

In this study, patients participated the practice day activity after patients passed the screening inclusion/exclusion criteria. Only patients who continued to meet the pre-randomized inclusion/exclusion criteria were randomized on Day 0. On study days 1 to 6, 8 to 13 and 15 to 20, patients attended the community school, took their assigned doses and continued their normal daily routine.

The efficacy parameters were evaluated across settings and raters. The IOWA Conners Scale along with 13 additional peer interaction and behavior items over the previous school week were evaluated by community school teachers on days 6, 13 and 20. On the same days, parents/caregivers also evaluated patient's ADHD symptoms over the previous 6 days using Conners Scale. In addition, on days 6, 13 and 20, the community school teacher and the parent/caregiver completed a global assessment of treatment effects and a SNAP-IV (Swanson, Nolan, and Pelham rating scale) questionnaire. On day 20, the parents/caregivers were asked about their treatment preference.

On study days 7, 14 and 21, patients went to the study site (laboratory classroom setting) and remained there from 0700 to 2000. Children were divided into two classrooms: one for younger children (approximately 6 to 9 years of age) and one for older children (approximately 10 to 12 years of age). Patients were asked to perform academic task and the laboratory school teacher evaluated their attention and behavior at specified times using SKAMP (Swanson, Kotkink, Agler, M-Flynn, and Pelham) rating scale. In addition, activity monitor levels (measured as the

number of movement per minutes using actigraphy) during structured and unstructured activities were collected every 30 minutes on days 7, 14 and 21. The laboratory school teacher also completed an IOWA Conners Rating Scale, rated its peer interaction items and completed global assessments at the end of the day on study days 7, 14, and 21.

The primary objectives of this trial is to compare the efficacy of OROS® versus placebo and Ritalin ® tid based on standardized attention and behavior scales. Additional objectives of this cross-over study is to evaluate the onset and duration of effect and overall efficacy.

Efficacy Endpoints

The primary efficacy endpoint was the community school teacher IOWA Conners Rating scale for inattention/overactivity (I/O subscale) evaluated at days 6, 13 and 20. The IOWA Conners scale focused on two subsets of symptoms of ADHD : Inattention/overactivity (I/O subscale) and oppositional/defiance (measured by the O/D subscale). Each subscale contains 5 items, each item ranging from 0 (not at all) to 3(very much), so score 15 is the maximum score that a patient can get for a subscale.

An important secondary efficacy endpoint was the onset and loss of efficacy based on SKAMP combined attention scale. The SKAMP scale items consist of two subsets: attention (including 7 items) and deportment (including 5 items). Each item is rated on a 7-point scale ranging from 0 (none) to 7 (maximum) to indicate the level of impairment. The SKAMP was evaluated at 1, 2, 3, 5, 7, 9, 10, 11, and 12 hours after the 0730/0800 treatment dose on days 7, 14 and 21.

Analysis Plan

The primary efficacy analysis was based on all randomized patients who have IOWA Conners scale assessment for all three periods. An additional per-protocol analysis was performed if a substantial number of protocol violations occurred. Protocol specified that all randomized patients with available data were used for the secondary analysis. However, in the report, patients who missed one or more doses on a laboratory school day were excluded from the secondary analysis for that day.

All statistical tests for the efficacy variables was performed at two sided α =0.05 level. The tests for the baseline variables was based on two sided α =0.1 level.

The primary hypothesis was that the treatment difference between OROS® and placebo was equal to zero. In addition, pairwise comparisons between Ritalin® and placebo, between OROS® and Ritalin® were also made. The protected least-significant-difference (LSD) approach was applied. The pairwise comparisons would be made only if the overall test was significant at the 0.05 level .

The primary efficacy analysis was based on a mixed effect analysis of variance (ANOVA) model that included the fixed-effect factors of treatment, sequence and period, and the random effect of

between and within subject factors. The least square estimates of the mean difference between the two active treatments and the 95% confidence interval was presented.

Provided the overall efficacy was found, the laboratory school SKAMP combined attention assessments at each time point was evaluated for the onset and duration of efficacy. For each scheduled assessment time, the laboratory school teacher SKAMP combined attention assessments averaged by patient for days 7, 14 and 21 was analyzed using the same mixed effect ANOVA model as the primary analysis. The maximum SKAMP score on a day was analyzed to show if the most extreme behavior over a day is different between treatments.

The time of onset of efficacy was defined as the one half of the time between the first assessment time showing statistical significance and the previous assessment time (note: protocol specified the SKAMP assessment time). The loss of efficacy was defined as one half of the time between an assessment time that shows significance and the subsequent time failed to show significance. If no loss of significance was found for OROS® and placebo comparison at the 12-hour assessment time (final assessment time), then the loss of efficacy was assigned at 12.5 hours.

Additional analysis of covariance (ANCOVA) models was used to adjust for the strata and baseline covariates, such as age (grouped as 6-9 years old versus 10-12 years old), body weight (grouped as ≥ median versus ≥ median), cohort, period and dose level. A subgroup analysis strategy was presented in the report. For each baseline variable, a separate ANCOVA model was run with each factor in the model and its interaction with treatment. If an interaction was found, the treatment effect within each subgroup was presented based on ANCOVA models.

Sponsor's Result

64 patients were randomized to the study. 61 out of 64 randomized patients had completed three treatment periods; one patient had never been treated; one discontinued before received placebo at the last period and one only received the Ritalin® treatment. Patients' methylphenidate dosages 4-week prior to randomization determined the active study medication dose level. The distribution of patients enrolled across three dose levels and sequence was shown in Table A.I.1. The active drug assignment was also shown: 10 patients were assigned to 18 mg/day dose level, 34 were assigned to 36 mg/day level and 20 were assigned to 54 mg/day level (Table A.I.1).

In the sponsor's report, demographic and some baseline clinical variables were summarized in all, not by sequence group (Table A.I.2). Similar percentage of young (51.6% for 6-9 years old) and old (48.4% for 10-12 years old) patients were randomized. The study population was predominated by boys (81.3%) and Caucasian (82.8%). 82.8% of these ADHD patients were diagnosed with combined inattention and hyperactive-impulsive.

TABLE A.I.1
Patient Enrollment

Active Dose Level [a]	Treatment Sequence [b]	Enrolled (n=64)
18 mg OROS/ 5 mg Ritalin	O R P	2 (3.1%)
	O P R	2 (3.1%)
	R O P	1 (1.6%)
	R P O	1 (1.6%)
	P O R	2 (3.1%)
	P R O	2 (3.1%)
36 mg OROS/10 mg Ritalin	O R P	6 (9.4%)
	O P R	5 (7.8%)
	R O P	5 (7.8%)
	R P O	6 (9.4%)
	P O R	6 (9.4%)
	P R O	6 (9.4%)
54 mg OROS/15 mg Ritalin	O R P	4 (6.3%)
	O P R	3 (4.7%)
	R O P	3 (4.7%)
	R P O	3 (4.7%)
	P O R	4 (6.3%)
	P R O	3 (4.7%)
All Dose Levels	O R P	12 (18.8%)
	O P R	10 (15.6%)
	R O P	9 (14.1%)
	R P O	10 (15.6%)
	P O R	12 (18.8%)
	P R O	11 (17.2%)

a OROS = OROS (methylphenidate HCl); Ritalin = Ritalin TID;
b Treatments:

O = OROS (methylphenidate HCl)
R = Ritalin TID
P = Placebo

For the community school teacher IOWA Conners I/O subscale, patients treated with OROS were observed to have significantly lower scores ($p< 0.001$) than the placebo patients (Table A.I.3). Since a significant overall treatment effect ($p<0.001$) was found, pairwise comparison was performed and demonstrated that patients taking OROS had significantly less inattention and overactivity than patients taking placebo. No difference in inattention and overactivity was found between Ritalin and OROS treated groups. Similar results were obtained from different raters (parent/caregiver, laboratory school teacher) in the IOWA Conners I/O subscale and in O/D subsacle.

From the mixed effect ANOVA model result for the primary parameter, no significant sequence effect (order of the treatment) or treatment by period interaction were found. However, the period effect was significant which showed the highest rating (worst) was observed at the first period. The sponsor claimed that this might be attributed to the learning effect for the community school teacher rating the IOWA Conners or the patient behavior might have improved overtime. In the sponsor's report, no significant baseline factor by treatment interaction was reported for the community school teach IOWA Conners-I/O ratings.

TABLE A.I.2
Demographics and Baseline Characteristics:
All Randomized Patients

	All Patients (n=64)
Age (year) - n (%)	64 (100.0%)
6 - 9	33 (51.6%)
10 - 12	31 (48.4%)
Mean (SD)	9.2 (1.8)
Median	9
(Min, Max)	(6, 12)
Sex - n (%)	64 (100.0%)
Male	52 (81.3%)
Female	12 (18.8%)
Race - n (%)	64 (100.0%)
Caucasian	53 (82.8%)
Black	4 (6.3%)
Asian	2 (3.1%)
Hispanic	5 (7.8%)
Other	0
History of Tics - n (%)	64 (100.0%)
No tics	50 (78.1%)
Motor tics	11 (17.2%)
Verbal tics	3 (4.7%)
Height (cm)	
n	64
Mean (SD)	135.2 (10.7)
Median	136.5
(Min, Max)	(115.0, 165.0)
Weight (kg)	
n	64
Mean (SD)	32.3 (7.8)
Median	31.3
(Min, Max)	(20.1, 50.4)

For the laboratory school teacher SKAMP ratings of combined attention, OROS (or Ritalin) start to show significant beneficial effect (compared with placebo) around 2 hours after dosing (7:00 am for classroom 1 and 7:30 am for classroom 2) until 12 hours post dosing (Table A.I.4). Using the sponsor's onset and loss of efficacy definition, the estimated onset and loss of efficacy time for OROS or Ritalin was 1.5 and 12.5, respectively. There was no significant difference in SKAMP ratings of combined attention found overtime for OROS and Ritalin. In Figure A.I.1, the sponsor showed the SKMAP ratings overtime, averaged across periods and by treatment.

Significantly higher SKAMP combined attention ratings were noted in period 1 and 2 than in period 3 for the 1000/1030 assessment. No treatment by period interaction was observed in the sponsor's analysis.

TABLE A.I.3
Analysis of Community School Teacher IOWA Conners Inattention/Overactivity Subscale: All Randomized Patients

Treatment Group	OROS (n=64)	Ritalin TID (n=64)	Placebo (n=64)
Inattention/ Overactivity - n(%)	61 (100.0%)	61 (100.0%)	61 (100.0%)
0	2 (3.3%)	3 (4.9%)	0
1 - 5	25 (41.0%)	20 (32.8%)	7 (11.5%)
6 - 10	27 (44.3%)	26 (42.6%)	10 (16.4%)
11 - 15	7 (11.5%)	12 (19.7%)	44 (72.1%)
Mean (SD)	6.54 (3.48)	6.89 (4.05)	11.60 (3.86)
(Min, Max)	(0, 15)	(0, 15)	(1, 15)
Overall comparison p-value [a]	< 0.001		
OROS versus Placebo			
n1,n2	61, 61		
LS Mean Difference (SEM)	-5.04 (0.53)		
95% C.I. for difference	(-6.09, -3.99)		
p-value [b]	< 0.001		
Ritalin versus Placebo			
n1,n2	61, 61		
LS Mean Difference (SEM)	-4.53 (0.53)		
95% C.I. for difference	(-5.59, -3.48)		
p-value [b]	< 0.001		
OROS versus Ritalin			
n1,n2	61, 61		
LS Mean Difference (SEM)	-0.51 (0.53)		
95% C.I. for difference	(-1.56, 0.55)		
p-value [b]	0.342		

Note: SD = Standard deviation; C.I. = Confidence interval;
n1 = Number of patients in test treatment group;
n2 = Number of patients in control treatment group;
The LS mean (least squares mean) difference and SEM (standard error of LS mean difference) are estimated from the mixed effects ANOVA model that includes treatment, period, sequence and subject within sequence factors.
The inattention/overactivity subscale is the sum of items 1 - 5 of the IOWA Conners rating scale.
Table includes only patients with data available for all three periods.

