Sponsor– Novartis	**Web Page/Link to Prescribing/Label Information**– www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Dexmethylphenidate HCl	
Therapeutic Area of Trial– Neuroscience	
Approved Indication– Attention hyperactivity deficit disorderADHD	
Study Number– CRIT124E2302	
Title– A 5-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group, fixed-dose study of the efficacy and safety of dexmethylphenidate HCl extended-release capsules administered once daily in adults with attention deficit hyperactivity disorder	
Phase of Development– Phase 3	
Study Start/End dates– 02-Apr-2003 / 03-Sep-2003	
Study Design/Methodology– This was a 5-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group, fixed-dose study using three daily doses of dexmethylphenidate HCl extended-release capsules: 20 mg, 30 mg, and 40 mg.	
Centres– 18 centers in the US	
Publication– Ongoing	
Objectives– • The primary objective of this study was to evaluate the efficacy and safety of dexmethylphenidate HCl 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 dexmethylphenidate HCl extended-release capsules in adults with ADHD.	
Test Product, Dose, and Mode of Administration–. Dexmethylphenidate HCl extended-release capsules was available in strengths of 10 and 20 mg for oral administration. Daily dose options included 10, 20, 30, or 40 mg, achieved by taking 2 capsules once daily (i.e., one 10-mg capsule plus one placebo capsule, two 10-mg capsules, one 20-mg capsule plus one 10-mg capsule, or two 20-mg capsules).	
Reference Product(s), Dose(s), and Mode(s) of Administration– Matching placebo control. All capsules of study drug were identical in appearance.	
Criteria for Evaluation– *Primary Efficacy:* The primary efficacy variable was change from baseline to final visit in the total score of the DSM-IV ADHD RS. *Secondary efficacy*: • the proportion of patients with at least 30% improvement in the total score of the DSM-IV ADHD RS 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; • the 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); • the proportion of patients at each level of improvement on the 7-point CGI-I scale at the final visit; • the 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);	

Safety/tolerability: Safety assessments consisted of monitoring and recording all adverse events (including serious adverse events), vital signs, and body weight. Laboratory parameters (including hematology, blood chemistry, and urine), ECGs, and results of physical examinations were also assessed for any abnormalities.

Other: No other assessments were made

Pharmacology: The pharmacokinetic evaluation was to be performed on blood samples collected at the final scheduled study visit, Visit 7. One blood sample was to be taken from all patients after all efficacy measurements had been performed. The objective was to explore the population pharmacokinetics of dexmethylphenidate HCl extended-release capsules in adults with ADHD.

Statistical Methods–

Data were summarized by treatment group with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements.

Evaluation of the primary efficacy variable was performed using an analysis of covariance (ANCOVA) model with treatment group, center and the baseline DSM-IV ADHD RS total score as explanatory variables. The primary comparison was between each of the two highest dose Dexmethylphenidate-HCl-extended-release capsules groups (30 and 40 mg) and placebo using Hochberg's procedure to adjust for multiplicity.

Secondary efficacy variables were analyzed as follows:

- 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;
- 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;
- Rating of the CGI-I at the final visit was analyzed by an extended Cochran-Mantel-Haenszel (CMH) test stratified by center.

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.

No adjustment for multiplicity was performed for analyses of the secondary variables. Last observation carried forward (LOCF) was used to impute missing values for all final visit analyses.

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-specified ranges. Other safety data (e.g., vital signs, electrocardiogram) were considered as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics–.

Adult male or female outpatients from 18 through 60 years of age who met DSM-IV criteria for ADHD (either combined or single type, DSM-IV codes 314.01 or 314.00, respectively), and had a history of childhood onset of ADHD. Patients were to have a DSM-IV ADHD Rating Scale total score greater than or equal to 24 at Screening and baseline, and functional impairment, defined as a Global Assessment of Functioning (GAF) score less than or equal to 60, at Screening and baseline. Female patients of childbearing potential must have been practicing an acceptable method of contraception and female patients who were pregnant or nursing were excluded. Patients with a history of alcohol or substance abuse or dependence within the last 6 months were excluded.

Number of Subjects	Dexmethylphenidate HCl extended-release capsules				
	20 mg n (%)	30 mg n (%)	40 mg n (%)	Placebo n (%)	All n (%)
Planned					220
Screened					295
Randomized	58 (100)	55 (100)	55 (100)	53 (100)	221 (100)
Completed	49 (84.5)	45 (81.8)	47 (85.5)	43 (81.1)	184 (83.3)
Safety population	57 (98.3)	54 (98.2)	54 (98.2)	53 (100.0)	218 (98.6)
Efficacy population	57 (98.3)	54 (98.2)	54 (98.2)	53 (100.0)	218 (98.6)
Discontinued (due to)	9 (15.5)	10 (18.2)	8 (14.5)	10 (18.9)	37 (16.7)
Adverse event(s)	6 (10.3)	7 (12.7)	5 (9.1)	4 (7.5)	22 (10.0)
Lost to follow-up	2 (3.4)	0 (0.0)	3 (5.5)	1 (1.9)	6 (2.7)
Subject withdrew consent	0 (0.0)	2 (3.6)	0 (0.0)	3 (5.7)	5 (2.3)
Protocol violation	1 (1.7)	1 (1.8)	0 (0.0)	1 (1.9)	3 (1.4)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)

