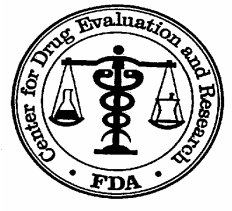

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-802/N_000
Drug Name:	Focalin^{TM} XR (dexmethylphenidate HCI) Extended-Release Capsules
Indication:	Attention-Deficit/Hyperactivity Disorder
Applicant:	Novartis Pharmaceuticals Corporation
Dates:	Date of Document: 7/28/04
	PDUFA Due Date: 5/28/05
Review Priority:	Standard
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring	Kun Jin, Ph.D.
Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Roberta Glass, M.D., Medical Reviewer
	Paul Andreason, M.D., Medical Team Leader
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1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

This reviewer agrees with the sponsor that the data in these two pivotal studies support the Focalin^{TM} XR's efficacy as a treatment in patients with Attention-Deficit/ Hyperactivity Disorder (ADHD). However, we should notice that these two pivotal trials were studying different patient populations based on two different kinds of dosage regimens. In other words, for either pediatric or adult patients, the sponsor only had one positive pivotal study to support the Focalin^{TM} XR's efficacy for each. In addition, this reviewer noticed that for the study on pediatric patients, only 17 patients were adolescents (i.e., 21% of all pediatric patients). For the study on adult patients, although the p-values for all three doses (20, 30, and 40 mg) were nominal significant even with multiplicity adjustment, (b) (4)

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor's clinical program of Focalin^{TM} XR included two double-blind, placebo-controlled pivotal studies, named studies 2301 and 2302; one in pediatric and one in adult patients with ADHD, respectively. The study in adults, i.e., Study 2302 was followed by a 6-month, open-label extension phase. Study 2301 was a flexible dose (5-30 mg q.d.) study with the primary endpoint based on the DSM-IV total subscale score of the CADS-T, and Study 2302 was a fixed dose (20, 30, 40 mg q.d.) study with the primary endpoint based on the total score of the DSM-IV ADHD rating scale. According to the sponsor, the Focalin^{TM} XR's efficacy as a treatment in patients with ADHD was demonstrated in both studies.

1.3 STATISTICAL ISSUES AND FINDINGS

- For both Studies 2301 and 2302, this reviewer confirmed all the sponsor's efficacy analysis results and agreed that the data supported the Focalin^{TM} XR's efficacy in treating patients with ADHD.

- For Study 2301, the sponsor found that the treatment-by-center interaction was significant when it was included in ANCOVA analysis for the primary endpoint and they provided reasons to explain this finding. After this reviewer's evaluation, this reviewer agrees with the sponsor that this significant interaction term does not invalid the drug's efficacy analysis results.

2. INTRODUCTION

2.1 OVERVIEW

The objective of this Focalin^{TM} XR program, which was originally named as Focalin^{TM} LA during its development under the IND stage, was to develop a long-acting form of

Focalin using the SODAS technology (extended-release dosage formulation), to characterize its pharmacokinetic profile and to demonstrate its safety and efficacy in pediatric and adult patients with Attention-Deficit/Hyperactivity Disorder (ADHD). Focalin (dexmethylphenidate tablets) is the pharmacologically active d-threo enantiomer of Ritalin® (racemic methylphenidate hydrochloride [MPH]) and it was approved by the FDA on the year of 2001 as a treatment for pediatric ADHD. The SODAS™ technology was earlier used as the basis to approve the once-a-day formulation for Ritalin on the year of 2002.

In this submission, the sponsor included two double-blind, placebo-controlled studies, one in pediatric and one in adult patients with ADHD to demonstrate the efficacy of Focalin LA. They were named Studies 2301 and 2302, respectively. The study in adults (i.e., Study 2302) was followed by a 6-month, open-label extension phase. The major feature of these studies are summarized in the following Table 2.1.

Table 2.1 Overview of Controlled Pivotal Efficacy Studies

Study No.	Study Objective, Population	Planned/ Enrolled Patients	Treatment Duration	Medication dose/day	Efficacy Endpoint
2301	efficacy/safety study in pediatric patients aged 6-17 years	100/103	7 weeks	5-30 mg q.d.	mean change from baseline to final visit in the DSM-IV total subscale score of the CADS-T
2302	efficacy/safety study in adults	220/221	5 weeks	20, 30, 40 mg q.d.	mean change from baseline to final visit in the total score of the DSM-IV ADHD Rating Scale

There was a third double-blind, placebo-controlled study, named Study US08, which was included in the clinical program to explore the duration of effect of a single dose of Focalin LA in school children aged 6-12 years, but it was not designed as a pivotal study for the general efficacy claim in pediatric patients. Therefore, this review only focused on the evaluation of efficacy for the aforementioned two pivotal studies.

2.2 DATA SOURCES

The sponsor's electronic submission was stored in the directory of \\CDSESUB1\N21802\N_000\2004-07-28 of the center's electronic document room.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 Description of Study 2301

This study was titled as "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Focalin LA (dexmethylphenidate HCI Extended-Release Capsules) at 5-30 mg/day Administered Once Daily in Pediatric Patients 6-17 Years of Age with Attention-Deficit/ Hyperactivity Disorder (ADHD)." There were 12 centers in the US participated in this study.

3.1.1.1 Study Objectives

The objectives of this study were to compare the safety and efficacy of Focalin^{TM} LA (dexmethylphenidate hydrochloride extended-release capsules) 5-30 mg/day administered once daily and placebo in pediatric patients with ADHD.

3.1.1.2 Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, two-arm, parallel group study in pediatric outpatients, 6-17 years old, diagnosed with ADHD. Approximately, 100 patients were to be randomized in a 1:1 ratio between treatment and placebo. Patients were required to meet the DSM-IV criteria for ADHD of any type. Evaluations were based on assessments conducted weekly during their normal routines at school and at home. The study consisted of two phases: pre-randomization phase and double-blind treatment phase.

Pre-Randomization Phase

A pre-randomization phase of up to two weeks preceded the double-blind treatment phase. During this phase patients were screened and eligibility was assessed via inclusion/exclusion criteria. It was determined that a teacher and a parent were to be available to make the required assessments throughout the course of the study. Medical history and a psychiatric screening evaluation were performed and the diagnosis of DSM-IV defined ADHD was to be verified by a qualified clinician. Physical examination, vital signs and laboratory tests were to be performed. Results for all screening assessments were to be available and assessed prior to baseline (Visit 2).

Double-Blind Treatment Phase (7 weeks)

This phase included a flexible dosing period and a maintenance period. At baseline (Visit 2), randomized patients received either Focalin^{TM} LA at 5 mg/day or placebo. Flexible dosing was allowed during the first five weeks of the study to determine the optimal dose for each patient. During the last two weeks of the study or the maintenance period, the patient remained at the optimal dose without change or interruption. Final safety and efficacy assessments were completed at the conclusion of the double-blind treatment phase (or at the time of premature discontinuation from the study).

3.1.1.3 Efficacy Assessments and Evaluation

Efficacy Assessments:

(1) Teacher Assessment

The teacher assessed behavior observed during the school day by completing weekly the Conners ADHD/DSM-IV Scales for teachers (CADS-T). The CADS-T includes the ADHD Index (12 items) and the DSM-IV total subscale (18 items); the latter is divided into the DSM-IV Inattentive subscale (9 items) and the DSM-IV Hyperactive-Impulsive subscale (9 items).

(2) Parent Assessment

The parent assessed behavior observed on the weekend by completing weekly the Conners ADHD/DSM-IV Scales for parents (CADS-P). The CADS-P includes the ADHD Index (12 items) and the DSM-IV total subscales (18 items); the latter is divided into the DSM-IV inattentive subscale (9 items) and the DSM-IV Hyperactive-Impulsive subscale (9 items). The CADS-P was to be completed on a single specified day each week (preferably Mondays) assessing ADHD symptoms during the past weekend at home.

(3) Investigator Assessment

The investigator (or designated experienced clinician) performed global assessments at the time of the Visit by completing weekly the Clinical Global Impressions Scale (CGI), which consists of the CGI-Severity of Illness subscale and CGI-Improvement subscale.