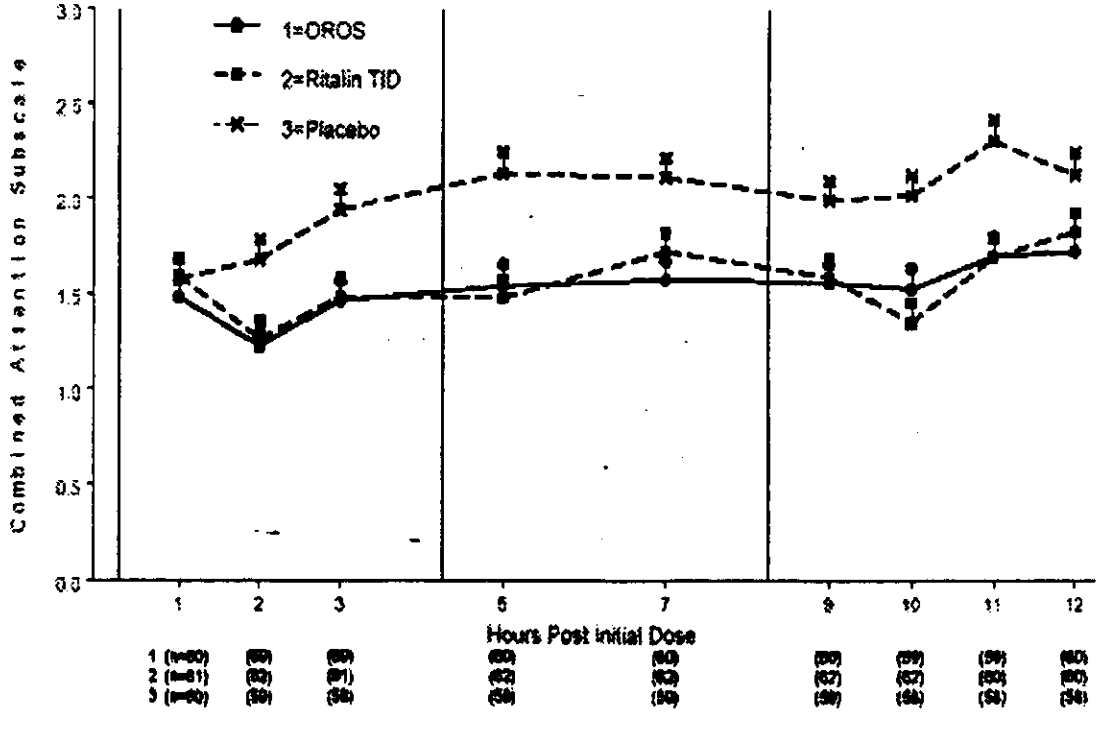
a p-value for the overall comparison among all treatment groups is based on type III analysis from the mixed effect model.
b p-values for the pairwise test of treatment effect are based on type III analysis from the mixed effect model.

TABLE A.I.4
Analysis of Laboratory School Teacher
SKAMP Combined Attention Ratings:
All Randomized Patients

Classroom 1	Classroom 2	Treatment Group: OROS mean (SD) n	Ritalin mean (SD) n	Placebo mean (SD) n	Overall p-value [a]	Treatment Difference p-value [b]: OROS vs Placebo	Ritalin vs Placebo	OROS vs Ritalin
07:45-08:15	08:15-08:45	1.48 (0.68) 60	1.59 (0.67) 61	1.58 (0.82) 60	0.519	0.310	0.955	0.336
08:45-09:15	09:15-09:45	1.23 (0.61) 59	1.26 (0.79) 62	1.68 (0.80) 59	< 0.001	< 0.001	< 0.001	0.689
09:45-10:15	10:15-10:45	1.46 (0.79) 59	1.48 (0.77) 61	1.94 (0.85) 58	< 0.001	< 0.001	< 0.001	0.930
11:45-12:15	12:15-12:45	1.54 (0.91) 60	1.48 (0.80) 62	2.13 (0.87) 58	< 0.001	< 0.001	< 0.001	0.615
13:45-14:15	14:15-14:45	1.57 (0.78) 60	1.72 (0.78) 62	2.11 (0.80) 59	< 0.001	< 0.001	< 0.001	0.094
15:45-16:15	16:15-16:45	1.56 (0.78) 60	1.59 (0.78) 62	1.99 (0.79) 59	< 0.001	< 0.001	< 0.001	0.609
16:45-17:15	17:15-17:45	1.53 (0.85) 59	1.35 (0.84) 62	2.01 (0.84) 58	< 0.001	< 0.001	< 0.001	0.102
17:45-18:15	18:15-18:45	1.70 (0.78) 59	1.69 (0.82) 60	2.31 (0.85) 58	< 0.001	< 0.001	< 0.001	0.948
18:45-19:15	19:15-19:45	1.72 (0.79) 60	1.82 (0.76) 60	2.13 (0.92) 58	< 0.001	< 0.001	0.005	0.272
Maximum Score		2.33 (0.76) 60	2.42 (0.73) 62	2.81 (0.78) 60	< 0.001	< 0.001	< 0.001	0.306

Note: Assessment scores for combined attention items are averaged at each of the nine evaluation time points and used in the mixed effects ANOVA model that includes treatment, period, sequence and subject within sequence factors.
SD = Standard Deviation
a p-value for the overall comparison among all treatment groups is based on type III analysis from the above mixed effect model.
b p-values for the pairwise test of treatment effect are based on type III analysis from the above mixed effect model.

Figure A.I.1
Laboratory School Teacher SKAMP Ratings – Mean (SED) of Combined Attention



Reviewer's Evaluation and Comments

This reviewer confirmed the sponsor's primary analysis results using the mixed effect ANOVA models (see Appendix A). Based on this model, the results showed that OROS and Ritalin are significant better than placebo and the statistical difference between OROS and Ritalin can not be confirmed. To provide an overview of the treatment effect across three periods, this reviewer plotted the Least Squared Means based on the sponsor's mixed effect ANOVA model with additional treatment by period term (Figure A.II.1). This reviewer did not find carry-over effect based on the sequence effect in the mixed effect ANOVA model.

This reviewer performed additional analysis to further confirm the sponsor's primary result and their claim of no carry over effect. The primary comparison in this study is between OROS and placebo, so only the data during the period while OROS or placebo was administered was used. The data was shown in the following table during the periods when the "O" (OROS) and "P" (Placebo) were present:

Sequence	Period		
	1	2	3
1	O		P
2	O	P	
3		O	P
4		P	O
5	P	O	
6	P		O

This additional analysis was based on the sum and difference of the within patient responses (see Fleiss, 1986, page 263-290 in [1]). The sequence difference of the intra-patient sum was used for testing the carry-over effect. If the carried over effect is not significant, the sequence difference of the intra-patient difference was used for testing the treatment effect.

Separated two-sample t-tests can be applied to sequence 1 versus sequence 6 and sequence 3 versus sequence 4 as well. Assuming no period effect, sequences 1, 2 and 3 and sequences 4, 5 and 6 can be pooled into two groups, respectively, to perform the two-sample t-test for the overall data. This assumption may not be true, so this reviewer fitted an ANOVA model with the 6 sequence as the factor for the patient's sum and difference data and the F-statistic was used to test the effect of each sequence pairs (1 versus 6, 2 versus 5, and 3 versus 4), simultaneously.

By testing sequence difference of the between-period patient sum or difference data (sequences 1 versus 6, 2 versus 5 and 3 versus 4, using F-test), the p-values were 0.92 and 0.0001 for testing the carry-over effect (using sum data) and treatment effect (using difference data), respectively. Again, the sponsor's results of significant OROS benefit compared with placebo and no carried-over effect were confirmed.

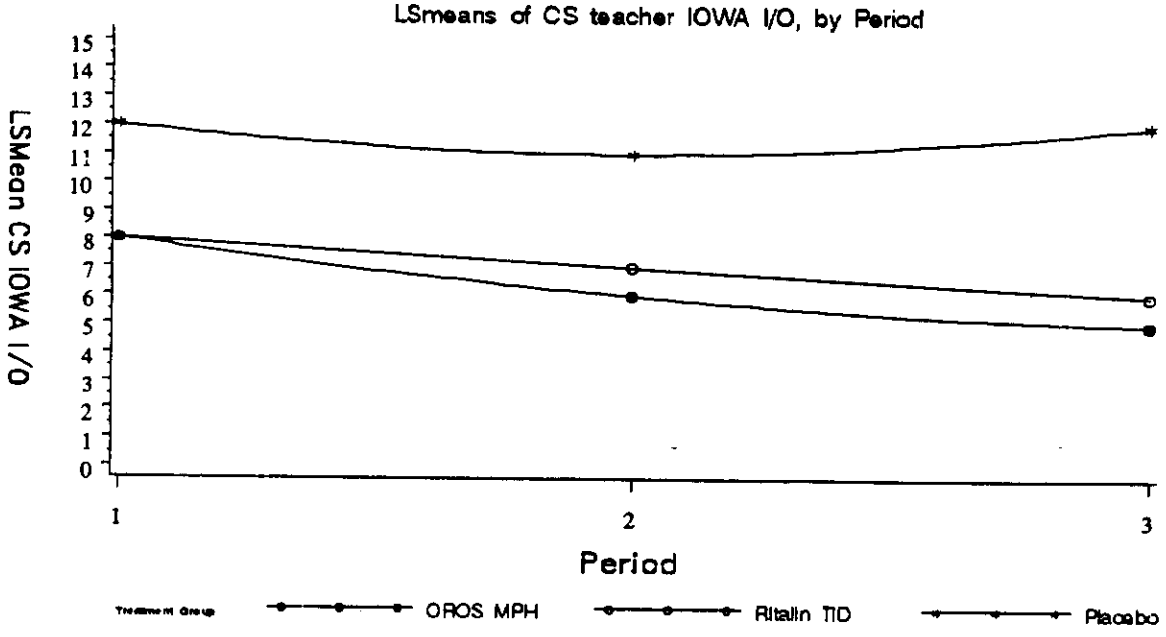
The only significant subgroup effect found in the sponsor's subgroup analysis for the primary endpoint is the period effect. No significant baseline factor by treatment interaction was reported in the sponsor's report. However, this reviewer noted a significant sex by treatment interaction showing a larger treatment effect in girls than in boys. Since the sex by treatment interaction may

be confounded by the baseline Conners score, the true treatment interaction can not be determined without knowing the baseline Conners score in the cross-over study.

This reviewer also obtained the same results for the assessment of the treatment onset and loss of efficacy time using the sponsor's analysis method. Since one of the main objective of this study is to demonstrate the time course of the treatment effect, this reviewer performed additional analysis to evaluate the sponsor's result.

