Sponsor– Novartis	**Web Page/Link to Prescribing/Label Information**– www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Methylphenidate-hydrochloride-long-acting	
Therapeutic Area of Trial– Neuroscience	
Approved Indication– Approved for the treatment of ADHD	
Study Number– CRIT124DUS02	
Title– A multicenter, double-blind, randomized, placebo-controlled, crossover study evaluating the efficacy and safety of methylphenidate-hydrochloride-long-acting in female adolescents diagnosed with attention deficit/hyperactivity disorder (ADHD)	
Phase of Development– Phase 4	
Study Start/End dates– 22-Mar-2003 / 29-Jan-2004	
Study Design/Methodology– This was a 10-week, multicenter, double-blind, randomized, placebo-controlled, crossover study in female adolescents, aged 12-17 years, with a confirmed diagnosis of ADHD in which the efficacy and safety of m methylphenidate-hydrochloride-long-acting 20-60 mg/day were compared with placebo.	
Centres– 15 centers in the USA	
Publication–Ongoing	
Objectives– *Primary outcome/efficacy objective(s)*– • To compare the efficacy of methylphenidate-hydrochloride-long-acting 20–60 mg/day to placebo in the symptomatic control of clinically confirmed ADHD in females aged 12-17 years *Secondary outcome/efficacy objective(s)*– • To compare the efficacy of methylphenidate-hydrochloride-long-acting to placebo in improving social functioning (peer and family relationships), self-esteem, mood and school performance in the same study population • To compare the safety profile of methylphenidate-hydrochloride-long-acting to placebo in the same study population	
Test Product, Dose, and Mode of Administration–. Methylphenidate-hydrochloride-long-acting 20-mg and 30-mg capsules were administered orally once daily. All capsules were over-encapsulated in a one-color capsule of the same size.	
Reference Product(s), Dose(s), and Mode(s) of Administration– Placebo capsules were administered orally once daily. All placebo capsules were identical in size and color to Methylphenidate-hydrochloride-long-acting capsules.	
Criteria for Evaluation– *Primary efficacy:* The primary efficacy variable was the total score on the Conners Parent Rating Scale (CPRS); *Secondary efficacy:* Secondary efficacy variables were total scores on the Conners-Wells Adolescent Self Report (CASS:S), the Piers-Harris Children's Self-Concept Scale (PHCSCS-2) and ratings on the Clinical Global Impression of Change (CGI-C) and the Clinical Global Impression of Severity (CGI-S). *Safety/tolerability:* Safety assessments included monitoring and recording all AEs, SAEs (with their severity and relationship to study drug), and pregnancies; clinical laboratory evaluations (hematology, blood chemistry, urinalysis, urine pregnancy testing, and urine drug screening); regular assessments of vital signs, physical condition and body weights; and performance of electrocardiograms. *Other:* No other assessments were made *Pharmacology:* No drug level or pharmacokinetic evaluations were made.	

Statistical Methods–

The data from all centers were pooled and summarized for all demographic and baseline measures and for all analyses of efficacy and safety variables. Demographic and baseline measures were summarized by treatment schedule; differences between patients randomized to the two treatment schedules were not analyzed. For the purpose of the primary efficacy analysis, all scores from both treatment schedules were combined by treatment (Methylphenidate-hydrochloride-long-acting vs placebo). The least squares mean difference (estimation of the mean value) was computed by subtracting between the LSM change (95% CIs) of CPRS total scores for Methylphenidate-hydrochloride-long-acting and placebo from pretreatment (Day 0) to the fourth week of treatment. The mean treatment difference was analyzed using a mixed model that included period and treatment as fixed effects and patient (sequence) as a random effect. A test to determine any carry-over between pretreatment scores for the two treatment periods was performed. Paired differences between the two pretreatment scores were analyzed by an ANOVA with a sequence effect. If the p-value from this test was less than 0.05, the data were to be analyzed for treatment period 1 only.
Two secondary efficacy variables, CASS:S and PHCSCS-2, were analyzed using the same methodology employed in the analysis of CPRS. Missing total scores on the CPRS, CASS-S, and PHCSCS-2 evaluations for questionnaires in which <= 20% of the questions had missing values were handled by imputing the total scores using the number of questions multiplied by the average score for the non-missing questions. If >20% of the questions had missing values, the total score was set as missing. Missing total scores for CPRS, CASS:S, or PHCSCS-2 for the fourth week of each treatment period were imputed using the LOCF of non-missing scores at the second week of the treatment period. The frequency distributions of CGI-C and CGI-S scores were summarized by visit and treatment schedule and by visit and treatment.
AE summaries were presented for all patients and by treatment schedule and treatment; separate listings were presented for AEs that resulted in discontinuation of study medication or adjustment or temporary interruption of study medication and for SAEs. The results of laboratory evaluations were summarized by presenting the number and percentage of patients in each category for categorical laboratory parameters and by presenting summary statistics of raw data and change from baseline values (sample sizes, means, standard errors, medians, and ranges) for continuous laboratory parameters. The number and percentage of patients with clinically notable abnormalities were summarized by laboratory parameter. All vital signs data were listed, with notable values flagged. No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics–.