Efficacy Evaluation:

All hypotheses were tested at the two-sided alpha level of 0.05. For the analysis of covariance (ANCOVA) of change from baseline in a rating scale score, Shapiro-Wilk test was used to check the normality of the ANCOVA model at the alpha level of 0.01. If the test was rejected, the Mann-Whitney-Wilcoxon test would be performed on the change from baseline in the rating scale score as the primary analysis.

(1) Primary Efficacy Variable

The primary efficacy variable was the change from baseline to final visit in the CADS-T DSM-IV total subscale score.

The primary analysis was an analysis of covariance (ANCOVA) with the following explanatory variables: treatment, center, and the baseline CADS-T DSM-IV total subscale score. The treatment-by-center interaction was explored by adding this interaction term to the ANCOVA model. If a treatment-by-center interaction was detected, the interaction would be explored in an ad-hoc manner.

The primary efficacy analysis was performed on the ITT population. The ANCOVA analysis was also performed on the completers population. The completers analysis served as a sensitivity analysis of the primary efficacy variable.

Within each age group, change from baseline to final visit in the CADS-T DSM-IV total subscale score was analyzed by an ANCOVA model similar to the analysis of the primary efficacy variable.

(2) Secondary Efficacy Variables

The following are the secondary efficacy variables:

- Change from baseline to final visit in the CADS-T DSM-IV Inattentive and Hyperactive-Impulsive subscale scores
- Change from baseline to final visit in the CADS-P DSM-IV total subscale score and subscale (Inattentive and Hyperactive-Impulsive) scores
- Proportion of patients with improvement on the CGI-I scale (defined as a final visit rating of 1 “very much improved” or 2 “much improved” on the CGI-I scale)
- Proportion of patients at each rating of the CGI-I scale at the final visit
- Proportion of patients at each rating of the CGI-I scale at each visit during the double-blind treatment phase
- Proportion of patients at each rating of the CGI-S scale at the final visit
- Change from Baseline to final visit in the CHQ Physical and Psychosocial component scores

Changes from baseline to final visit in the CADS-T DSM-IV subscale scores, the CADS-P DSM-IV total subscale score and subscale scores were analyzed by ANCOVA models similar to the analysis of the primary efficacy variable with treatment, center, and the corresponding baseline measurement as explanatory variables. Within each age group, change from baseline to final visit in the CADS-P DSM-IV total subscale score was analyzed by an ANCOVA model similar to the analysis of the primary efficacy variable.

Proportion of patients with improvement on the CGI-I scale was analyzed using a logistic regression model with treatment and center as explanatory variables. Proportion of patients at each rating of the CGI-I scale at the final visit was compared between Focalin LA and placebo using the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Proportion of patients at each rating of the CGI-I scale was summarized by treatment and visit on the OC data set of the ITT population. In addition, the CGI-I rating at Visit 9 was compared between Focalin LA and placebo using the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Proportion of patients at each rating of the CGI-S scale at the final visit was analyzed by the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Within each age group, proportion of patients with improvement on the CGI-I scale was analyzed using a logistic regression model with treatment and center as explanatory variables. Proportions of patients at each rating of the CGI-I and the CGI-S scales at the final visit were analyzed by the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Changes from Baseline to final visit in the CHQ component scores were also analyzed by ANCOVA models similar to the analysis of the primary efficacy variable with treatment, center, and the corresponding baseline CHQ component score as explanatory variables.

3.1.2 Efficacy Results for Study 2301

3.1.2.1 Patient Disposition, Population and Baseline Demographic Characteristics

Table 3.1 shows the patient disposition for the study. As observed from the table, one hundred and forty-one patients were screened, 103 patients were randomized and 38 were screening failures. The most common reason for screen failure was the patient not meeting the diagnostic/severity criteria. According to the table, patients were evenly randomized across the treatment groups. The discontinuation rate was higher in the placebo group (26.0%) compared to the Focalin LA group (9.4%). This was due to a greater percentage of patients in the placebo group lost to follow-up (12.0%), discontinuing because of an unsatisfactory therapeutic effect (8.0%) or withdrawal of consent (4.0%) compared to the Focalin LA group (3.8%, 3.8% and 0.0%, respectively).

There was only one patient in the study (placebo) who discontinued due to an adverse event. No Focalin LA treated patients discontinued due to an adverse event or withdrew their consent for participation in the study.

Table 3.1 Patient Disposition by Treatment Group (All Patients) for Study 2301

	Focalin LA N (%)	Placebo N (%)	All N (%)
All Patients			
Screened			141
Randomized	53 (100)	50 (100)	103 (100)
Completed	48 (90.6)	37 (74.0)	85 (82.5)
Discontinued	5 (9.4)	13 (26.0)	18 (17.5)
Adverse Event(s)	0 (0)	1 (2.0)	1 (1.0)
Unsatisfactory Therapeutic Effect	2 (3.8)	4 (8.0)	6 (5.8)
Lost to Follow-Up	2 (3.8)	6 (12.0)	8 (7.8)
Administrative Problems	1 (1.9)	0 (0)	1 (1.0)
Patient withdrew Consent	0 (0)	2 (4.0)	2 (1.9)

Table 3.2 shows the number of patients in the analysis populations by treatment group and Table 3.3 shows baseline demographic and background characteristics by treatment group for all randomized patients. Of the 103 randomized patients, 100 were included in the safety population. Three patients, all in the placebo group, had no

safety evaluation after baseline, were lost to follow up and subsequently excluded from the safety population. Of the 103 randomized patients, 97 were included in the ITT population. Six patients were unable to obtain CADS-T rating scores after baseline and were subsequently excluded from the ITT population.

Table 3.2 Number (%) of Patients in Analysis Populations by Treatment Group for Study 2301

Population	Focalin LA N (%)	Placebo N (%)	All N (%)
All Randomized	53 (100)	50 (100)	103 (100)
Safety	53 (100)	47 (94.0)	100 (97.1)
Intent-to-Treat	52 (98.1)	45 (90.0)	97 (94.2)
Completer	47 (88.7)	33 (66.0)	80 (77.7)

Table 3.3 Demographic and Background Characteristics by Treatment Group for Study 2301

	Focalin LA **N = 53**	**Placebo** **N = 50**	**All** **N = 103**
Age (years)			
Mean	9.6	10.4	10.0
SD	2.75	2.70	2.74
Median	10.0	10.0	10.0
Range	6.0 – 17.0	6.0 – 16.0	6.0 – 17.0
Sex – n (%)			
Male	31 (58.5)	35 (70.0)	66 (64.1)
Female	22 (41.5)	15 (30.0)	37 (35.9)
Race – n (%)			
Caucasian	33 (62.3)	29 (58.0)	62 (60.2)
Black	13 (24.5)	11 (22.0)	24 (23.3)
Other	7 (13.2)	10 (20.0)	17 (16.5)
DSM-IV ADHD Diagnosis – n (%)			
Inattentive	8 (15.1)	14 (28.0)	22 (21.4)
Hyperactive-Impulsive	1 (1.9)	1 (2.0)	2 (1.9)
Combined Type	44 (83.0)	35 (70.0)	79 (76.7)
Baseline CADS-T DSM-IV Total Subscale Score			
N	52	47	99
Mean	33.4	35.2	34.3
SD	8.95	10.04	9.47
Median	33.0	36.0	34.0
Range	16.0 – 54.0	16.0 – 53.0	16.0 – 54.0

As observed from the above table, demographic and background characteristics were comparable for both treatment groups. In both treatment groups, the majority of patients were Caucasian with a mean age of 10.0 years. The percentage of male patients in the placebo group (70.0%) was greater than that in the Focalin LA group (58.5%); however, this difference was not statistically significant.

3.1.2.2 Dosage

Capsules of Focalin LA were available in strengths of 5, 10 and 20 mg. During the Titration period of the Double-blind Treatment Phase, patients randomized to the Focalin LA treatment group could be receiving 5, 10, 15, 20 or 30 mg/day in a flexible dose titration for the 5 week duration. For the following 2 weeks, the patients were to be maintained at the optimal dose without changes or interruption.