In the SKAMP combined attention rating assessment, a nested repeated measure scheme within a patient were embedded in the design: 1) A patient received different treatment at different period (based on the cross-over design); 2) A patient was measured at multiple times within each period. The sponsor's analysis method handled the repeated measured data due to the cross-over design by fitting the mixed ANOVA at each time point. The results reported was based on the estimated treatment effect from the mixed model which is conceptually an **average of the treatment effects over three periods** at each time point. The sponsor found some treatment by period interaction for SKAMP combined attention assessment at few time points. However, the sponsor's analysis did not show that the **treatment effect was consistent between periods**.

Figure A.II.1



To simplify the analysis by avoiding using any statistical models, this reviewer plotted the mean SKAMP combined attention score by treatment, period and time points (see Figures A.II.2a, A.II.2b and A.II.2c) to descriptively demonstrate the treatment effect across time in three periods. The three figures showed that the time courses of the treatment effect were not consistent across periods: no apparent treatment difference was observed in period 1 but more favorable results of OROS and Ritalin were observed in periods 2 and 3 at and after 2 hours, as compared with controls. The sponsor's claimed onset and loss of treatment efficacy time was obtained **by averaging over all three periods**, but the evidence was not consistent across periods.

Figure A.II.2a

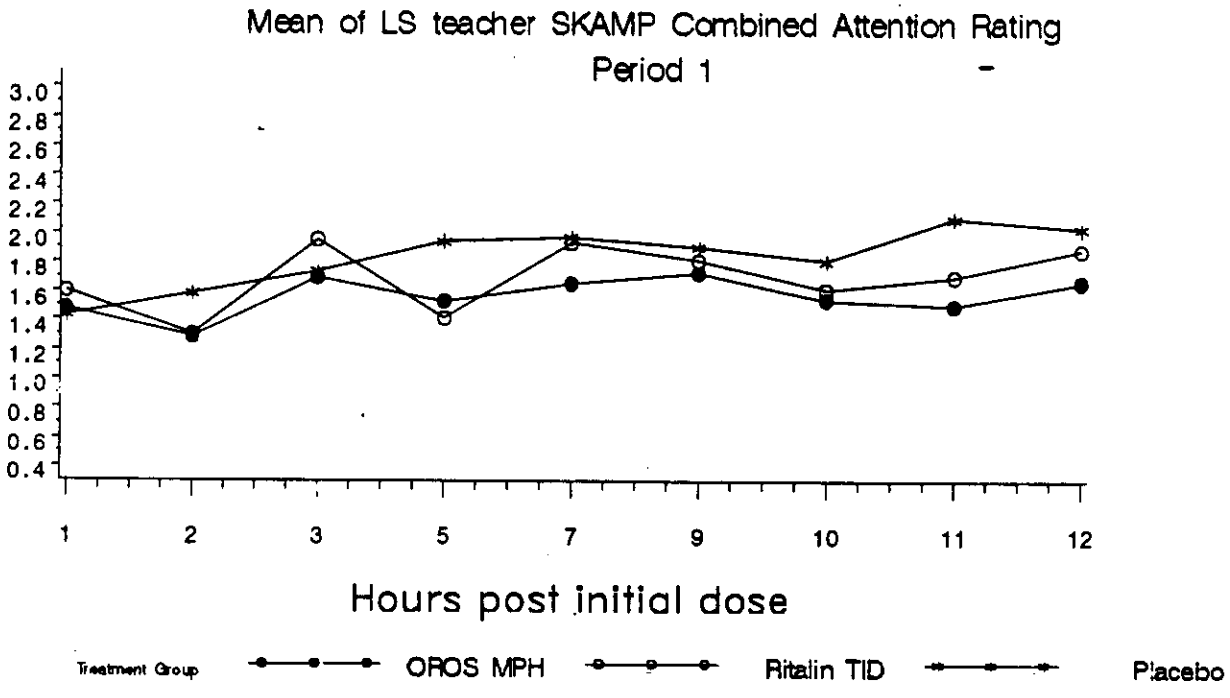


Figure A.II.2b

Mean of LS teacher SKAMP Combined Attention Rating

Period 2

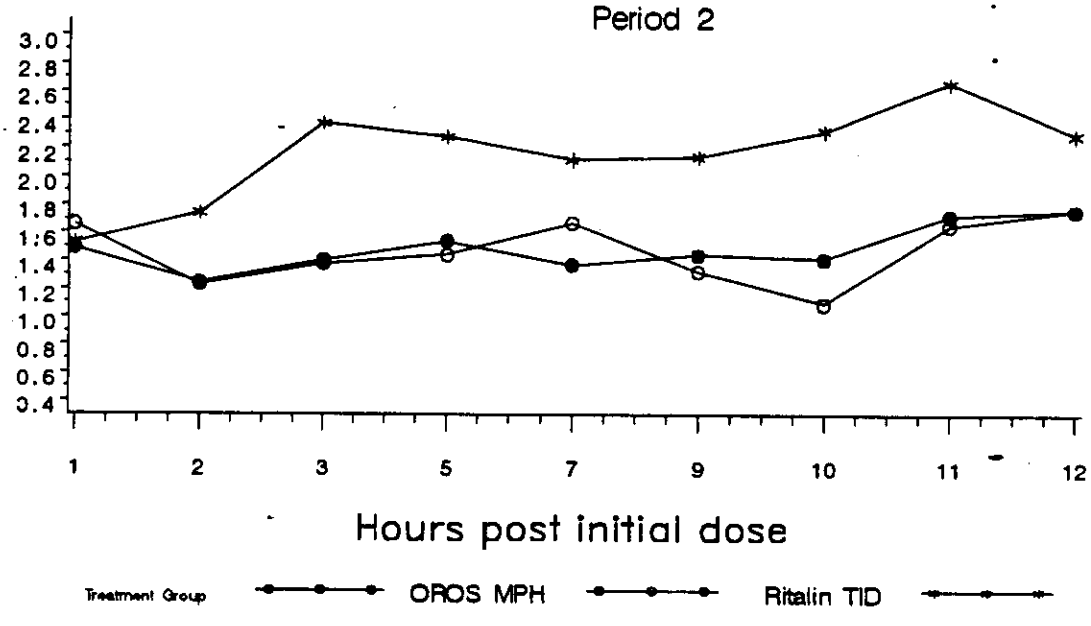
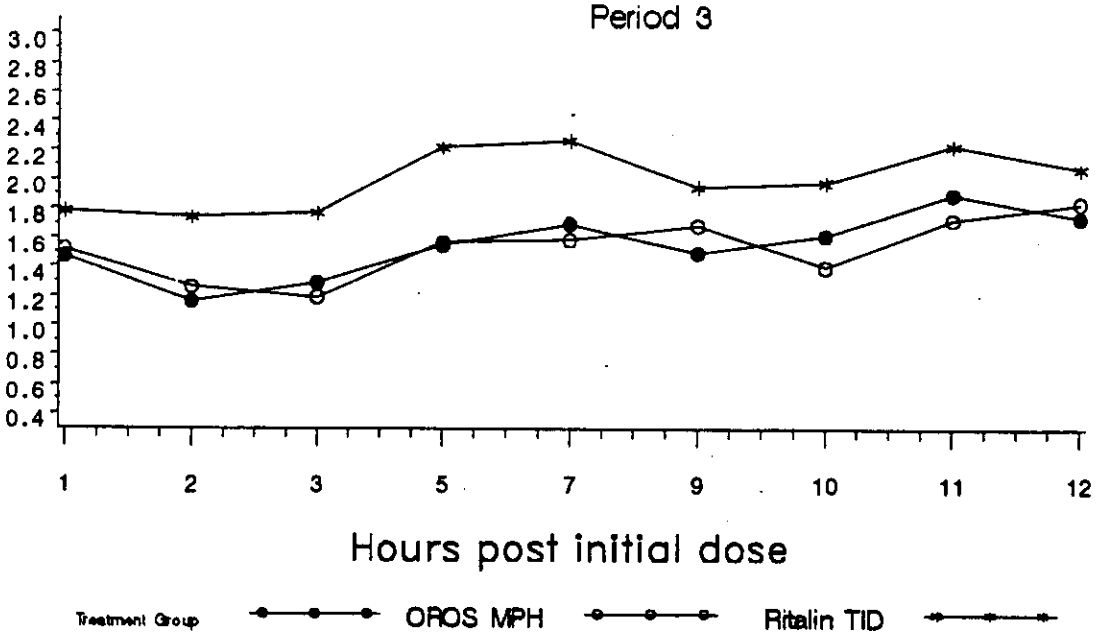


Figure A.II.2c

Mean of LS teacher SKAMP Combined Attention Rating

Period 3



Protocol C-97-025

Design and Objective

Protocol C-97-025 basically had the same design and the same objective as protocol C-98-003, except those patients eligible for protocol C-97-025 were required to complete a screening and practice-day study (Protocol C-97-006). Actigraphy, SNAP-IV ratings and home situations questionnaire were not applied for this study. Other measurements were performed and school counselors were used as additional raters in this study.

One interim analysis was performed after approximately one-third of the patients completed the study.

Efficacy Endpoint

Similar to protocol C-98-003, the community school teacher evaluated IOWA Conners I/O subscale was the primary efficacy endpoint and the laboratory school teacher SKAMP combined attention assessments was one of the secondary endpoints to evaluate the onset and duration of treatment effect.

Analysis Plan

The test hypotheses and significance levels as well as the analysis population and handling of dropouts were similar to study C-98-003.

Sponsor's Results

70 patients from screening study C-97-006 were randomized to treatments. Two patients were terminated early due to using non-study methylphenidate. The disposition of all randomized patients was shown in Table B.I.1.

A patient's active study drug level was decided by the pre-randomization methylphenidate dosage. 17 patients were assigned to dose level 1 (18 mg OROS/5 mg Ritalin), 39 to dose level 2 (36 mg OROS/ 10 mg Ritalin) and 14 to dose level 3 (54 mg OROS/15 mg Ritalin).

Similar to the distribution of demographic information in study C-98-003, majority of patients were male, Caucasian and had combined inattention and hyperactive-impulsive diagnosis (Table B.I.2).