	Dexmethylphenidate HCl extended-release capsules				
Demographic and background characteristics	**20 mg N=58**	**30 mg N=55**	**40 mg N=55**	**Placebo N=53**	**All N=221**
Age (yr)					
N	58	55	55	53	221
Mean	39.1	39.1	38.2	38.1	38.7
SD	10.75	10.55	10.25	10.79	10.53
Sex - n (%)					
Male	32 (55.2)	34 (61.8)	34 (61.8)	27 (50.9)	127 (57.5)
Female	26 (44.8)	21 (38.2)	21 (38.2)	26 (49.1)	94 (42.5)
Race - n (%)					
Caucasian	58 (100)	48 (87.3)	43 (78.2)	40 (75.5)	189 (85.5)
Black	0 (0.0)	3 (5.5)	4 (7.3)	3 (5.7)	10 (4.5)
Oriental	0 (0.0)	0 (0.0)	4 (7.3)	3 (5.7)	7 (3.2)
Other	0 (0.0)	4 (7.3)	4 (7.3)	7 (13.2)	15 (6.8)
DSM-IV ADHD diagnosis - n (%)					
Inattentive	17 (29.3)	14 (25.5)	16 (29.1)	12 (22.6)	59 (26.7)
Hyperactive-impulsive	2 (3.4)	3 (5.5)	1 (1.8)	1 (1.9)	7 (3.2)
Combined type	39 (67.2)	38 (69.1)	38 (69.1)	40 (75.5)	155 (70.1)
Duration of ADHD symptoms (yr)					
N	58	55	54	52	219
Mean	32.9	33.5	31.9	31.1	32.4
SD	10.90	10.54	11.60	10.99	10.98
Confirmed childhood onset of ADHD - n (%)					
Yes	58 (100)	55 (100)	55 (100)	53 (100)	221 (100)
Received medication for ADHD in the past - n (%)					
Yes	20 (34.5)	12 (21.8)	22 (40.0)	26 (49.1)	80 (36.2)

No	38 (65.5)	43 (78.2)	33 (60.0)	27 (50.9)	141 (63.8)
baseline DSM-IV ADHD RS total score					
N	58	55	55	53	221
Mean	36.9	36.9	36.7	37.5	37.0
SD	7.18	8.01	8.33	7.82	7.79
baseline GAF score					
N	58	55	55	53	221
Mean	53.9	54.2	55.8	54.8	54.6
SD	4.60	4.16	3.80	3.42	4.07

Primary Efficacy Results

Change from baseline to final visit in the total score of the DSM-IV ADHD RS.

		dexmethylphenidate-HCl-extended-release capsules			
Change from baseline in the DSM-IV ADHD RS total score by treatment		**20 mg**	**30 mg**	**40 mg**	**Placebo**
Visit 2 (baseline)	n	57	54	54	53
	Mean	36.8	36.9	36.9	37.5
	SD	7.20	8.07	8.25	7.82
Visit 7 / Final DB Visit	n	57	54	54	53
	Mean	23.1	23.5	20.0	29.6
	SD	11.65	11.80	11.50	13.58
Change from baseline	n	57	54	54	53
	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	

Secondary efficacy result(s)–intent to treat population

Proportion of patients with at least 30% improvement in the total score of the DSM-IV ADHD RS

	dexmethylphenidate-HCl-extended-release capsules			
Proportion of patients with ³ 30% improvement in the DSM-IV ADHD RS total score	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**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	

Change from baseline to final visit in the Inattention subscore and Hyperactivity/Impulsivity subscore

		Dexmethylphenidate HCl extended-release capsules			
Change from baseline in the DSM-IV ADHD RS Inattentive subscale score		**20 mg**	**30 mg**	**40 mg**	**Placebo**
Visit 2 (baseline)	n	57	54	54	53
	Mean	21.2	21.0	21.4	21.1
	SD	3.43	3.91	3.82	4.13
Visit 7 / Final DB Visit	n	57	54	54	53

	Mean	13.5	12.9	11.7	16.4
	SD	6.74	6.10	7.23	7.32
Change from baseline	n	57	54	54	53
	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	
Change from baseline in the DSM-IV ADHD RS Hyperactive-Impulsive subscale score		**20 mg**	**30 mg**	**40 mg**	**Placebo**
Visit 2 (baseline)	n	57	54	54	53
	Mean	15.6	15.9	15.6	16.4
	SD	6.03	6.45	6.94	5.99
Visit 7 / Final DB Visit	n	57	54	54	53
	Mean	9.6	10.5	8.4	13.2
	SD	5.84	6.62	6.30	7.69
Change from baseline	n	57	54	54	53
	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	