Table 3.4 shows the final dose of study drug by treatment for the Intent-to-treat population. The mean final dose for patients in the Focalin LA group was 24.0 mg/day. The majority of the Focalin LA patients were maintained at high daily doses of 20 or 30 mg/day. There were 28 of 52 patients (53.8%) in the Focalin LA group with a final dose of 30 mg/day and 15 of 52 patients (28.8%) with a final dose of 20 mg/day. Only 9 patients (17.3%) had a final dose of 5, 10 or 15 mg/day. In the placebo group, 82.2% of patients were given the highest dose level. The final dose of study drug by treatment for the completers population is shown in Table 3.5.

Table 3.4 Level of Final Dose by Treatment Groups for Intent-to-Treat Population

Level of Final Dose	Focalin LA N=52 n (%)	Placebo N = 45 n (%)
5 mg/day	1 (1.9)	1 (2.2)
10 mg/day	3 (5.8)	4 (8.9)
15 mg/day	5 (9.6)	1 (2.2)
20 mg/day	15 (28.8)	2 (4.4)
30 mg/day	28 (53.8)	37 (82.2)
Mean (SD)	24.0 (7.14)	26.9 (7.09)

Table 3.5 Level of Final Dose by Treatment for Completers Population

Level of Final Dose	Focalin LA N=47 n (%)	Placebo N = 33 n (%)
10 mg/day	2 (4.3)	0 (0.0)
15 mg/day	5 (10.6)	0 (0.0)
20 mg/day	13 (57.4)	2 (6.1)
30 mg/day	27 (57.4)	31 (93.9)
Mean (SD)	24.8 (6.51)	29.4 (2.42)

3.1.2.3 Sponsor's Primary Efficacy Results

The primary efficacy variable was change from baseline to the final rating in the DSM-IV total subscale score of the CADS-T. Decrease in the CADS-T DSM-IV total subscale score indicates improvement. The primary analysis results on the ITT population are shown in Table 3.6. The adjusted mean change from Baseline to final visit in the CADS-T DSM-IV total subscale score was 16.3 for Focalin LA and 5.7 for placebo; the difference between the treatment groups is statistically significant ($p<0.001$).

According to the sponsor, the primary efficacy analysis was also performed on the completers population and Focalin LA was statistically significantly superior compared to placebo (p=0.004).

Table 3.6 Change from Baseline in the CADS-T DSM-IV Total Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	33.3 (9.18)	34.9 (10.03)
Final Visit (Visit 9)	Mean (SD)	17.4 (12.42)	29.0 (15.62)
Change from Baseline*	Mean (SD)	15.8 (15.39)	5.9 (13.18)
	Adjusted Mean Change	16.3	5.7
	P-Value	<0.001	

* The reported values are the amount of changes

3.1.2.4 Sponsor's Secondary Efficacy Results

Variables Based on Conners ADHD/DSM-IV Scales

The difference between the treatment groups, with respect to the changes from baseline to final visit in the CADS-T DSM-IV Inattentive (p=0.001) and Hyperactive-Impulsive subscale scores (p<0.001), was statistically significantly in favor of Focalin LA. The detailed results are shown in Tables 3.7 and 3.8.

Table 3.7 Change from Baseline in the CADS-T DSM-IV Inattentive Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	18.6 (5.15)	18.7 (4.58)
Final Visit (Visit 9)	Mean (SD)	10.5 (7.92)	15.5 (7.23)
Change from Baseline*	Mean (SD)	8.1 (8.07)	3.2 (6.77)
	Adjusted Mean Change	8.1	3.3
	P-Value	0.001	

* The reported values are the amount of changes

Table 3.8 Change from Baseline in the CADS-T DSM-IV Hyperactive-Impulsive Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	14.7 (6.58)	16.2 (7.32)
Final Visit (Visit 9)	Mean (SD)	7.0 (5.75)	13.5 (9.34)
Change from Baseline*	Mean (SD)	7.8 (8.38)	2.7 (6.96)
	Adjusted Mean Change	8.2	2.5
	P-Value	<0.001	

* The reported values are the amount of changes

The change from baseline to the final rating in the DSM-IV total subscale score of the CADS-P is shown in Table 3.9. The adjusted mean change from baseline to final visit in the CADS-P DSM-IV total subscale score was 17.6 for Focalin LA and 6.5 for placebo, and the difference between treatment groups was statistically significant (p<0.001).

Table 3.9 Change from Baseline in the CADS-P DSM-IV Total Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	39.9 (9.29)	39.4 (8.55)
Final Visit (Visit 9)	Mean (SD)	22.3 (13.65)	33.4 (11.72)
Change from Baseline*	Mean (SD)	17.6 (14.00)	6.0 (12.30)
	Adjusted Mean Change	17.6	6.5
	P-Value	<0.001	

* The reported values are the amount of changes

The differences between the treatment groups, with respect to the changes from baseline to final visit in the CADS-P DSM-IV Inattentive ($p<0.001$) and Hyperactive-Impulsive subscale scores ($p<0.001$), were both statistically significantly in favor of Focalin LA. The detailed results are shown in Tables 3.10 and 3.11, respectively.

Table 3.10 Change from Baseline in the CADS-P DSM-IV Inattentive Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	21.4 (3.77)	21.5 (4.56)
Final Visit (Visit 9)	Mean (SD)	12.1 (6.95)	18.5 (5.72)
Change from Baseline*	Mean (SD)	9.3 (6.89)	3.0 (6.41)
	Adjusted Mean Change	9.5	3.2
	P-Value	<0.001	

* The reported values are the amount of changes

Table 3.11 Change from Baseline in the CADS-P DSM-IV Hyperactive-Impulsive Subscale Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 52	Placebo N = 45
Baseline (Visit 2)	Mean (SD)	18.5 (6.71)	17.9 (6.00)
Final Visit (Visit 9)	Mean (SD)	10.2 (7.43)	14.9 (7.25)
Change from Baseline*	Mean (SD)	8.3 (7.90)	3.0 (6.47)
	Adjusted Mean Change	8.2	3.3
	P-Value	<0.001	

* The reported values are the amount of changes

Variables based on the Clinical Global Impressions Scale

The CGI improvement scale was used to assess the overall change of illness relative to baseline at final visit. The proportion of patients with improvement at final visit is shown in Table 3.12. As observed from the table, there were 35 (67.3%) patients in the Focalin LA group who were rated as very much improved or much improved at final visit compared to 6 (13.3%) patients in the placebo group ($p<0.001$). Seventeen (32.7%) patients in the Focalin LA group had a final rating of minimally improved, no change or minimally worse at final visit compared to 39 (86.7%) patients in the placebo group.

Table 3.12 Proportion of Patients with Improvement on the CGI-I Scale by Treatment/ LOCF (ITT Population) for Study 2301

	Focalin LA N = 52 n (%)	Placebo N = 45 n (%)
Improvement*	35 (67.3)	6 (13.3)
No Improvement	17 (32.7)	39 (86.7)
P-Value	p < 0.001	

* Improvement is defined as having a final visit score of 1 or 2 on the CGI-I scale.

The distribution of the clinician rated CGI-I ratings at the final visit using the LOCF approach is presented in Table 3.13. The distribution of CGI-I ratings for the Focalin LA group was statistically significantly different from placebo (p<0.001).

Table 3.13 CGI-I Rating at Final Visit by Treatment / LOCF (ITT Population) for Study 2301

	Focalin LA N = 52 n (%)	Placebo N = 45 n (%)
Very Much Improved	22 (42.3)	0 (0.0)
Much Improved	13 (25.0)	6 (13.3)
Minimally Improved	7 (13.5)	11 (24.4)
No Change	10 (19.2)	21 (46.7)
Minimally Worse	0 (0.0)	7 (15.6)
Much Worse	0 (0.0)	0 (0.0)
P-Value	p < 0.001	

The sponsor also found the distribution of the CGI-I Ratings by visit and treatment group on the observed cases dataset of the ITT population. The distribution of CGI-I ratings at final visit (Visit 9) was statistically significantly different for the Focalin LA group compared to placebo (p<0.001). At each visit the Focalin LA treatment group had greater proportions of patients with improvement rated by the clinician as “very much improved” or “much improved” compared to placebo.