Patients were female adolescents, aged 12-17 years, with a diagnosis of ADHD confirmed by performance on the C-DISC4 during screening. Inclusion criteria included the ability and willingness of a parent or other caregiver and the patient to complete questionnaires; patients had to function at an age-appropriate academic level. Exclusion criteria included presence of a medical condition that would interfere with study participation, pregnancy, difficulty in swallowing capsules, a known sensitivity to the study drug or other drugs in the same class, or use of any investigational medication in the past 30 days.

Number of Subjects	**All patients**
Planned N	108
Randomised n	109
Completed n (%)	83 (76)
Withdrawn n (%)	26 (24)
Included in the primary analysis n (%)	Safety: 109 (100%); Efficacy: 107 (98.1%)
Withdrawn due to adverse events n (%)	0 (0)
Withdrawn due to lack of efficacy n (%)	10 (9)
Administrative reasons	3 (3)
Withdrew consent	8 (7)
Abnormal laboratory value	2 (2)
Lost to follow-up	3 (3)
Demographic and Background Characteristics	
N (ITT)	109
Females:males	100:0

Mean age, years (SD)	13.8 (1.6)	
Mean weight, kg (SD)	58.3 (15.4)	
Race White n (%) Black n (%) Asian n (%) Other n (%)	 76 (70) 22 (20) 1 (1) 10 (9)	
Age at onset (years)	Mean (SD)	5.1 (2.0)
Age at diagnosis (years)	Mean (SD)	10.0 (3.7)
Subtype of ADHD–n (%)	Inattentive	48 (44)
	Hyperactive/impulsive	1 (0.9)
	Combined	60 (55)
Family history of ADHD–n (%)	No	41 (38)
	Yes	65 (60)
	Unknown	3 (3)

Primary Efficacy Result(s)–intent to treat population

Conners Parent Rating Scale (CPRS)

Comparison of least squares mean treatment difference in change in CPRS scores[1] between Methylphenidate-hydrochloride-long-acting or placebo (efficacy population)

Treatment group	**n**	**Mean pretreatment score** (absolute score) (SD)	**Mean change** (absolute score) (SD)	**LSM (95% CI)**	**LSM treatment difference (95% CI)** (Methylphenidate HCl change – placebo change)	**p-value**
Methylphenidate HCl LA	102	47.2 (14.3)	-20.0 (13.8)	-20.1 (-22.8, -17.3)	-10.1 (-13.4, -6.9)	<0.001
Placebo	99	43.3 (16.3)	-9.7 (13.3)	-9.9 (-12.8, -7.1)		

[1]CPRS scores ranged from 0 to 81, with 0 indicated preferred behavior and 81 indicating undesirable behavior

Secondary efficacy result(s)–intent to treat population

Conners-Wells Adolescent Self Report (CASS:S) & Piers-Harris Children's Self-Concept Scale (PHCSCS-2)

Treatment Comparison of Change from Baseline	Methylphenidate HCl LA	Placebo	Treatment Difference
Change from Baseline in CASS:S Total Score [2]			
After Second Week of Treatment			
Mean (SD)	-8.8 (10.4)	-8.1 (10.2)	-0.7 (10.7)
Least Squares Mean [3]	-9.2	-8.1	-1.1
95% Confidence Interval	(-11.2,-7.1)	(-10.1,-6.1)	(-3.0,0.8)
After Fourth Week of Treatment (primary analysis)			
Mean (SD)	-11.5 (11.3)	-9.7 (12.0)	-1.7 (9.6)
Least Squares Mean [3]	-11.6	-9.6	-1.9
95% Confidence Interval	(-13.9,-9.2)	(-12.0,-7.2)	(-3.8,-0.1)
Change from Baseline in PHCSCS-2 Total Score [2]			
After Second Week of Treatment			
Mean (SD)	4.6 (6.6)	4.0 (6.5)	0.4 (5.7)
Least Squares Mean [3]	4.8	4.1	0.7
95% Confidence Interval	(3.5,6.1)	(2.8,5.4)	(-0.4,1.7)
After Fourth Week of Treatment (primary analysis)			
Mean (SD)	5.8 (6.9)	5.2 (7.0)	0.4 (5.0)
Least Squares Mean [3]	5.8	5.3	0.5
95% Confidence Interval	(4.4,7.2)	(3.9,6.8)	(-0.5,1.5)

Clinical Global Impression of Change (CGI-C) & Clinical Global Impression of Severity (CGI-S)