TABLE B.I.1
Patient Enrollment

Active Dose Level [a]	Treatment Sequence [b]	Enrolled (n=70)
18 mg OROS/ 5 mg Ritalin	O R P	2 (2.9%)
	O P R	3 (4.3%)
	R O P	3 (4.3%)
	R P O	3 (4.3%)
	P O R	3 (4.3%)
	P R O	3 (4.3%)
36 mg OROS/10 mg Ritalin	O R P	7 (10.0%)
	O P R	7 (10.0%)
	R O P	6 (8.6%)
	R P O	6 (8.6%)
	P O R	6 (8.6%)
	P R O	7 (10.0%)
54 mg OROS/15 mg Ritalin	O R P	3 (4.3%)
	O P R	2 (2.9%)
	R O P	2 (2.9%)
	R P O	2 (2.9%)
	P O R	2 (2.9%)
	P R O	3 (4.3%)
All Dose Levels	O R P	12 (17.1%)
	O P R	12 (17.1%)
	R O P	11 (15.7%)
	R P O	11 (15.7%)
	P O R	11 (15.7%)
	P R O	13 (18.6%)

a OROS = OROS (methylphenidate HCl); Ritalin = Ritalin TID;
b Treatments:

O = OROS (methylphenidate HCl)
R = Ritalin TID
P = Placebo

TABLE B.I.2
Demographics and Baseline Characteristics:
All Randomized Patients

	All Patients (n=70)
Age (year) - n (%)	70 (100.0%)
6 - 9	41 (58.6%)
10 - 12	29 (41.4%)
Mean (SD)	9.1 (1.6)
Median	9
(Min, Max)	(6, 12)
Sex - n (%)	70 (100.0%)
Male	62 (88.6%)
Female	8 (11.4%)
Race - n (%)	70 (100.0%)
Caucasian	66 (94.3%)
Black	0
Asian	0
Hispanic	3 (4.3%)
Other	1 (1.4%)
History of Tics - n (%)	70 (100.0%)
No tics	63 (90.0%)
Motor tics	7 (10.0%)
Verbal tics	0
Height (cm) n	70
Mean (SD)	135.0 (10.9)
Median	135.0
(Min, Max)	(114.0, 156.0)
Weight (kg) n	70
Mean (SD)	34.7 (10.1)
Median	32.0
(Min, Max)	(19.4, 60.6)
ADHD Diagnosis - n(%)	70 (100.0%)
Combined	53 (75.7%)
Predominantly Inattentive	15 (21.4%)
Predominantly hyperactive-impulsive	2 (2.9%)

Three patients who had missing one or more periods of community school teacher IOWA Conners I/O ratings were excluded from the primary analysis. Based on the primary analysis, OROS was found to be significantly better than placebo ($p<0.001$, Table B.I.3). The result did not show statistical significant difference between OROS and Ritalin. Similar results were found across different raters (laboratory school teacher and counselor, parent/caregiver) in IOWA Conners I/O ratings and O/D ratings.

Unlike the study C-98-003 that period was found to be significant based on the mixed effect ANOVA model, no significant sequence or period effect was found in this study. In the subgroup analysis, age and weight were found to be significant baseline confounding factors for the treatment effect. There were significant treatment by age, cohort (three cohort was determined based on the randomization date) or dose level interaction. The sponsor found that younger patients (6-9 years old) showed larger OROS (or Ritalin) effect compared with placebo. The second and third cohorts had larger treatment effect than the first cohort. In addition, the sponsor

indicated that there was progressively higher treatment benefit as the dose level increased. The treatment effect was still significant regardless whether the baseline factors were adjusted for or not.

A similar conclusion as study C-98-003 was drawn for the analysis of the SKAMP combined attention score in determination of onset and loss of treatment efficacy, i.e. onset and loss of efficacy were estimated to be 1.5 and 12.5 hours, respectively, for both OROS and Ritalin (Table B.I.4, Figure B.I.1). Age group, weight and period by treatment interactions were shown to be significant in some time points.

TABLE B.I.3
Analysis of Community School Teacher IOWA Conners
Inattention/Overactivity Subscale:
All Randomized Patients

	Treatment Group		
	OROS (n=70)	Ritalin (n=70)	Placebo (n=70)
Inattention/ Overactivity - n(%)	67 (100.0%)	67 (100.0%)	67 (100.0%)
0	6 (9.0%)	4 (6.0%)	0
1 - 5	39 (58.2%)	39 (58.2%)	11 (16.4%)
6 - 10	16 (23.9%)	16 (23.9%)	16 (23.9%)
11 - 15	6 (9.0%)	8 (11.9%)	40 (59.7%)
Mean (SD)	4.69 (3.31)	5.03 (3.71)	10.30 (4.22)
(Min, Max)	(0, 12)	(0, 14)	(1, 15)
Overall comparison p-value [a]	< 0.001		
OROS versus Placebo			
n1,n2	67, 67		
LS Mean Difference (SEM)	-5.61 (0.48)		
95% C.I. for difference	(-6.56, -4.66)		
p-value [b]	< 0.001		
Ritalin versus Placebo			
n1,n2	67, 67		
LS Mean Difference (SEM)	-5.26 (0.48)		
95% C.I. for difference	(-6.21, -4.31)		
p-value [b]	< 0.001		
OROS versus Ritalin			
n1,n2	67, 67		
LS Mean Difference (SEM)	-0.35 (0.48)		
95% C.I. for difference	(-1.30, 0.60)		
p-value [b]	0.467		

Note: SD = Standard deviation; C.I. = Confidence interval;
n1 = Number of patients in test treatment group;
n2 = Number of patients in control treatment group;
The LS mean (least squares mean) difference and SEM (standard error of LS mean difference) are estimated from the mixed effects ANOVA model that includes treatment, period, sequence and subject within sequence factors.
The inattention/overactivity subscale is the sum of items 1 - 5 of the IOWA Conners rating scale.
Table includes only patients with data available for all three periods.
a p-value for the overall comparison among all treatment groups is based on type III analysis from the mixed effect model.
b p-values for the pairwise test of treatment effect are based on type III analysis from the mixed effect model.

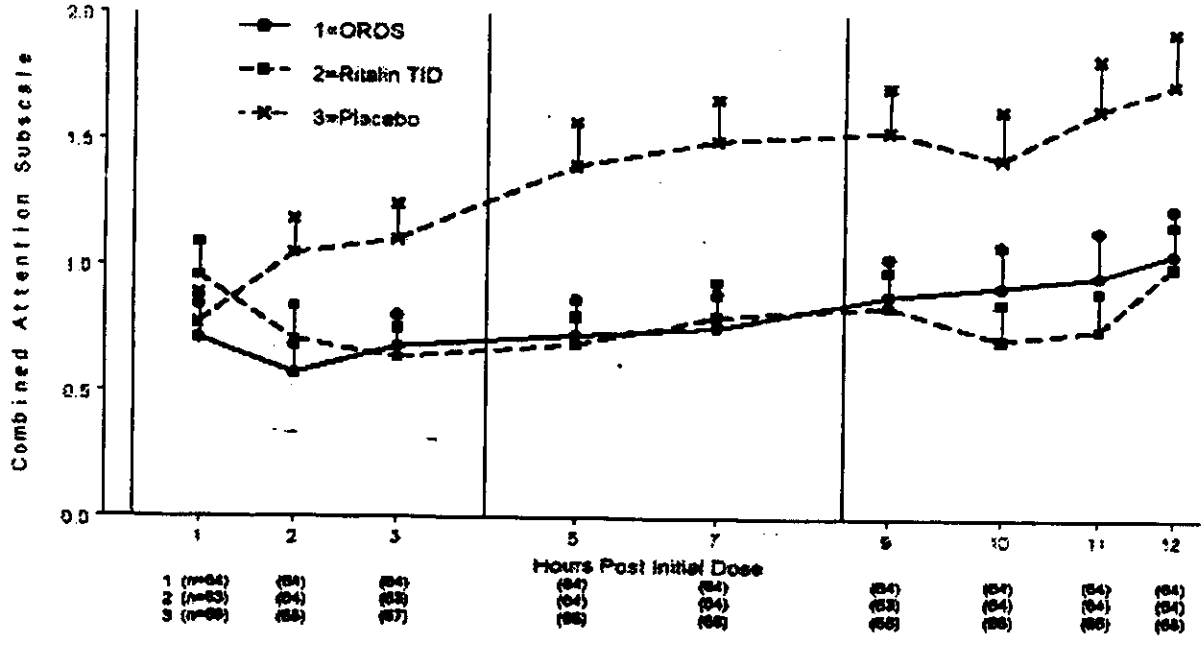
TABLE B.I.4
Analysis of Laboratory School Teacher
SKAMP Combined Attention Ratings:
All Randomized Patients

Session	Treatment Group OROS mean (SD) n	Ritalin mean (SD) n	Placebo mean (SD) n	Overall p-value [a]	Treatment Difference p-value [b] OROS vs Placebo	Ritalin vs Placebo	OROS vs Ritalin
08:15 - 08:45	0.71(1.04) 64	0.95 (1.07) 63	0.77 (0.95) 68	0.159	0.665	0.150	0.068
09:20 - 09:50	0.57(0.89) 64	0.70 (1.06) 64	1.04 (1.13) 68	< 0.001	< 0.001	0.004	0.310
10:30 - 11:00	0.68(0.99) 64	0.63 (0.92) 63	1.10 (1.15) 67	< 0.001	< 0.001	< 0.001	0.587
12:30 - 13:00	0.72(1.12) 64	0.68 (0.89) 64	1.39 (1.43) 68	< 0.001	< 0.001	< 0.001	0.636
14:05 - 14:35	0.75(1.06) 64	0.79 (1.13) 64	1.49 (1.37) 68	< 0.001	< 0.001	< 0.001	0.849
16:00 - 16:30	0.88(1.20) 64	0.83 (1.13) 63	1.53 (1.47) 68	< 0.001	< 0.001	< 0.001	0.693
17:15 - 17:45	0.92(1.33) 64	0.71 (1.17) 64	1.42 (1.60) 68	< 0.001	0.004	< 0.001	0.109
18:20 - 18:50	0.96(1.45) 64	0.75 (1.20) 64	1.62 (1.68) 68	< 0.001	< 0.001	< 0.001	0.109
19:10 - 19:40	1.05(1.44) 64	1.00 (1.34) 64	1.72 (1.71) 68	< 0.001	< 0.001	< 0.001	0.484
Maximum Score	1.45(1.44) 64	1.63 (1.54) 64	2.24 (1.65) 68	< 0.001	< 0.001	< 0.001	0.412

Note: Assessment scores for combined attention items are averaged at each of the nine evaluation time points and used in the mixed effects ANOVA model
that includes treatment, period, sequence and subject within sequence factors.
SD = Standard Deviation

a p-value for the overall comparison among all treatment groups is based on type III analysis from the above mixed effect model.
b p-values for the pairwise test of treatment effect are based on type III analysis from the above mixed effect model.

Figure B.I.1
Laboratory School Teacher SKAMP Ratings - Mean(SEM) of Combined Attention



Reviewer's Evaluation and Comments

The beneficial OROS effect was confirmed based on the sponsor's primary analysis of the community school teacher IOWA Conners I/O rating. As before, no statistical significance difference of OROS and Ritalin was found. Figure B.II.1 showed the least squared means for each treatment and by treatment period. The graphical display was used to show the consistent treatment effect across three periods based on community school teacher IOWA Conners I/O rating scale.

Based on the between-period sum and difference data (as described in the Reviewer's evaluation and comments section for Protocol C-98-003), the p-values were 0.582 and 0.0001 for testing the carry-over and treatment effects (OROS versus placebo), respectively. So, once again, the OROS treatment effect was confirmed.

This reviewer also confirmed the sponsor's finding of age group and dose level by treatment interactions for the primary endpoint. There was no sex by treatment interaction, although gender effect was found to be significant in the model that showed community school teacher IOWA Conner's score was higher in boys. Again, since baseline Conner's score may be a confounded for the gender effect, no conclusive result can be drawn with regard to the gender effect.

The sponsor noted a progressive benefit of OROS as dose level increased based on the significant dose level by treatment interaction. They claimed that there was a dose responding treatment effect since the community school teacher IOWA Conners rating of the placebo group was constant across three dose levels. Because dose level was not blinded, the distribution of the community school IOWA Conners rating among dose level may be subject to possible rater bias. Furthermore, no such trend was noted in study C-98-003. Therefore, the sponsor's claimed progressive benefit of OROS can not be confirmed based on the cross-over studies.