In addition to CGI-I ratings, the CGI severity of illness subscale was used to assess the patient’s current illness state. According to the sponsor’s analyses, the distribution of the CGI-S ratings for the Focalin LA group was statistically significantly different from placebo at final visit (p<0.001). There were 32 (64.0%) patients in the Focalin LA group with a final visit rating of 1 (not at all ill), 2 (borderline ill), or 3 (mildly ill) compared to 5 (11.9%) patients in the placebo group. In the Focalin LA group, 16 (32.0%) patients were rated as moderately ill and 2 (4.0%) patients were rated as markedly ill. In the placebo group, 27 (64.3%) patients were rated as moderately ill, 9 (21.4%) patients were rated as markedly ill, and 1 (2.4%) patient was rated as severely ill.

Child Health Questionnaire

The Child Health Questionnaire (CHQ) Parent Form 50 was completed at baseline and at the end of the study to assess social and family functioning. The change from

baseline to final visit in the CHQ physical component score and the change from baseline to final visit in the CHQ Psychosocial component score are presented in Tables 3.14 and 3.15, respectively. As we can observe from the tables, for the CHQ Physical Component Score, the difference between the Focalin LA group and the placebo group was not significant, but for the CHQ Psychosocial component, the improvement was seen and it was statistically significantly greater for Focalin LA compared to placebo ($p<0.001$).

Table 3.14 Change from Baseline in the CHQ Physical Component Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 51	Placebo N = 40
Baseline (Visit 2)	Mean (SD)	57.2 (6.97)	58.6 (4.72)
Final Visit (Visit 9)	Mean (SD)	55.6 (6.91)	58.1 (4.60)
Change from Baseline	Mean (SD)	-1.6 (7.74)	-0.5 (4.80)
	P-Value*	0.212	

* by Mann-Whitney-Wilcoxon test

Table 3.15 Change from Baseline in the CHQ Psychosocial Component Score by Treatment / LOCF (ITT Population) for Study 2301

		Focalin LA N = 51	Placebo N = 40
Baseline (Visit 2)	Mean (SD)	33.0 (10.2)	33.6 (8.92)
Final Visit (Visit 9)	Mean (SD)	45.2 (9.44)	37.7 (9.10)
Change from Baseline	Mean (SD)	12.2 (13.3)	4.1 (9.88)
	Adjusted Mean Change	11.9	4.3
	P-Value*	<0.001	

* Based on the ANCOVA model

3.1.2.5 Sponsor's Efficacy Conclusions

Focalin LA administered once-daily in doses of 5 to 30 mg was safe and effective in treating ADHD symptoms in pediatric patients. For the primary efficacy variable, the teacher rated CADS-T total subscale score, the difference from baseline to final visit between treatment groups was statistically significant in favor of Focalin LA ($p<0.001$). The results of all secondary analyses, with the exception of the CHQ physical component, were statistically significantly in favor of Focalin LA.

3.1.2.6 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's efficacy analysis results for all primary and secondary endpoints. No inconsistent finding was found.

2. For the primary endpoint, the sponsor mentioned in the study report that the treatment-by-center interaction was found to be significant ($p=0.04$) when it was added into the ANCOVA model. The sponsor' finding was because of two sites (0501 and 0510) which showed a greater mean change from baseline to final visit on the CARD-T DSM-IV total score for placebo than for Focalin LA (See Table 6.1

of the Appendices for detailed change values). The sponsor further explained that in both centers the 95% confidence intervals for the treatment effect based on the CADS-T DSM-IV total subscale score cover the estimate of the overall treatment effect, and that numerical superiority of placebo at both centers was only restricted to the teacher's assessment. They also pointed out one specific patient who had unusual pattern of variations in the primary efficacy variable across post-baseline visits. After replacing a reasonable value in that patient's last visit data, an exploratory ANCOVA analysis showed that the treatment-by-center interaction would no longer be significant (p=0.116) and the treatment effect was still significant.

For Site 501, this reviewer found that the 95% confidence interval for the treatment effect based on the CADS-T DSM-IV total subscale score does not cover the estimate of the overall treatment effect. For the above mentioned exploratory analysis, this reviewer confirmed the sponsor's finding. Since the Focalin LA's effect showed on almost all centers except few outliers in three centers, and when the center factor was excluded from the ANCOVA model, this reviewer found the p-value was very small (<0.0001), overall, this reviewer agrees with the sponsor this significant treatment-by-center interaction does not invalidate the drug's efficacy analysis results.

3.1.3 Description of Study 2302

This study was titled as "A 5-Week, Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Fixed-Dose Study of the Efficacy and Safety of Focalin^{TM} LA (Dexmethylphenidate Hydrochloride Extended-Release Capsules) Administered Once Daily in Adults with Attention-Deficit/Hyperactivity Disorder (ADHD)". There were 18 centers in the US participated in this study.

3.1.3.1 Study Objectives

The primary objective of this study was to evaluate the efficacy and safety of Focalin LA (dexmethylphenidate hydrochloride extended-release capsules) administered once daily as compared with placebo in adults who meet DSM-IV criteria for ADHD.

A secondary objective was to explore the population pharmacokinetics of Focalin LA in adults with ADHD.

3.1.3.2 Study Design

This was a 5-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group fixed-dose (20mg, 30 mg and 40 mg) study followed by a 6-month, flexible-dose, open-label extension. Results of the extension will be reported separately. Patients were required to meet DSM-IV criteria for ADHD (either combined or single type), and have a history of childhood onset of ADHD. The study consisted of three phases: pre-randomization, double-blind treatment, and open-level extension.

A 5-week treatment period was selected based on a review of clinical trials in adult ADHD patients. A 5-week treatment period is consistent with the currently available trials as well as the study dosing regimen: 10 mg/day starting dose, titration in increments of 10 mg/week to the randomly assigned fixed dose, and a minimum of 2 weeks of stable dosing at the randomized fixed dose (2 weeks has been shown to be an adequate period of time to observe an effect in this indication).

3.1.3.3 Efficacy Assessments and Evaluation

Primary Efficacy Variable

The primary efficacy variable was change from baseline to final visit in the total score of the DSM-IV ADHD RS.

The primary comparisons were between each of the two highest doses of Focalin LA (30 and 40 mg) vs. placebo, using the last observation carried forward (LOCF) approach and Hochberg's procedure to adjust for multiple comparisons. A secondary comparison between the 20 mg Focalin LA treatment group and placebo was made at the two-sided type I error level of 5%.

The treatment groups were compared using least square means derived by an analysis of covariance (ANCOVA) model with the following explanatory variables: treatment, center and the baseline DSM-IV ADHD RS total score. Ninety-five percent confidence intervals for the differences between active treatments and placebo based on the ANCOVA model were also reported. An additional analysis was performed for the exploration of treatment-by-center interaction by adding this interaction term to the above ANCOVA model.

Secondary Efficacy Variables

The secondary efficacy variables were as follows:

- Proportion of patients with at least 30% improvement in the DSM-IV ADHD RS total score at the final visit as compared with baseline
- Change from baseline to final visit in the Inattention subscore and Hyperactivity/ Impulsivity subscore of the DSM-IV ADHD RS
- Proportion of patients with improvement on the CGI-I scale (defined as patients with a final visit score of 1 "very much improved" or 2 "much improved" on the CGI-I scale)
- Proportion of patients at each level of improvement on the 7-point CGI-I scale at the final visit
- Proportion of patients with improvement on the CGI-S scale (defined as patients with a decrease on the CGI-S score at final visit as compared with baseline)
- Change from Baseline to final visit in the total score and subscale scores of the CAARS (Observer and Self-Report separately)
- Change from baseline to final visit in the GAF score
- Change from baseline to final visit in the Q-LES-Q total score

Proportion of patients with at least 30% improvement in the DSM-IV ADHD RS total score was analyzed using a logistic regression model with treatment, center, and baseline DSM-IV ADHD RS total score as explanatory variables.

Changes from baseline to final visit in the DSM-IV ADHD RS subscale scores were analyzed by ANCOVA models similar to the analysis of the primary efficacy variable with treatment, center, and the corresponding baseline measurement as explanatory variables.

Proportions of patients with improvement on the CGI-I and on the CGI-S scales were analyzed using logistic regression models with treatment and center as explanatory variables.
Proportion of patients at each rating of the CGI-I scale at the final visit was compared between active treatments and placebo using the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Proportion of patients at each rating of the CGI-I scale at each visit of the Double-blind Treatment Phase was summarized by treatment for the OC dataset of the ITT population. In addition, the rating at final visit was compared between active treatments and placebo using the Cochran-Mantel-Haenszel (CMH) test stratifying on centers.