Frequency Distribution of Response Categories by Visit and by Schedule	**Schedule A (1)** Methylphenidate HCl LA/Placebo (N=57)	**Schedule B** Placebo/ Methylphenidate HCl LA (N=50)
Clinical Global Impression of Change (CGI-C) - n(%)		
Visit 4 (Week 2) [2]	Ritalin LA	Placebo
N	55 (100.0)	46 (100.0)
Very much improved	3 (5.5)	0 (0.0)
Much improved	18 (32.7)	5 (10.9)
Minimally improved	15 (27.3)	14 (30.4)
No change	14 (25.5)	26 (56.5)
Minimally worse	3 (5.5)	1 (2.2)
Much worse	1 (1.8)	0 (0.0)
Very much worse	0 (0.0)	0 (0.0)
Missing	1 (1.8)	0 (0.0)
Clinical Global Impression of Severity (CGI-S) - n(%)		
Visit 7 (Week 5)	Placebo	Ritalin LA
N	49 (100.0)	45 (100.0)
Not assessed	0 (0.0)	0 (0.0)
Normal, not at all ill	0 (0.0)	0 (0.0)
Borderline mentally ill	5 (10.2)	3 (6.7)
Mildly ill	8 (16.3)	8 (17.8)
Moderately ill	31 (63.3)	27 (60.0)
Markedly ill	5 (10.2)	6 (13.3)
Severely ill	0 (0.0)	1 (2.2)
Among the most extremely ill patients	0 (0.0)	0 (0.0)

Safety Results

	All patients	Methylphenidate-HCL LA	Placebo	Placebo Washout
No. (%) of patients studied	109	102	101	97
No. (%) of patients with AE(s)	84 (77.1)	69 (67.6)	52 (51.5)	26 (26.8)
System organ class affected	n (%)	n (%)	n (%)	n (%)
Nervous system disorders	47 (43.1)	29 (28.4)	23 (22.8)	7 (7.2)
Gastrointestinal disorders	36 (33.0)	28 (27.5)	13 (12.9)	2 (2.1)
Infections and infestations	34 (31.2)	18 (17.6)	14 (13.9)	6 (6.2)
Metabolism and nutrition disorders	30 (27.5)	23 (22.5)	2 (2.0)	7 (7.2)
Psychiatric disorders	29 (26.6)	17 (16.7)	11 (10.9)	2 (2.1)
General disorders and administration site disorders	15 (13.8)	12 (11.8)	1 (1.0)	2 (2.1)
Respiratory, thoracic and mediastinal disorders.	12 (11.0)	7 (6.9)	5 (5.0)	-
Injury, poisoning and procedural complications	10 (9.2)	6 (5.9)	5 (5.0)	1 (1.0)
Reproductive system and breast disorders.	8 (7.3)	8 (7.8)	-	-
Musculoskeletal and connective tissue disorders.	9 (8.3)	3 (2.9)	5 (5.0)	1(1.0)
Skin and subcutaneous tissue disorders.	6 (5.5)	-	5 (5.0)	1 (1.0)

Number (%) of patients with the most frequent AEs (>= 5%) by MedDRA preferred term (safety population)	All patients	Methylphenidate HCl LA	Placebo	Placebo Washout
No. (%) of patients studied	109	102	101	97
No. (%) of patients with AE(s)	84 (77.1)	69 (67.6)	52 (51.5)	26 (26.8)
AE preferred term	n (%)	n (%)	n (%)	n (%)
Headache	38 (34.9)	24 (23.5)	17(16.8)	6 (6.2)
Decreased appetite	19 (17.4)	15 (14.7)	-	4 (4.1)
Abdominal pain upper	18 (16.5)	13 (12.7)	6 (5.9)	1 (1.0)
Upper respiratory tract infection	15 (13.8)	7 (6.9)	5 (5.0)	4 (4.1)
Nausea	11(10.1)	7 (6.9)	3 (3.0)	1(1.0)
Insomnia	11 (10.1)	5 (4.9)	5 (5.0)	1 (1.0)
Nasopharyngitis	10 (9.2)	4 (3.9)	5 (5.0)	2 (2.1)
Vomiting	8 (7.3)	7 (6.9)	1 (1.0)	-
Initial insomnia	8 (7.3)	3 (2.9)	5 (5.0)	-
Anorexia	9 (8.3)	6 (5.9)	2 (2.0)	2 (2.1)

Number (%) of patients with any serious or significant adverse events (Safety population)

Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (safety population)

	All Patients	Methylphenidate HCl LA	Placebo	Placebo Washout
No. (%) of patients studied	109	102	101	97
Number (%) of patients with serious or other significant events	n (%)	n (%)	n (%)	n (%)
Death	-	-	-	-
Number of patients reporting at least one serious adverse event s)	-	-	1 (1.0)	-
Clinically significant AE(s)	-	-	1 (1.0)	-
Discontinued due to SAE(s)	-	-	0	-
Discontinued due to clin. sign. AE(s)	-	-	0	-

Other relevant findings: Not applicable

Date Updated: September 9, 2005