The means of the SKAMP combined attention ratings were again plotted overtime (see Figures B.II.2a, B.II.2b and B.II.2c) by period and treatment to show the time course of treatment effect across periods. In this study, no clear treatment difference was observed in the first 1 or 2 hours post dosing in periods 2 and 3 but a more beneficial treatment effect was observed in period 1 as compared with placebo. Although the treatment by period interaction was demonstrated in both cross-over studies, the trend of the treatment effect over periods was not consistent. For study C-98-003, the large treatment difference (active treatment versus placebo) was shown in period 2 and 3, but the large difference was shown in period 1 for this study. In either study, the sponsor presented the results **by averaging over three periods** and failed to show the inconsistent results across periods. This reviewer's analysis demonstrated inconsistent estimates of time to onset and loss of efficacy across periods.

Although SKAMP was validated by Wigal et al. (1998) [2], the items that were validated in the article (5 items for attention subscale) was not the same version as those in the current study (7 items for combined attention subscale). Also, SKAMP may be sensitive to detect the difference between active treatments and placebo, but it was not as sensitive and reliable to differentiate the two active treatment groups [2]. The authors in [2] interpreted this circumstance was attributed to the restriction of range of the SKAMP. Therefore, using SKAMP to distinguish the two active treatments may be questionable.

In this study, this reviewer noticed an overall increasing trend overtime (Figure B.I.1) that suggested a possible wearing-off treatment effect. But since the upward trend also occurred in placebo group and it was not present in study C-98-003 (Figure A.I.1), further studies are warranted to confirm whether the increasing trend is just a random phenomenon.

Figure B.II.1
LSmeans of CS teacher IOWA I/O, by Period

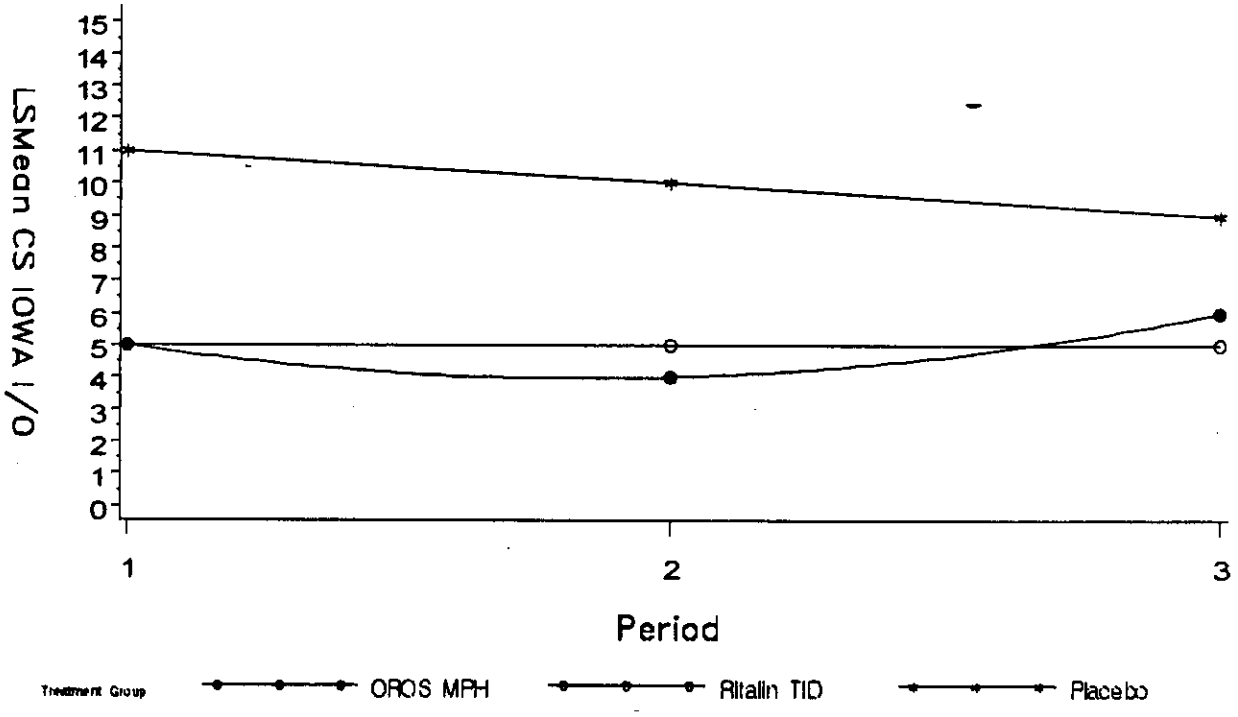


Figure B.II.2a

Mean of LS teacher SKAMP Combined Attention Rating

Period 1

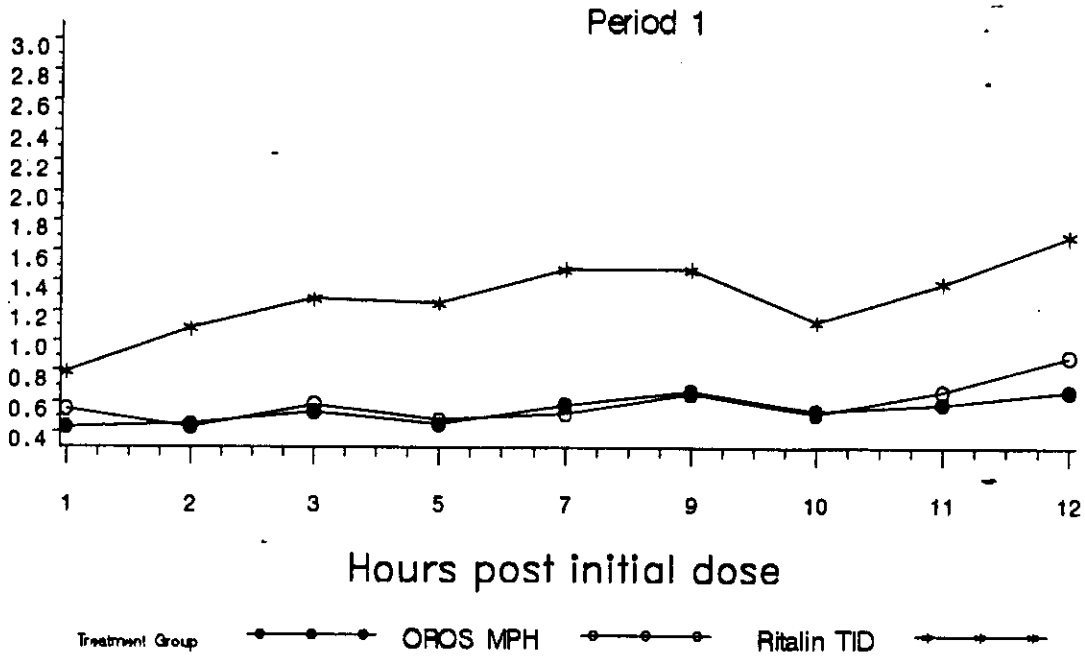


Figure B.II.2b

Mean of LS teacher SKAMP Combined Attention Rating

Period 2

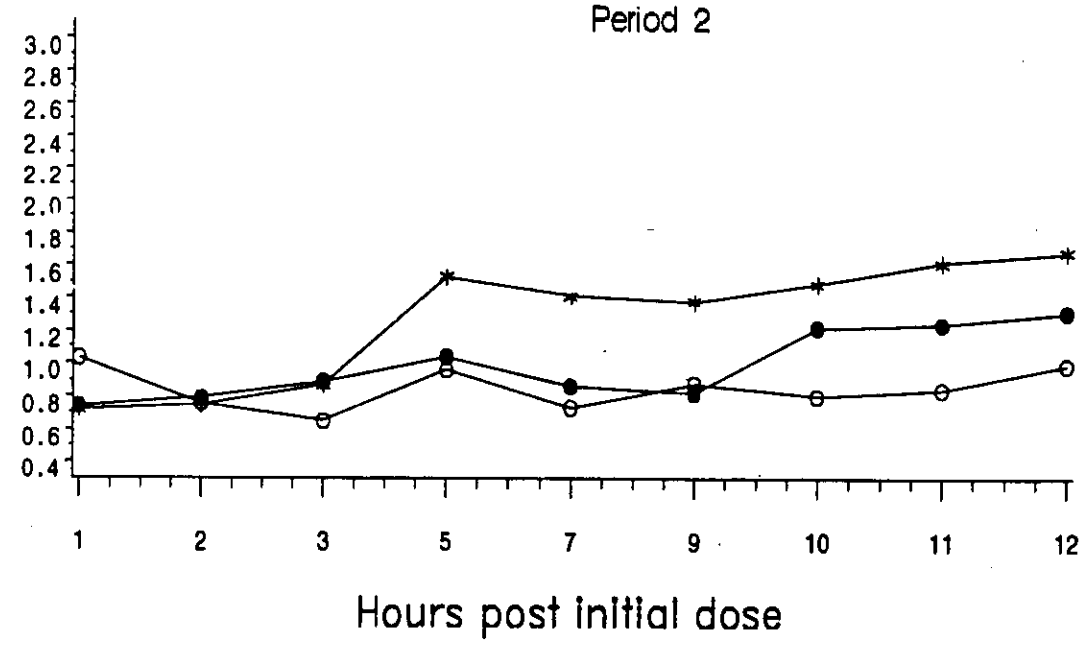
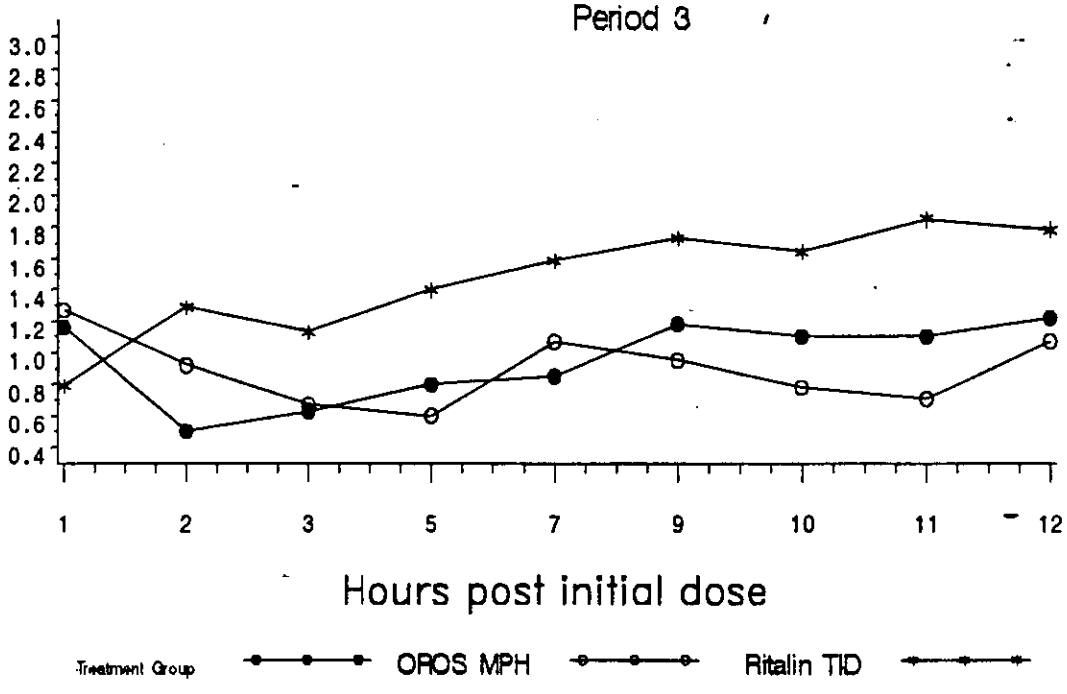


Figure B.II.2c

Mean of LS teacher SKAMP Combined Attention Rating

Period 3



APPEARS THIS WAY
ON ORIGINAL

Protocol C-98-005

Design and Objectives

This was a multicenter, double-blind, double-dummy, randomized, placebo-controlled, active-controlled, parallel group comparison of OROS, with Ritalin and placebo. Based on the pre-study titrated therapeutic dose level and regimen, patients aged 6-12 years old were equally randomized to one of three treatments : OROS(O), Ritalin(R) and Placebo(P).