Changes from Baseline to final visit in the CAARS total scores and subscale scores, the GAF score, and the Q-LES-Q total score were analyzed by ANCOVA models similar to the analysis of the primary efficacy variable with treatment, center, and the corresponding baseline measurement as explanatory variables.

3.1.4 Efficacy Results for Study 2302

3.1.4.1 Patient Disposition, Population and Baseline Demographic Characteristics

Table 3.16 shows patient disposition. As observed from the table, patients were evenly randomized across the four treatment groups. Discontinuation rate was slightly higher in the placebo group (18.9%) compared to the Focalin LA groups (15.5% for 20 mg; 18.2% for 30 mg and 14.5% for 40 mg). This was primarily attributed to a greater proportion of patients discontinuing due to withdrawal of consent in the placebo group (5.7%) compared to Focalin LA (1.2% “All Focalin LA” group).

Across all groups the most common reason for discontinuation was adverse events. No Flcalin LA-treated patient was discontinued from the double-blind treatment phase due to unsatisfactory therapeutic effect. Among the Focalin LA treatment groups, the 30 mg group had a slightly higher rate of discontinuation for adverse events (12.7%) and withdrawal of consent (3.6%) compared to the 20 mg and 40 mg groups.

Table 3.16 Patient Disposition by Treatment for Study 2302

	Focalin LA 20 mg N (%)	Focalin LA 30 mg N (%)	Focalin LA 40 mg N (%)	All Focalin LA N (%)	Placebo N (%)	All N (%)
Screened						295
Randomized	58 (100)	55 (100)	55 (100)	168 (100)	53 (100)	221 (100)
Completed	49 (84.5)	45 (81.8)	47 (85.5)	141 (83.9)	43 (81.1)	184 (83.3)
Discontinued	9 (15.5)	10 (18.2)	8 (14.5)	27 (16.1)	10 (18.9)	37 (16.7)
Adverse Event(s)	6 (10.3)	7 (12.7)	5 (9.1)	18 (10.7)	4 (7.5)	22 (10.0)
Lost to Follow-Up	2 (3.4)	0 (0.0)	3 (5.5)	5 (3.0)	1 (1.9)	6 (2.7)
Subject Withdrew Consent	0 (0.0)	2 (3.6)	0 (0.0)	2 (1.2)	3 (5.7)	5 (2.3)
Protocol Violation	1 (1.7)	1 (1.8)	0 (0.0)	2 (1.2)	1 (1.9)	3 (1.4)
Unsatisfactory Therapeutic Effect	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)

Table 3.17 shows the number of patients in the analysis populations by treatment group. As observed from the table, of the 221 randomized patients, 218 were included in both the ITT and safety populations and were evaluable for efficacy and safety. The ITT and safety populations were identical.

Table 3.17 Number (%) of Patients in Analysis Populations by Treatment for Study 2302

Population	Focalin LA 20 mg N (%)	Focalin LA 30 mg N (%)	Focalin LA 40 mg N (%)	All Focalin LA N (%)	Placebo N (%)	All N (%)
All Randomized	58 (100)	55 (100)	55 (100)	168 (100)	53 (100)	221 (100)
Treated	58 (100)	55 (100)	54 (98.2)	167 (99.4)	53 (100)	220 (99.5)
Safety	57 (98.3)	54 (98.2)	54 (98.2)	165 (98.2)	53 (100)	218 (98.6)
Intent-to-Treat	57 (98.3)	54 (98.2)	54 (98.2)	165 (98.2)	53 (100)	218 (98.6)

Table 3.18 shows the baseline demographic and background characteristics by treatment group for all randomized patients. As observed from the table, the demographic and background characteristics were comparable across treatment groups with the exception of race. In all treatment groups, the majority of patients were Caucasian with a mean age 38.7 years. The Focalin LA 20 mg group had a statistically significantly higher proportion of Caucasians (100%) compared to Focalin LA 30 mg, 40 mg and placebo groups (87.3%, 78.2% and 75.5%, respectively). This difference was not considered to impact the study results since ADHD is not known to be specific to any particular race. The gender distribution was 59.5% males and 40.5% females in the “All Focalin LA” group compared to 50.9% and 49.1% for the placebo group, this difference was not statistically significant.

Table 3.18 Demographic Characteristics by Treatment for Study 2302

	Focalin LA 20 mg N (%)	Focalin LA 30 mg N (%)	Focalin LA 40 mg N (%)	All Focalin LA N (%)	Placebo N (%)	All N (%)
Age (yr)						
N	58	55	55	168	53	221
Mean	39.1	39.1	38.2	38.8	38.1	38.7
SD	10.75	10.55	10.25	10.47	10.79	10.53
Median	40.0	41.0	38.0	40.0	40.0	40.0
Range	19.0 – 59.0	18.0 – 59.0	19.0 – 59.0	18.0 – 59.0	19.0 – 62.0	18.0 – 62.0
Sex – n (%)						
Male	32 (55.2)	34 (61.8)	34 (61.8)	100 (59.5)	27 (50.9)	127 (57.5)
Female	26 (44.8)	21 (38.2)	21 (38.2)	68 (40.5)	26 (49.1)	94 (42.5)
Race – n (%)						
Caucasian	58 (100)	48 (87.3)	43 (78.2)	149 (88.7)	40 (75.5)	189 (85.5)
Black	0 (0.0)	3 (5.5)	4 (7.3)	7 (4.2)	3 (5.7)	10 (4.5)
Oriental	0 (0.0)	0 (0.0)	4 (7.3)	4 (2.4)	3 (5.7)	7 (3.2)
Other	0 (0.0)	4 (7.3)	4 (7.3)	8 (4.8)	7 (13.2)	15 (6.8)
DSM-IV ADHD Diagnosis – n (%)						
Inattentive	17 (29.3)	14 (25.5)	16 (29.1)	47 (28.0)	12 (22.6)	59 (26.7)
Hyperactive-Impulsive	2 (3.4)	3 (5.5)	1 (1.8)	6 (3.6)	1 (1.9)	7 (3.2)
Combined Type	39 (67.2)	38 (69.1)	38 (69.1)	115 (68.5)	40 (75.5)	155 (70.1)
Baseline DSM-IV ADHD RS Total Score						
N	58	55	55	168	53	221
Mean	36.9	36.9	36.7	36.8	37.5	37.0
SD	7.18	8.01	8.33	7.80	7.82	7.79
Median	37.0	36.0	36.0	36.5	38.0	37.0
Range	24.0 – 54.0	24.0 – 51.0	24.0 – 54.0	24.0 – 54.0	25.0 – 54.0	24.0 – 54.0

3.1.4.2 Sponsor's Primary Efficacy Results

The primary efficacy variable was change from baseline to final visit in the clinician-rated DSM-IV ADHD RS total score. The primary comparisons were between each of the two highest doses of Focalin LA (30 and 40 mg) vs. placebo, using the last observation carried forward (LOCF) approach and Hochberg's procedure to adjust for multiple comparisons. The results of the primary comparisons are presented in Table 3.19. As observed from the table, in both primary comparisons, Focalin LA was statistically significantly superior to placebo on the primary efficacy variable. In the secondary comparison, Focalin LA 20 mg was also statistically significantly superior compared to placebo. According to the sponsor, similar results were observed using the observed cases (OC) approach. In addition, no statistically significant treatment-by-center interactions were found and the normality assumption for the ANCOVA model was not violated.