Proportion of patients with improvement on the CGI-I scale & Proportion of patients at each level of improvement on the 7-point CGI-I scale scale

	Dexmethylphenidate HCl extended-release capsules			
CGI-I rating at final visit	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**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	
Patients with improvement on the CGI-I scale	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**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	

Proportion of patients with improvement on the CGI-S

Proportion of patients with improvement on the CGI-S scale by treatment
Last observation carried forward
(Intent-to-treat population)

	Focalin LA 20 mg N=57	Focalin LA 30 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*	

Safety Results

	Dexmethylphenidate HCl extended-release capsules				
Number (%) of patients with AEs by primary system organ class	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**40 mg N=54 n (%)**	**30&40 mg N=108 n (%)**	**Placebo N=53 n (%)**
n (%) of patients with AEs (total)	48 (84.2)	51 (94.4)	46 (85.2)	97 (89.8)	36 (67.9)
Psychiatric disorders	23 (40.4)	23 (42.6)	25 (46.3)	48 (44.4)	16 (30.2)
Nervous system disorders	21 (36.8)	21 (38.9)	27 (50.0)	48 (44.4)	15 (28.3)
Gastro-intestinal disorders	16 (28.1)	17 (31.5)	24 (44.4)	41 (38.0)	10 (18.9)
Metabolism and nutrition disorders	15 (26.3)	12 (22.2)	13 (24.1)	25 (23.1)	8 (15.1)
General disorders and administration site conditions	10 (17.5)	11 (20.4)	15 (27.8)	26 (24.1)	9 (17.0)
Respiratory, thoracic and mediastinal disorders	9 (15.8)	5 (9.3)	8 (14.8)	13 (12.0)	4 (7.5)
Infections and infestations	7 (12.3)	4 (7.4)	6 (11.1)	10 (9.3)	6 (11.3)
Skin & subcutaneous tissue disorders	2 (3.5)	10 (18.5)	4 (7.4)	14 (13.0)	0 (0.0)
Musculoskeletal, connective tissue and bone disorders	4 (7.0)	7 (13.0)	2 (3.7)	9 (8.3)	3 (5.7)

	Dexmethylphenidate HCl extended-release capsules				
Number (%) of patients with most frequent AEs by preferred term	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**40 mg N=54 n (%)**	**30&40 mg N=108 n (%)**	**Placebo N=53 n (%)**
n (%) of patients with AEs (total)	48 (84.2)	51 (94.4)	46 (85.2)	97 (89.8)	36 (67.9)
Adverse events					
Headache	15 (26.3)	16 (29.6)	21 (38.9)	37 (34.3)	10 (18.9)
Decreased appetite	11 (19.3)	9 (16.7)	10 (18.5)	19 (17.6)	6 (11.3)
Insomnia	10 (17.5)	7 (13.0)	10 (18.5)	17 (15.7)	6 (11.3)
Dry mouth	4 (7.0)	11 (20.4)	11 (20.4)	22 (20.4)	2 (3.8)
Feeling jittery	5 (8.8)	10 (18.5)	5 (9.3)	15 (13.9)	1 (1.9)
Anxiety	3 (5.3)	6 (11.1)	6 (11.1)	12 (11.1)	1 (1.9)

Dyspepsia	3 (5.3)	5 (9.3)	5 (9.3)	10 (9.3)	1 (1.9)
Irritability	3 (5.3)	5 (9.3)	4 (7.4)	9 (8.3)	3 (5.7)
Dizziness	5 (8.8)	2 (3.7)	3 (5.6)	5 (4.6)	1 (1.9)
Nausea	6 (10.5)	1 (1.9)	3 (5.6)	4 (3.7)	2 (3.8)
Anorexia	3 (5.3)	2 (3.7)	3 (5.6)	5 (4.6)	2 (3.8)
Fatigue	2 (3.5)	1 (1.9)	5 (9.3)	6 (5.6)	6 (11.3)
Pharyngolaryngeal pain	2 (3.5)	2 (3.7)	4 (7.4)	6 (5.6)	1 (1.9)
Hyperhidrosis	0 (0.0)	5 (9.3)	2 (3.7)	7 (6.5)	0 (0.0)

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

	Dexmethylphenidate-HCl-extended-release capsules				
Number (%) of patients who died, had serious AEs, or discontinued because of AEs	**20 mg N=57 n (%)**	**30 mg N=54 n (%)**	**40 mg N=54 n (%)**	**30&40 mg N=108 n (%)**	**Placebo N=53 n (%)**
Serious/significant AEs					
Death	0	0	0	0	0
SAEs (other than death)	0	0	2 (3.7)	2 (1.9)	0
Discontinued due to SAEs	0	0	0	0	0
Discontinued due to AEs	6 (10.5)	7 (13.0)	5 (9.3)	12 (11.1)	4 (7.5)

Other relevant findings; Not applicable

Date Updated: September 9, 2005