Patients who were currently receiving methylphenidate for ADHD could enter the study after they had their ADHD diagnosis confirmed within 6 months in the screening study (Protocol C-98-011). While patients who were not currently taking methylphenidate for ADHD could complete Protocol C-98-007 before entering the study.

The duration of the treatment is 28 days which included four study visits: day –1 (preferably on the Friday immediately prior to randomization), 7, 14 and 28. On days –1 6, 13, 20 and 27, the community school teacher and parent/caregiver rated the IOWA Conners scale and on –1 and 27, rated SNAP-IV rating scale. On days –1 and 7, the community school teacher also rated peer interaction items and parents used Home situation Questionnaire to evaluate evening behavior. At the end of the study, global assessment of the treatment effect was determined by parent/caregiver, community school teacher, and the investigator.

The objective of the study is to compare the efficacy and safety of OROS with placebo and immediate release Ritalin TID.

Efficacy Endpoints

The primary efficacy parameter was the community school teach IOWA Conners Rating scale (Inattention/Overactivity subscale) on the last evaluation for each patient.

Analysis Plan

A total of 300 evaluable patients was planned to provide more than 99% power to detect a 3 units difference in IOWA Conners Rating scale (I/O subscale) between OROS and placebo. This calculation was based on a t-test with standard deviation of 3 and alpha level=0.05. This sample size also provided 80% power to show therapeutic equivalence between OROS and Ritalin based on the primary endpoint. The sponsor claimed that the two treatments would be considered as equivalent if the 95% confidence interval of the treatment difference (OROS versus Ritalin), fell within ± 1.2 units based on two one-sided tests with alpha level=0.025. Assuming 15% overall drop-out rate, 354 patients were planned for this study.

The primary hypothesis is to test the difference between OROS and placebo in the primary endpoint is equal to zero. All tests were two-sided at 0.05 significance level. Tests for the

baseline variables were performed at 0.10 significant level. Based on LSD approach, pairwise comparisons were not considered as significant unless the overall treatment effect was significant.

The primary analysis population included all randomized patients who received study medication and had at least one post treatment assessment while on study or within 10 days of discontinuing study medication. The protocol specified that all available data would be used for the secondary analysis. In the report, ratings that were made before dosing or more than 10 days after last day of dosing were excluded from the study. The last observation carried forward (LOCF) method was used for the primary analysis and the observed cases (OC) analysis was used for the secondary analysis as suggested by the agency (March 29, 1999).

The primary efficacy endpoint was analyzed with an ANOVA model **that included treatment only**. Treatment effect on the primary efficacy parameter was presented for each center using ANOVA model that included treatment and center. ANCOVA model was used for the subgroup analysis by including individual baseline factors such as site, sex and age (grouped as male 6-9 years, male 10 to 12 years, female 6 to 9 years and female 10 to 12 years), site, previous therapy, comorbidity, ADHD diagnosis, baseline rating and dose level. The interaction of each baseline factor and treatment was also tested.

Sponsor's Result

312 patients were randomized into this study based on pre-study dose levels within each site. A total of 14 study sites had enrolled patients. 30 patients from site 3 were excluded from the efficacy analyses due to the data from this site was not reliable and verifiable. The sponsor notified the agency about the termination of site 3 in a letter to the Division dated January 11, 1999. In this letter, the sponsor wrote that they discovered the lack of adherence to the on-going study protocols of site 3 which resulted in multiple protocol violations. Subsequently, the sponsor submitted a protocol amendment to exclude site 3 from the primary efficacy data and a brief analysis plan was provided to assess the impact of excluding site 3 on the results (March 17, 1999).

Among 282 patients randomized at 13 sites, 90 patient were randomized within dose level 1(18 mg OROS, 5 mg Ritalin or placebo), 122 patients within dose level 2 (36 mg OROS, 10 mg Ritalin or placebo) and 70 within dose level 3 (54 mg OROS, 15 mg Ritalin or placebo).

5 out of the 282 randomized patients did not receive any study medication. Of the 277 patients who received medication, 94 received OROS, 94 received Ritalin and 89 received placebo (Table C.I.1). 71 patients prematurely discontinued (25.6%): placebo group had the highest percentage of early terminated patients (48.3%) than OROS and Ritalin groups (16% and 18.3%, respectively). The most dominant reason for discontinuation is lack of efficacy. Among 71 prematurely terminated patients, 59 were due to lack of efficacy. Placebo group had more patients dropped out due to lack of efficacy (n=38, 42.7 % of the 89 placebo patients who received medication). OROS and Ritalin group had comparable numbers of patients dropped out due to lack of efficacy (n=11, 11.7% for OROS and n=10, 10.6% for Ritalin) (Table C.I.1).

Most patient demographic variables were comparable between treatment groups (table C.I.2). The majority of patients were males (82.6%) and Caucasians (84.4%). More young kids (age 6-9 years old) were randomized to OROS (66%) and Placebo (63%) than Ritalin (53%). Overall, more young patients (60%) were enrolled into this study. More boys were in Placebo (83%) and Ritalin group (87%) than in OROS (78%). Majority of patients received methylphenidate (73%, 64% and 67% for OROS, Ritalin and placebo, respectively) prior to the study. The most dominant ADHD diagnosis is the combined subtype (73.4%, see Table C.I.3). Comorbidities were present in 41.1%, 48.5% and 50.0% of OROS, Ritalin and placebo patients, respectively. Oppositional defiance disorder was the major comorbidity in these three treatment groups.

TABLE C.I.1 Reasons for Discontinuation of Study Medication: All Randomized Patients (Site 3 Excluded)

Treatment Group	OROS (n=95)	Ritalin (n=97)	Placebo (n=90)	Total (n=282)
Number (%) of Patients Who Received the Study Medication	94 (100.0%)	94 (100.0%)	89 (100.0%)	277 (100.0%)
Number (%) of Patients Who Completed the Study Medication	79 (84.0%)	81 (86.2%)	46 (51.7%)	206 (74.4%)
Number (%) of Patients Who Discontinued the Study Medication Prematurely	15 (16.0%)	13 (13.8%)	43 (48.3%)	71 (25.6%)
Number (%) of Patients Who Discontinued Study Medication Prematurely by Termination Reason:				
Adverse Event/Intercurrent Illness	1 (1.1%)	0	1 (1.1%)	2 (0.7%)
Protocol Violation	0	1 (1.1%)	1 (1.1%)	2 (0.7%)
Noncompliance	1 (1.1%)	1 (1.1%)	1 (1.1%)	3 (1.1%)
Lost to Follow-up	1 (1.1%)	0	0	1 (0.4%)
Lack of Efficacy	11 (11.7%)	10 (10.6%)	38 (42.7%)	59 (21.3%)
Adverse Event Requiring Dose Reduction	0	1 (1.1%)	0	1 (0.4%)
Other	1 (1.1%)	0	2 (2.2%)	3 (1.1%)

The baseline community school teacher IOWA Conners I/O subscale appears to be comparable between treatment groups (Table C.I.4). Placebo group seems to have higher baseline community school O/D IOWA Conner scores than OROS and Ritalin.

Among 277 patients who received medication (with site 3 excluded), 16 patients were excluded from the primary analysis because of no available community school teacher IOWA Conners ratings, or the ratings were before the first day of drug or 10 days after the last dose. Based on the community school teacher IOWA Conners rating (exclude site 3, use last observation carried over approach), OROS and Ritalin were significantly superior to placebo in controlling the inattention and overactivity ($p<0.001$, Table C.I.5). No statistical significant difference was found between OROS and Ritalin.

TABLE C.I.2
Demographics Summary
(Site 3 Excluded)

Treatment Group	OROS (n=95)	Ritalin (n=97)	Placebo (n=90)	Total (n=282)
Age (years) - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)	282 (100.0%)
6 - 9	63 (66.3%)	51 (52.6%)	57 (63.3%)	171 (60.6%)
10 - 12	32 (33.7%)	46 (47.4%)	33 (36.7%)	111 (39.4%)
Mean (SD)	8.8 (1.7)	9.1 (1.9)	8.9 (1.8)	9.0 (1.8)
Median	9.0	9.0	8.5	9.0
(Min, Max)	(5, 12)	(6, 13)	(6, 13)	(5, 13)
Sex - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)	282 (100.0%)
Male	74 (77.9%)	84 (86.6%)	75 (83.3%)	233 (82.6%)
Female	21 (22.1%)	13 (13.4%)	15 (16.7%)	49 (17.4%)
Race - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)	282 (100.0%)
Caucasian	79 (83.2%)	87 (89.7%)	72 (80.0%)	238 (84.4%)
Black	7 (7.4%)	4 (4.1%)	10 (11.1%)	21 (7.4%)
Asian	0	1 (1.0%)	0	
1 (0.4%)				
Hispanic	4 (4.2%)	2 (2.1%)	4 (4.4%)	10 (3.5%)
Other	5 (5.3%)	3 (3.1%)	4 (4.4%)	12 (4.3%)
Prior ADHD Stimulant Therapy [a] - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)	282 (100.0%)
None	20 (21.1%)	18 (18.6%)	19 (21.1%)	57 (20.2%)
No Drug	3 (3.2%)	9 (9.3%)	6 (6.7%)	18 (6.4%)
Non-methylphenidate	3 (3.2%)	8 (8.2%)	5 (5.6%)	16 (5.7%)
Methylphenidate	69 (72.6%)	62 (63.9%)	60 (66.7%)	191 (67.7%)
Height				
Mean (SD)	136.0 (11.1)	137.5 (11.7)	135.0 (12.3)	136.2 (11.7)
Median	135.9	135.5	132.2	134.8
(Min, Max)	(109, 163)	(117, 162)	(113, 166)	(109, 166)
Weight				
Mean (SD)	33.4 (9.7)	34.0 (10.7)	33.1 (12.1)	33.5 (10.8)
Median	30.7	31.1	29.5	30.7
(Min, Max)	(20, 64)	(20, 66)	(19, 80)	(19, 80)

Note: Patient 159010 turned 6 years old while on study medication and is categorized under the 6 - 9 year age group. Patients 19185 and 29091 were randomized at age 13 although the protocol specified the maximum age was to be 12; they are categorized under the 10 - 12 year age group.

a Prior stimulant therapy status refers to methylphenidate therapy received prior to C-98-005 study medication and to other therapies received prior to C-98-007 study medication.