Table 3.19 Change from baseline in the DSM-IV ADHD RS Total Score by Treatment/ LOCF (ITT Population) for Study 2302

		Focalin LA 20 mg (N=57)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=54)	Placebo (N=53)
Visit 2 (Baseline)	Mean	36.8	36.9	36.9	37.5
	SD	7.20	8.07	8.25	7.82
Final DB Visit	Mean	23.1	23.5	20.0	29.6
	SD	11.65	11.80	11.50	13.58
Change from Baseline	Mean	13.7	13.4	16.9	7.9
	SD	10.69	10.81	13.34	11.20
Adjusted Mean Change		13.3	12.9	16.5	7.6
P-Value		0.006	0.012	<0.001	

3.1.4.3 Sponsor's Secondary Efficacy Results

Variables based on DSM-IV ADHD Rating Scale

Table 3.20 shows the proportion of patients with at least 30% improvement in the clinician-rated DSM-IV ADHD RS total score at the final visit. At the final visit, over half of the patients in the "All Focalin LA" group had at least 30% improvement in the DSM-IV ADHD RS total score (57.9%, for the 20mg; 53.7% for the 30mg and 61.1% for the 40mg) compared to 34.0% for placebo. Thirty percent improvement on the ADHD RS total scores was statistically significant for Focalin LA 20 mg and 40 mg compared to placebo (p=0.017 and 0.007, respectively), and approached statistical significance for Focalin LA 30 mg group (p=0.054). Among the Focalin LA treatment groups, the 40 mg group demonstrated the greatest effect size.

Table 3.20 Proportion of Patients with ≥ 30% improvement in the DSM-IV ADHD RS Total Score by Treatment / LOCF (ITT Population) for Study 2302

	Focalin LA 20 mg N = 57 n (%)	Focalin LA 30 mg N = 54 n (%)	Focalin LA 40 mg N = 54 n (%)	Placebo N = 53 n (%)
≥ 30 % improvement	33 (57.9)	29 (53.7)	33 (61.1)	18 (34.0)
< 30 % improvement	24 (42.1)	25 (46.3)	21 (38.9)	35 (66.0)
p-value	0.017	0.054	0.007	

The results for change from baseline to final visit in the clinician-rated DSM-IV ADHD RS subscale scores (Inattentive and Hyperactive-Impulsive) are presented in Tables 3.21 and 3.22, respectively. As shown in Table 3.19, the adjusted mean change from baseline to final visit for the DSM-IV RS Inattentive subscale score was 7.5 for Focalin LA 20 mg (p=0.021), 7.8 for Focalin LA 30 mg (p=0.011), 9.4 for Focalin LA 40 mg (p<0.001), and 4.7 for placebo (All p-values vs. placebo). As shown in Table 3.20, the adjusted mean change from baseline to final visit for the DSM-IV RS Hyperactive-Impulsive subscale score was 5.8 for Focalin LA 20 mg (p=0.005), 5.1 for Focalin LA 30 mg (p=0.037), 7.1 for Focalin LA 40 mg (p<0.001), and 2.9 for placebo (all p-values vs. placebo).

Table 3.21 Change from Baseline in the DSM-IV ADHD RS Inattentive Subscale Score by Treatment/LOCF (ITT Population) for Study 2302

		Focalin LA 20 mg (N=57)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=54)	Placebo (N=53)
Visit 2 (Baseline)	Mean	21.2	21.0	21.4	21.1
	SD	3.43	3.91	3.82	4.13
Final DB Visit	Mean	13.5	12.9	11.7	16.4
	SD	6.74	6.10	7.23	7.32
Change from Baseline	Mean	7.7	8.0	9.7	4.7
	SD	6.69	5.94	7.84	6.80
Adjusted Mean Change		7.5	7.8	9.4	4.7
P-Value		0.021	0.011	<0.001	

Table 3.22 Change from Baseline in the DSM-IV ADHD RS Hyperactive-Impulsive Subscale Score by Treatment/LOCF (ITT Population) for Study 2302

		Focalin LA 20 mg (N=57)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=54)	Placebo (N=53)
Visit 2 (Baseline)	Mean	15.6	15.9	15.6	16.4
	SD	6.03	6.45	6.94	5.99
Final DB Visit	Mean	9.6	10.5	8.4	13.2
	SD	5.84	6.62	6.30	7.69
Change from Baseline	Mean	6.0	5.4	7.2	3.2
	SD	5.63	6.33	6.84	5.57
Adjusted Mean Change		5.8	5.1	7.1	2.9
P-Value		0.005	0.037	<0.001	

CGI Ratings

The distribution of the clinician-rated CGI-I ratings at the final visit using the LOCF approach is presented in Table 3.23. As observed from the table, the distribution of CGI-I ratings for all three doses of Focalin LA were statistically significantly different from placebo (p-values = 0.004, 0.021, and <0.001, for Focalin LA 20 mg, 30 mg and 40 mg, respectively).

Table 3.23 CGI-I Rating for Final Visit by Treatment/LOCF (ITT Population) for Study 2302

	Focalin LA 20 mg N=57 n (%)	Focalin LA 30 mg N = 54 n (%)	Focalin LA 40 mg N = 54 n (%)	Placebo N = 53 n (%)
Very Much Improved	10 (17.5)	11 (20.4)	14 (25.9)	7 (13.2)
Much Improved	17 (29.8)	9 (16.7)	16 (29.6)	7 (13.2)
Minimally Improved	16 (28.1)	18 (33.3)	11 (20.4)	9 (17.0)
No Change	14 (24.6)	14 (25.9)	12 (22.2)	28 (52.8)
Minimally Worse	0 (0.0)	2 (3.7)	1 (1.9)	1 (1.9)
Much Worse	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
P-Value +	0.004	0.021	<0.001	

+ P-values are based on comparison between the Foclain LA group and Placebo using the Cochran-Mantel Haenszel (CMH) test.

The proportion of patients with improvement on the CGI-I scale (CGI-I of 1 "very much improved" or 2 "much improved") at the final visit is presented in Table 3.24. As observed from the table, the results were statistically significantly superior for the Focalin LA 20 mg group (47.4%) and 40 mg group (55.6%) compared to placebo (26.4%). The Focalin LA 30 mg group was numerically superior to placebo (37%), but the difference was not statistically significant (p=0.261).

Table 3.24 Proportion of Patients with Improvement on the CGI-I Scale by Treatment/LOCF (ITT Population) for Study 2302

	Focalin LA 20 mg N=57 n (%)	Focalin LA 30 mg N=54 n (%)	Focalin LA 40 mg N=54 n (%)	Placebo N=53 n (%)
Improvement	27 (47.4)	20 (37.0)	30 (55.6)	14 (26.4)
No Improvement	30 (52.6)	34 (63.0)	24 (44.4)	39 (73.6)
P-Value+	0.027	0.261	0.003	

+ P-values are based on comparison between the Focalin lA group and Placebo from the logistic regression model.

The proportion of patients with improvement on the CGI-S scale is presented in Table 3.25. As observed from the table, the results were statistically significant for Focalin LA 20 mg (68.4%, p=0.009) and 40 mg (64.8%, p=0.031) compared to placebo (41.5%). The Focalin LA 30 mg group was numerically superior to placebo (61.1%), but the difference was not statistically significant (p=0.138). This finding is consistent with that for CGI-I at final visit. It was observed that 3 of the 18 sites did not have any patients in the Focalin LA 30 mg group with improvement on the CGI-S, compared to the 20 and 40 mg groups.

Table 3.25 Proportion of Patients with Improvement on the CGI-S scale by Treatment/ LOCF (ITT Population) for Study 2302

	Focalin LA 20 mg N=57	Focalin LA30 mg N=54	Focalin LA 40 mg N=54	Placebo N=53
n (%)	39 (68.4)	33 (61.1)	35 (64.8)	22 (41.5)
Odds-Ratio*	3.07	1.86	2.52	
95% C.I. for Odds-Ratio	(1.32, 7.16)	(0.82, 4.23)	(1.09, 5.86)	
P-Value	0.009	0.138	0.031	

* The odds of a Focalin LA-treated patient having improvement on the CGI-S scale relative to the odds of a placebo-treated patient based on the logistic regression model that includes treatment and center as explanatory variables.

CAARS Scores (Observer and Self-Report Versions)

Changes from baseline in the observer version of the CAARS total score are presented in Table 3.26. As shown in the table, all three doses of Focalin LA were statistically significantly superior to placebo for the total score. At the final visit, the adjusted mean change from baseline for the CAARS Observer version total score was 9.9 for Focalin LA 20 mg (p=0.005), 10.8 for Focalin LA 30 mg (p=0.004), 11.3 for Focalin LA 40 mg (p<0.001), and 2.5 for placebo (all p-values vs. placebo).

Changes from baseline in the CAARS Self-reported version for the total score are presented in Table 3.27. As shown in the table, all three doses of Focalin LA were statistically significantly superior to placebo. At the final visit, the adjusted mean change from baseline for the CAARS-Self Report total score was 14.8 for Focalin LA 20 mg (p=0.003), 12.1 for Focalin LA 30 mg (p=0.045), and 16.5 for Focalin LA 40 mg (p<0.001), and 6.6 for placebo (all p-values vs. placebo), where we noticed that the greatest improvement was observed in the Focalin LA 40 mg group. In addition to the total scores, the sponsor's analyses for the subscale scores are presented in Table 6.2 of the Appendices.

Table 3.26 Changes from Baseline in the CAARS Observer Version Total Score for Study 2302

Total Score		Focalin LA 20 mg (N=44)	Focalin LA 30 mg (N=33)	Focalin LA 40 mg (N=45)	Placebo (N=38)
Visit 2 (Baseline)	Mean	44.0	49.5	40.5	45.4
	SD	13.09	14.00	12.63	10.14
Final DB Visit	Mean	34.0	36.7	30.9	42.4
	SD	12.47	14.85	12.44	12.69
Change from Baseline	Mean	10.0	12.8	9.6	3.1
	SD	11.08	13.97	16.12	10.88
Adjusted Mean Change		9.9	10.8	11.3	2.5
P-Value		0.005	0.004	<0.001	

Table 3.27 Changes from Baseline in the CAARS Self-Report Version Total Score for Study 2302

Total Score		Focalin LA 20 mg (N=54)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=52)	Placebo (N=49)
Visit 2 (Baseline)	Mean	52.0	50.4	46.8	51.6
	SD	9.54	11.07	10.65	11.29
Final DB Visit	Mean	36.0	37.7	31.2	44.4
	SD	13.86	16.76	14.73	15.62
Change from Baseline	Mean	16.0	12.7	15.6	7.2
	SD	13.86	14.46	17.64	12.62
Adjusted Mean Change		14.8	12.1	16.5	6.6
P-Value		0.003	0.045	<0.001	

GAF Score

Change from baseline in the clinician-rated GAF score is presented in Table 6.3 of the Appendices. For the GAF score, an increase from baseline indicates improvement. As shown in the table, mean baseline GAF scores were similar across all treatment groups. The clinician-rated global functioning (i.e., psychological, social, and occupational domains) substantially improved in the Focalin LA treatment groups compared to placebo despite the short 5 week treatment period. Moreover, all three Focalin LA treatment groups were statistically significantly superior to placebo. Since the GAF score data were not normally distributed; therefore, the main analysis for the GAF was a non-parametric analysis based on the Mann-Whitney-Wilcoxon test.

Q-LES-Q Total Score

Change from baseline in the self-reported Q-LES-Q total score is presented in Table 6.4 of Appendices. For the Q-LES-Q total score, an increase from baseline indicates improvement. The results for all three doses of Focalin LA were similar to placebo. There was no improvement seen in quality of life parameters over the five week treatment period.

3.1.4.4 Sponsor's Efficacy Conclusions

Focalin LA administered once-daily in doses of 20, 30, and 40 mg was safe and effective in treating ADHD symptoms in adult patients. Focalin LA 20 mg, 30 mg, and 40 mg treatment groups were statistically significantly superior to placebo on the DSM-IV ADHD rating scale total score. In most secondary analyses, Focalin LA 40 mg was the most efficacious dose.

3.1.4.5 Statistical Reviewer's Findings and Comments

1. This reviewer confirmed the sponsor's efficacy analysis on the primary endpoint and all secondary efficacy endpoints. Not any inconsistency was found. In conclusion, the significant results were shown on all three dose groups of Focalin on the primary endpoint although the primary comparisons originally designed for this study were only for evaluating the Focalin's efficacy on the 30mg and 40 mg dose groups.

3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor performed the subgroup analyses for the primary endpoint separately for Studies 2301 and 2302 without pooling data from the two controlled studies. The variables used to define patient subgroups were gender and age for both studies. For Study 2301, the age groups analyzed were children (age 6-12) and adolescents (age 13-17). For Study 2302, the age groups analyzed were ≤ 40 and > 40 years, using the median age in the total patient sample as a cut-off point. Race was not used as a subgroup variable because the majority of the patients in both studies were Caucasian. Notice that three Focalin LA treatment groups in Study 2302 (20, 30, and 40 mg/day) were combined for these subgroup analyses. For these subgroup analyses, this reviewer confirmed the sponsor's analysis results.

4.1 GENDER, RACE AND AGE

4.1.1 Gender

For Study 2301, the ITT population included 60 male and 37 female pediatric patients.

Of the 60 male patients, 30 were treated with Focalin LA and 30 with placebo. Of the 37 female patients, 22 were treated with Focalin LA and 15 with placebo. As we can observe from the analysis results in Table 4.1, both male and female patients showed a statistically significant treatment effect in favor of Focaln LA.

Table 4.1 Sponsor's Analysis of Change from Baseline in the CADS-T Total Subscale Score for Gender Subgroups for Study 2301

Male		Focalin LA N = 30	Placebo N = 30
Baseline (Visit 2)	Mean (SD)	34.8 (7.61)	36.4 (9.99)
Final Visit (Visit 9)	Mean (SD)	22.2 (12.29)	31.4 (15.73)
Change from Baseline*	Mean (SD)	12.6 (14.69)	5.0 (12.96)
	Adjusted Mean Change	14.2	5.2
	P-Value	0.010	
Female		Focalin LA N = 22	Placebo N = 15
Baseline (Visit 2)	Mean (SD)	31.3 (10.82)	31.8 (9.70)
Final Visit (Visit 9)	Mean (SD)	11.0 (9.54)	24.3 (14.79)
Change from Baseline*	Mean (SD)	20.3 (15.54)	7.5 (13.91)
	Adjusted Mean Change	20.8	7.9
	P-Value	0.004	

* change is calculated as Visit 2 – Visit 9 value

For Study 2302, the ITT population included 126 male and 92 female adult patients. Of the 126 male patients, 99 were treated with Focalin LA and 27 with placebo. Of the 92 female patients, 66 were treated with Focalin LA and 26 with placebo. As we can observe from the analysis results in Table 4.2, both male and female patients showed a statistically significant treatment effect in favor of Focalin LA.

Table 4.2 Analysis of Change from Baseline in the DSM-IV ADHD RS Total Score for Gender Subgroups for Study 2302

Male		Focalin LA N = 99	Placebo N = 27
Baseline (Visit 2)	Mean (SD)	36.6 (8.04)	34.1 (6.75)
Final Visit (Visit 7)	Mean (SD)	22.4 (10.94)	25.9 (12.77)
Change from Baseline*	Mean (SD)	14.2 (11.63)	8.2 (11.62)
	Adjusted Mean Change	14.3	9
	P-Value	0.025	
Female		Focalin LA N = 66	Placebo N = 26
Baseline (Visit 2)	Mean (SD)	37.3 (7.46)	41.0 (7.35)
Final Visit (Visit 7)	Mean (SD)	21.9 (12.79)	33.5 (13.55)
Change from Baseline*	Mean (SD)	15.3 (11.86)	7.5 (10.97)
	Adjusted Mean Change	15.6	6.1
	P-Value	0.001	

* change is calculated as Visit 2 – Visit 7 value

4.1.2 Age

For Study 2301, the sponsor performed the age subgroup analysis for children 6 to12 years old and adolescent patients 13 to 17 years old. There were a total of 80 patients

in the ITT population aged 6 to 12 and 17 adolescent patients aged 13 to 17 years. Only in children aged 6 to 12 years old, Focalin LA showed statistically significant superior than the placebo. The detailed subgroup analysis results for age are shown in Table 4.3.