TABLE C.I.3
Diagnostic Criteria - ADHD Diagnosis and Comorbidities:
All Randomized Patients
(Site 3 Excluded)

	Treatment Group			
	OROS (n=95)	Ritalin (n=97)	Placebo (n=90)	All (n=282)
ADHD diagnosis - n(%)	95 (100.0%)	97 (100.0%)	90 (100.0%)	282 (100.0%)
Combined	74 (77.9%)	64 (66.0%)	9 (76.7%)	207 (73.4%)
Predominantly inattentive	16 (16.8%)	27 (27.8%)	12 (13.3%)	55 (19.5%)
Predominantly hyperactive -impulsive	5 (5.3%)	6 (6.2%)	9 (10.0%)	20 (7.1%)
Comorbidities - n(%)	39 (41.1%)	47 (48.5%)	45 (50.0%)	131 (46.5%)
Oppositonal Defiance Disorder	35 (36.8%)	40 (41.2%)	43 (47.8%)	118 (41.8%)
Conduct Disorder	9 (9.5%)	9 (9.3%)	14 (15.6%)	32 (11.3%)
Tics Disorder	6 (6.3%)	5 (5.2%)	4 (4.4%)	15 (5.3%)
Anxiety Disorder	0	0	4 (4.4%)	4 (1.4%)
Depresssion	0	1 (1.0%)	1 (1.1%)	2 (0.7%)

Note: Data is summarized from the C-98-011 screening study. A patient may be reported in more than one comorbidity category.

The analyses including site 3 or excluding site 3 did not have substantial change of the results. Similar results were obtained from observed case only analyses (include or exclude site 3). These results were consistent at home setting based on parent/caregiver ratings. The results from different scale evaluations, such as IOWA Conners O/D, peer interaction and SNAP-IV scores were also consistent in favor of OROS.

The protocol specified that OROS and Ritalin were to be considered as therapeutically equivalent if the 95% confidence interval of the treatment difference in the IOWA I/O Conners subscale fell within $\pm$ 1.2 units. The sponsor claimed that the confidence interval obtained (95% C.I.= (-1.57,0.83)) met this criteria.

For the subgroup analysis, no significant treatment by baseline factor interaction was found. Age and sex combined, previous therapy, comorbidity, ADHD type and baseline Conner rating were the significant baseline factors in predicting the Community school teacher IOWA Conners I/O ratings. The sponsor found that the treatment effect was still significant after adjusting for these baseline factors separately.

TABLE C.I.4
Community School Teacher and Parent/caregiver Baseline IOWA Conners,
All Randomized Patients
(Site 3 Excluded)

	Treatment Group				
	OROS (n=95)	Ritalin (n=97)	Placebo (n=90)	Total (n=282)	p-value[a]
Community School Teacher					
Inattention/					
Overactivity - n(%)	94 (100.0%)	94 (100.0%)	88 (100.0%)	276 (100.0%)	
0	1 (1.1%)	0	0	1 (0.4%)	
1 - 5	15 (16.0%)	15 (16.0%)	13 (14.8%)	43 (15.6%)	
6 - 10	32 (34.0%)	31 (33.0%)	22 (25.0%)	85 (30.8%)	
11 - 15	46 (48.9%)	48 (51.1%)	53 (60.2%)	147 (53.3%)	
Mean (SD)	9.7 (4.1)	9.9 (3.7)	10.3 (3.8)	10.0 (3.8)	0.636
Median	10.0	11.0	11.0	11.0	
(Min, Max)	(0, 15)	(2, 15)	(1, 15)	(0, 15)	
P-value[b]:	OROS vs Placebo	0.346			
	Ritalin vs Placebo	0.559			
	OROS vs Ritalin	0.715			
Oppositional/					
Defiance - n(%)	94 (100.0%)	94 (100.0%)	88 (100.0%)	276 (100.0%)	
0	24 (25.5%)	30 (31.9%)	15 (17.0%)	69 (25.0%)	
1 - 5	37 (39.4%)	39 (41.5%)	35 (39.8%)	111 (40.2%)	
6 - 10	26 (27.7%)	15 (16.0%)	27 (30.7%)	68 (24.6%)	
11 - 15	7 (7.4%)	10 (10.6%)	11 (12.5%)	28 (10.1%)	
Mean (SD)	4.3 (4.2)	3.8 (4.4)	5.4 (4.5)	4.5 (4.4)	0.043
Median	3.0	2.0	5.0	4.0	
(Min, Max)	(0, 15)	(0, 15)	(0, 15)	(0, 15)	
P-value[b]:	OROS vs Placebo	0.091			
	Ritalin vs Placebo	0.014			
	OROS vs Ritalin	0.427			
Parent/Caregiver					
Inattention/					
Overactivity - n(%)	95 (100.0%)	96 (100.0%)	90 (100.0%)	281 (100.0%)	
1 - 5	2 (2.1%)	11 (11.5%)	8 (8.9%)	21 (7.5%)	
6 - 10	35 (36.8%)	46 (47.9%)	36 (40.0%)	117 (41.6%)	
11 - 15	58 (61.1%)	39 (40.6%)	46 (51.1%)	143 (50.9%)	
Mean (SD)	11.1 (2.6)	9.9 (3.2)	10.4 (3.0)	10.5 (3.0)	0.022
Median	11.0	10.0	11.0	11.0	
(Min, Max)	(2, 15)	(2, 15)	(4, 15)	(2, 15)	
P-value[b]:	OROS vs Placebo	0.141			
	Ritalin vs Placebo	0.211			
	OROS vs Ritalin	0.006			
Oppositional/					
Defiance - n(%)	95 (100.0%)	96 (100.0%)	(100.0%)	281 (100.0%)	
0	4 (4.2%)	5 (5.2%)	0	9 (3.2%)	
1 - 5	27 (28.4%)	29 (30.2%)	26 (28.9%)	82 (29.2%)	
6 - 10	34 (35.8%)	37 (38.5%)	39 (43.3%)	110 (39.1%)	
11 - 15	30 (31.6%)	25 (26.0%)	25 (27.8%)	80 (28.5%)	
Mean (SD)	8.1 (4.4)	7.3 (4.0)	8.2 (3.8)	7.9 (4.1)	0.276
Median	8.0	7.0	8.0	8.0	
(Min, Max)	(0, 15)	(0, 15)	(1, 15)	(0, 15)	
P-value[b]:	OROS vs Placebo	0.941			
	Ritalin vs Placebo	0.158			
	OROS vs Ritalin	0.175			

Note: IOWA-Conners, Peer Interaction and Other Behavior Ratings are determined as follows:
Inattention/overactivity - sum of IOWA-Conners items 1-5.
The IOWA-Conners were taken from C-98-011 screening study when patients were off medication.
a 2-sided p-values for overall comparison among all treatment groups were obtained from one way ANOVA.
b 2-sided p-values for pairwise comparison between specified two treatment groups were obtained from one way ANOVA.

TABLE C.I.5
Analysis of Community School Teacher IOWA Conners Inattention/Overactivity Subscale at Final Assessment: All Randomized Patients (Site 3 Excluded)

Treatment Group	OROS (n= 95)	Ritalin (n= 97)	Placebo (n= 90)
Inattention/ Overactivity - n(%)	90 (100.0%)	90 (100.0%)	81 (100.0%)
0	7 (7.8%)	4 (4.4%)	0
1 - 5	36 (40.0%)	41 (45.6%)	17 (21.0%)
6 - 10	36 (40.0%)	29 (32.2%)	22 (27.2%)
11 - 15	11 (12.2%)	16 (17.8%)	42 (51.9%)
Mean (SD)	5.98 (3.91)	6.35 (4.31)	9.77 (4.02)
(Min, Max)	(0, 14)	(0, 15)	(1, 15)
Overall comparison p-value [a]	< 0.001		
OROS versus Placebo			
n1,n2	90, 81		
LS Mean Difference (SEM)	-3.79 (0.63)		
95% C.I. for difference	(-5.03, -2.56)		
p-value [b]	< 0.001		
Ritalin versus Placebo			
n1,n2	90, 81		
LS Mean Difference (SEM)	-3.42 (0.63)		
95% C.I. for difference	(-4.65, -2.19)		
p-value [b]	< 0.001		
OROS versus Ritalin			
n1,n2	90, 90		
LS Mean Difference (SEM)	-0.38 (0.61)		
95% C.I. for difference	(-1.57, 0.82)		
p-value [b]	0.539		

Note: SD = Standard deviation; C.I. = Confidence interval;
n1 = Number of patients in test treatment group;
n2 = Number of patients in control treatment group;
The LS mean (least squares mean) difference and SEM (standard error of LS mean difference) are estimated from the fixed effects ANOVA model that includes the factor treatment only.
The inattention/overactivity subscale is the sum of items 1 - 5 of the IOWA Conners rating scale.

a 2-sided p-value for the overall comparison among all treatment groups is based on type III analysis from the ANOVA model.

b 2-sided p-values for the pairwise test of treatment effect are based on type III analysis from the ANOVA model.

Reviewer's Evaluation and Comments

This reviewer confirmed the sponsor's primary results that OROS is more effective than placebo in the community teacher IOWA Conners rating based on the intent to treat, LOCF approach. The more favorable result of OROS was consistent based on the secondary analysis using "observed cases only" population.

No significant difference on the primary endpoint between OROS and Ritalin was found. However, this reviewer did not agree with the sponsor's claim on the equivalence between two active treatments. The issue on equivalence between two active treatments had been raised on the agency's February 24, 1999 letter to the sponsor. The agency was not convinced that the proposed 1.2 points as the upper limit for the confidence interval of difference between treatments was clinically sufficient.

This reviewer also confirmed the sponsor's subgroup analysis result on the primary endpoint. The significant OROS benefit were not changed by including baseline confounding factors (e.g. age and sex combined, site, previous therapy, comorbidity, ADHD type, baseline Conners rating and dose level) into the ANCOVA model. This reviewer noticed a marginal significant dose level by treatment interaction (p-value=0.06) and a significant effect of age group ($\leq 9, > 9$ years old) alone (p-value=0.003). Since patients were not randomized to dose level, the progressive effective trend due to dose level increased can not be confirmed.

In the sponsor's subgroup analysis, the baseline scores were found to be highly significant (p-value <0.001). The other baseline factors (ADHD type, previous therapy, co-morbidity status and age and sex combined factor) were also found to be significant. This reviewer noticed that without adjusting for the baseline Conners scores, these results may be confounded by the baseline Conners scores. The significant baseline factor effect can be either attributed to the factor itself or due to the baseline Conners scores were different between subgroups. A summary of the mean baseline, final measurement results and change from baseline of the Conners score was presented in Table C.II.1 to show the treatment effect across various subgroups. Note that the baseline Conners scores were different between age group, sex, ADHD type, prior stimulant therapy and co-morbidity status. However, when the mean change from baseline result was presented, the differential OROS benefit between some subgroups became less substantial (e.g. age subgroup, previous stimulant therapy). A cautious note about reading table C.II.1 is that the sample size in some subgroups was too small to make accurate estimates of treatment effect and the treatment group may not be comparable, so no inferential conclusion should be drawn.