Table 4.3 Analysis of Change from Baseline in the CADS-T Total Subscale Score for Age Subgroups for Study 2301

Age: 6-12 years		Focalin LA N = 45	Placebo N = 35
Baseline (Visit 2)	Mean (SD)	34.0 (9.04)	35.0 (9.15)
Final Visit (Visit 9)	Mean (SD)	17.1 (12.74)	28.5 (14.84)
Change from Baseline*	Mean (SD)	16.9 (15.97)	6.5 (13.03)
	Adjusted Mean Change	17.5	6
	P-Value	<0.001	
Age: >12 - <18 years		Focalin LA N = 7	Placebo N = 10
Baseline (Visit 2)	Mean (SD)	29.0 (9.57)	34.4 (13.23)
Final Visit (Visit 9)	Mean (SD)	19.7 (10.73)	30.7 (18.92)
Change from Baseline*	Mean (SD)	9.3 (9.12)	3.7 (14.15)
	Adjusted Mean Change	9.6	3.3
	P-Value	0.361	

* change is calculated as Visit 2 – Visit 9 value

For Study 2302, the sponsor performed the age subgroup analysis for patients ≤ 40 years old and patients > 40 years old. There were 115 patients in the younger age group (≤ 40) and 103 patients in the older age group. As we can observe from the analysis results in Table 4.4, both younger and older patients showed a statistically significant treatment effect in favor of Focalin LA.

Table 4.4 Analysis of Change from Baseline in the DSM-IV ADHD RS Total Score for Age Subgroups for Study 2302

Age: ≤ 40 years		Focalin LA N = 87	Placebo N = 28
Baseline (Visit 2)	Mean (SD)	37.3 (7.63)	38.3 (7.33)
Final Visit (Visit 7)	Mean (SD)	22.7 (11.23)	29.9 (13.40)
Change from Baseline*	Mean (SD)	14.6 (11.82)	8.4 (11.21)
	Adjusted Mean Change	14.3	7.5
	P-Value	0.006	
Age: > 40 years		Focalin LA N = 78	Placebo N = 25
Baseline (Visit 2)	Mean (SD)	36.3 (7.99)	36.6 (8.40)
Final Visit (Visit 7)	Mean (SD)	21.6 (12.21)	29.3 (14.06)
Change from Baseline*	Mean (SD)	14.7 (11.64)	7.3 (11.40)
	Adjusted Mean Change	14.1	6.8
	P-Value	0.006	

* change is calculated as Visit 2 – Visit 7 value

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

There is no special/subgroup population subgroup analysis performed for this submission.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

- For both studies 2301 and 2302, this reviewer confirmed all the sponsor's efficacy analysis results and agreed that the data supported the Focalin^{TM} XR's efficacy in treatment patients with ADHD.

- For Study 2301, the sponsor found that the treatment-by-center interaction was significant when it was included in ANCOVA analysis for the primary endpoint and they provided reasons to explain this finding. After this reviewer's evaluation, this reviewer agrees with the sponsor that this significant interaction term does not invalid the drug's efficacy analysis results.

5.2 CONCLUSIONS AND RECOMMENDATIONS

This reviewer agrees with the sponsor that the data in these two pivotal studies support the Focalin^{TM} XR's efficacy as a treatment in patients with Attention-Deficit/ Hyperactivity Disorder (ADHD). However, we should notice that these two pivotal trials were studying different patient populations based on two different kinds of dosage regimens. In other words, for either pediatric or adult patients, the sponsor only had one positive pivotal study to support the Focalin^{TM} XR's efficacy for each. In addition, this reviewer noticed that for the study on pediatric patients, only 17 patients were adolescents (i.e., 21% of all pediatric patients). For the study on adult patients, although the p-values for all three doses (20, 30, and 40 mg) were nominal significant even with multiplicity adjustment, (b) (4)

_____

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-802
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Glass
HFD-120/Ms. Taylor
HFD-700/Dr. Anello
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Jin

This review consists of 28 pages. MS Word: C:/yfchen/NDA21802/review.doc.

6. APPENDICES

Table 6.1 Change from Baseline on CADS-T DSM-IV Total Subscale Score by Treatment Groups and Centers for Study 2301

Center ID	Change from Baseline in Focalin LA (N)	Change from Baseline in Placebo (N)	Difference between Focalin LA and Placebo
501	-11.83 (6)	-17.20 (5)	5.37
502	-28.50 (2)	1.00 (2)	-29.50
503	-17.67 (3)	3.25 (4)	-20.92
504	-19.25 (4)	-5.00 (4)	-14.25
505	-16.00 (4)	-4.33 (3)	-11.67
507	5 (1)	-21 (2)	26
508	-19.00 (8)	5.00 (7)	-24.00
509	-16.50 (4)	-15.00 (3)	-1.50
510	-3.00 (8)	-5.29 (7)	2.29
512	-28.25 (4)	-19.67 (3)	-8.58
513	-12.00 (2)		
514	-21.33 (6)	-2.40 (5)	-18.93

Table 6.2 Sponsor's Analysis of Observer Version of the CAARS Subscale Scores for Study 2302

Inattention/Memory Problem		Focalin LA 20 mg (N=54)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=52)	Placebo (N=49)
Visit 2 (Baseline)	Mean	12.1	11.4	11.1	12.2
	SD	2.31	3.12	3.07	2.41
Final DB Visit	Mean	8.7	8.2	7.7	10.5
	SD	3.32	3.37	4.11	3.70
Change from Baseline	Mean	3.3	3.2	3.4	1.8
	SD	3.67	3.52	4.34	3.27
P-Value		0.023	0.027	0.106	
Hyperactivity/Restlessness		Focalin LA 20 mg (N=54)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=52)	Placebo (N=49)
Visit 2 (Baseline)	Mean	10.7	10.2	9.7	10.3
	SD	2.85	3.17	3.09	3.46
Final DB Visit	Mean	7.3	8.0	6.3	8.8
	SD	3.61	3.95	3.51	3.80
Change from Baseline	Mean	3.4	2.2	3.4	1.5
	SD	3.14	3.02	3.92	3.26
Adjusted Mean Change		3.1	2.1	3.5	1.5
P-Value		0.007	0.288	0.002	
Impulsivity/Emotional Lability		Focalin LA 20 mg (N=54)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=52)	Placebo (N=49)
Visit 2 (Baseline)	Mean	6.9	7.0	6.1	7.0
	SD	3.26	3.29	3.12	3.85
Final DB Visit	Mean	4.6	5.2	4.1	6.3
	SD	2.99	3.57	2.64	4.30
Change from Baseline	Mean	2.3	1.8	1.9	0.7
	SD	2.59	3.60	3.58	2.07
Adjusted Mean Change		2.2	1.6	2.1	0.6
P-Value		0.003	0.060	0.005	

Self Concept		Focalin LA 20 mg (N=54)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=52)	Placebo (N=49)
Visit 2 (Baseline)	Mean	9.4	9.2	8.0	9.0
	SD	3.64	4.37	4.74	3.86
Final DB Visit	Mean	6.6	7.4	5.3	8.1
	SD	3.80	4.51	4.58	4.24
Change from Baseline	Mean	2.7	1.8	2.6	0.9
	SD	3.47	2.80	4.03	2.82
Adjusted Mean Change		2.6	1.6	2.8	0.9
P-Value		0.006	0.204	0.002	

Table 6.3 Sponsor's Analysis for Change from Baseline in the GAF Score for Study 2302

Total Score		Focalin LA 20 mg (N=55)	Focalin LA 30 mg (N=54)	Focalin LA 40 mg (N=51)	Placebo (N=48)
Visit 2 (Baseline)	Mean	54.2	54.2	55.7	54.9
	SD	4.38	4.20	3.62	3.38
Final DB Visit	Mean	65.3	62.9	67.0	60.3
	SD	8.99	9.11	11.09	10.26
Change from Baseline	Mean	11.1	8.7	11.3	5.4
	SD	9.41	8.99	12.06	9.31
P-Value*		<0.001	0.004	<0.003	

* P-Values were based on the Mann-Whitney-Wilcoxon test

Table 6.4 Sponsor's Analysis for Change from Baseline in the Q-LES-Q Total Score for Study 2302

Self Concept		Focalin LA 20 mg (N=55)	Focalin LA 30 mg (N=53)	Focalin LA 40 mg (N=52)	Placebo (N=48)
Visit 2 (Baseline)	Mean	49.3	48.2	48.6	49.0
	SD	7.95	8.59	8.45	7.59
Final DB Visit	Mean	51.5	50.7	51.8	50.9
	SD	6.95	7.82	8.11	8.62
Change from Baseline	Mean	2.2	2.5	3.2	1.9
	SD	7.55	8.21	9.87	7.13
Adjusted Mean Change		2.4	2.2	3	2.2
P-Value		0.915	0.971	0.587	

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/s/

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