TABLE C.II.1
Summary of Community School Teacher IOWA Conners
Inattention/Overactivity Subscale at Final Assessment by Subgroups

Subgroup	Level	Treat Group	Mean Baseline Scores(n)	Mean Final Scores (n)	Mean Change from baseline Scores(n)
Age	6-9 yrs	OROS	10.26 (62)	6.32 (60)	-4.11 (59)
		Ritalin	10.24 (49)	6.70 (47)	-3.48 (46)
		Placebo	11.04 (56)	10.79 (52)	-0.22 (51)
	10-12 yrs	OROS	8.72 (32)	5.30 (30)	-3.57 (30)
		Ritalin	9.61 (45)	5.97 (43)	-3.81 (43)
		Placebo	8.95 (32)	7.95 (29)	-0.63 (28)

TABLE C.II.1
Summary of Community School Teacher IOWA Conners
Inattention/Overactivity Subscale at Final Assessment by Subgroups
(Continued)

Subgroup	Level	Treat group	Mean Baseline Scores(n)	Mean Final Scores (n)	Mean Change from baseline Scores(n)
Sex	Male	OROS	10.14 (73)	6.17 (71)	-4.09 (70)
		Ritalin	10.01 (81)	6.65 (78)	-3.39 (77)
		Placebo	10.40 (73)	9.78 (67)	-0.53 (65)
	Female	OROS	8.33 (21)	5.26 (19)	-3.32 (19)
		Ritalin	9.54 (13)	4.42 (12)	-5.25 (12)
		Placebo	9.67 (15)	9.71 (14)	0.43 (14)
Race	Caucasian	OROS	9.79 (79)	6.01 (75)	-3.98 (75)
		Ritalin	9.89 (86)	6.38 (82)	-3.58 (82)
		Placebo	10.29 (71)	9.95 (65)	-0.21 (64)
	Black	OROS	9.67 (6)	7.00 (6)	-2.40 (5)
		Ritalin	11.0 (4)	6.00 (3)	-4.00 (3)
		Placebo	8.67 (9)	9.30 (10)	-0.00 (9)
Dose Level	18mg OROS/ 5mg Ritalin	OROS	9.63 (30)	7.27 (30)	-2.62 (29)
		Ritalin	9.86 (29)	7.88 (26)	-1.73 (26)
		Placebo	10.21 (28)	8.92 (26)	-1.36 (25)
	36mg OROS/ 10mg Ritalin	OROS	9.69 (41)	5.60 (40)	-4.33 (40)
		Ritalin	10.00 (39)	5.51 (39)	-4.61 (38)
		Placebo	10.26 (39)	9.90 (36)	-0.25 (35)
	54mg OROS/ 15mg Ritalin	OROS	9.96 (23)	4.80 (20)	-5.0 (20)
		Ritalin	9.94 (26)	6.07 (25)	-4.15 (25)
		Placebo	10.38 (21)	10.68 (19)	0.74 (19)
Previous Stimulant Therapy	Never	OROS	10.05 (20)	5.32 (19)	-5.26 (19)
		Ritalin	9.56 (18)	5.53 (17)	-4.12 (17)
		Placebo	8.91 (19)	7.08 (18)	-1.93 (18)
	No drug in past 4 weeks	OROS	13.00 (3)	4.67 (3)	-8.33 (3)
		Ritalin	10.56 (9)	2.75 (8)	-8.00 (8)
		Placebo	12.83 (6)	9.60 (5)	-3.20 (5)
	ADHD Stimulants	OROS	9.51 (71)	6.22 (68)	-3.35 (67)
		Ritalin	9.96 (67)	7.01 (65)	-2.96 (64)
		Placebo	10.44 (63)	10.62 (58)	0.39 (56)
ADHD type	Combined	OROS	10.37 (73)	6.36 (70)	-4.12 (69)
		Ritalin	10.76 (61)	7.00 (59)	-3.82 (58)
		Placebo	10.63 (67)	10.27 (63)	-0.08 (61)
	Predominantly inattentive	OROS	7.13 (16)	5.13 (15)	-2.47 (15)
		Ritalin	8.33 (27)	4.56 (25)	-3.76 (25)
		Placebo	8.69 (12)	7.50 (11)	-0.61 (11)
	Predominantly hyperactive/impulsive	OROS	8.80 (5)	3.20 (5)	-5.60 (5)
		Ritalin	8.83 (6)	7.50 (6)	-1.33 (6)
		Placebo	9.78 (9)	8.86 (7)	-2.43 (7)
Comorbidity	Oppositional/defiance	OROS	10.60 (35)	6.03 (32)	-4.69 (32)
		Ritalin	11.07 (39)	7.53 (38)	-3.76 (38)
		Placebo	10.79 (43)	10.66 (38)	0.13 (38)
	Non-Opposition/defiance	OROS	9.22 (59)	5.95 (58)	-3.50 (57)
		Ritalin	9.14 (55)	5.50 (52)	-3.55 (51)
		Placebo	9.78 (45)	8.99 (43)	-0.82 (41)

TABLE C.II.1
Summary of Community School Teacher IOWA Conners
Inattention/Overactivity Subscale at Final Assessment by Subgroups
(Continued)

Subgroup	Level	Treat group	Mean Baseline Scores(n)	Mean Final Scores (n)	Mean Change from baseline Scores(n)
Baseline Conners score	First tertile	OROS Ritalin Placebo	4.97 (32) 5.68 (33) 5.34 (27)	4.10 (29) 4.57 (31) 7.50 (25)	-1.0 (29) -1.12 (31) 2.09 (25)
	Second tertile	OROS Ritalin Placebo	10.75 (35) 10.73 (33) 11.09 (32)	6.06 (34) 6.97 (32) 10.90 (31)	-4.65 (34) -3.81 (32) -0.23 (31)
	Third tertile	OROS Ritalin Placebo	14.07 (27) 14.04 (28) 13.97 (29)	7.88 (26) 7.62 (26) 10.70 (23)	-6.23 (26) -6.42 (26) -3.22 (23)

To further confirm the result by taking account of the baseline Conners score, this reviewer performed the sponsor's primary analysis adjusting for the baseline Conners score. The Conners score difference between OROS and placebo was still highly significant (p=0.0001). The 95% confidence interval for the OROS versus Ritalin comparison became [-1.45, 0.78] which did not deviate much from the sponsor's result.

The drop-out rate of this study (48%) was considerably larger than the rates of the two cross-over studies (3 out of 64 patients in C-98-003 and 2 out of 70 patients in C-97-025). There are several possible explanations of this situation. One of the explanations could be that patient in the cross-over studies knew they will receive different treatment in the following period, so they tend to come back with expectation of receiving a "better" treatment (as pointed out by the medical officer, Dr. Masholder). Also, the parallel study did have longer exposure to the same treatment than the cross-over studies. In this reviewer's opinion, the different drop-out rates between two different study designs may not be unreasonable. Since the results based on "observed case only" (OC) population also showed the beneficial OROS effect and it is known that the OC analysis is biased in favor of placebo (i.e. patients who completed the study in the placebo group were better responders), the high drop-out rate does not seem to have substantial impact on the conclusion.

Summary

- The sponsor showed OROS was more effective than placebo across all three studies based on the primary endpoint (community school teacher IOWA Conners I/O rating). The results were robust based on other statistical analysis approaches conducted by this reviewer. In addition, the results were not changed by adjusting for various subgroups: age, gender, race and dose level.

- In Study C-98-005, about 48% placebo patient prematurely terminated the study medication (most of them were due to lack of efficacy). The OROS efficacious result was not changed based on "observed case only" analysis. The results were also not changed by including or excluding site 3.

- The baseline community school IOWA Conners I/O score was a significant predictor for the final Conners I/O score. The sponsor did not adjust for the baseline score in their analysis. The reviewer found the OROS beneficial effect was very consistent across various subgroups based on the "change from baseline" data.

- The sponsor showed that the estimated onset and loss of efficacy times for OROS were, 1.5 and 12.5, respectively, based on laboratory school teacher SKAMP combined attention rating in two cross-over studies. The sponsor claimed that the sustained benefit was comparable between OROS and Ritalin. However, the sponsor's result was based on average estimates over three periods. This reviewer demonstrated an inconsistent treatment effect across periods. These inconsistent period-by-period treatment effects were shown in different directions based on the two cross-over studies.

- The sponsor noticed a progressive benefit of OROS as dose level increased in Study C-97-025. Since the same result was not found in Study C-98-003 and patients were not randomized to dose levels, the sponsor's claimed progressive OROS benefit can not be confirmed.

- With regard to the comparison between OROS and Ritalin, no significant difference was found based on the primary endpoint across three studies. However, the equivalence can not be claimed based on the insufficient clinical meaningful difference of the primary endpoint. The sponsor wants to show the comparability of OROS and Ritalin based on a graphical display of the SKAMP combined attention score. Due to a possible drug effect wearing-off trend over-time in one of the cross-over studies and the issue of non-sensitive instrument for active treatment comparisons, a further investigation of the comparability of OROS and Ritalin is warranted.

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Mathematical Statistician

Concur :

Dr. Jin /S/ Dr. Chi /S/

CC:
NDA: 21-121
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Mosholder
HFD-120/Ms. Homonnay
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Shen

Note : This document was saved in c:\

Note : The numbering scheme used in this documentation is as follows:
The first letter was used to indicate the study (A: C-98-003, B: C-97-025, C: C: C-98-005); the second number indicates either the sponsor's results or the reviewer's (I: the sponsor's result; II: the reviewer's result); and the third number indicates the numbering within a study for the sponsor's or the reviewer's results.

Reference :

[1] J. Fleiss, The Design and Analysis of Clinical Experiments,1986, John Wiley & Sons.

[2] S. B. Wigal, S. Gupta, D. Guinta and J. M. Swanson, 'Reliability and Validity of the SKAMP Rating Scale in a Laboratory School Setting', Psychopharmacology Bulletin 34(1):47-53, 1998.

Appendix A

The sponsor proposed Mixed effect ANOVA model can be formulated as follows [reference]:

$$y_{ijkl} = \tau + \mu_l + \alpha_i + \gamma_k + \rho_{j(i)} + e_{ijkl} \qquad [1]$$

where y_{ijkl} is the response for the j th patient, l th treatment, i th sequence and k th period,
τ is the reference value,
μ_l is the fixed effect, i.e. the increment for l th treatment (l =1,2),
α_i is the fixed effect, i.e. the increment for i th sequence (i =1,..,5),
γ_k is the fixed effect, i.e. the increment for the k th period (k =1,2),
$\rho_{j(i)}$ is the random subject effect within a sequence assumed independently distributed as $N(0, \sigma^2_b)$,
and e_{ijkl} is the error term assumed independently distributed as $N(0, \sigma^2_\omega)$.

The covariance matrix of the vector y can be formulated as

$$Var(y) = \sigma^2_b \, I_n \otimes J_3 + \sigma^2_\omega \, I_n \otimes I_3,$$

where J_x is an x by x matrix with element 1, I_x is an identity matrix and $A \otimes B$ denotes the Kronecker product of the matrices A and B. The variance-covariance of y had $\sigma^2_b + \sigma^2_\omega$ on the diagonal (i.e. $Var(y_{ijkl})$) and σ^2_b off the diagonal (i.e. $Cov(y_{ijkl}, y_{ijkl'})$).

The sponsor's results was computed using SAS PROC Mixed which used REML (Restricted Maximum Likelihood) estimates of the variance-covariance components to compute the F-statistic.

Reference :

R. Littell, G. Milliken, W. Stroup and W. Russell, SAS System for Mixed Models, SAS Institute Inc., 1996.