Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Methylphenidate hydrochloride

Therapeutic Area of Trial

Neuroscience/Psychiatry

Approved Indication

Methylphenidate hydrochloride is currently indicated in the treatment of ADHD in children aged 6 years or older, and in adults. Methylphenidate hydrochloride is also indicated in the treatment of narcolepsy.

Protocol Number

CRIT124D2302E1

Title

A 6-month, open-label extension to a 40-week, randomized, double-blind, placebo-controlled, multicenter efficacy and safety study of Ritalin®LA in the treatment of adult patients with childhood-onset of attention deficit hyperactivity disorder (ADHD).

Study Phase

Phase IIIb

Study Start/End Dates

Study initiation date: 12-Apr-2011 (first patient first visit)

Study completion date: 05-Feb-2013 (last patient last visit)

Study Design/Methodology

This was a 6-month, open-label, multicenter extension study to the 40-week, randomized, double-blind, placebo-controlled, efficacy and safety core study CRIT124D2302 in adult patients with childhood-onset of ADHD. All patients entering the extension study began treatment with Ritalin®LA 20 mg/day and were titrated to their optimal dose (the dose at which an optimal balance between control of symptoms and adverse effects could be achieved) of 40, 60, or 80 mg/day in increments of 20 mg on a weekly basis. The investigator had the flexibility to adjust the doses as necessary as long as the dose remained in the range of Ritalin LA 40-80 mg. The 6-month duration of treatment provided an adequate exposure to Ritalin LA for an assessment of its long-term safety in adults with ADHD.

Centers

International, multicenter trial: 48 centers in 6 countries (Germany, Belgium,

Denmark, Sweden, Colombia and United States)

Publication

Results are not yet published. It is under process.

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational therapy was Ritalin LA (a racemic mixture of d- and l-threo-methylphenidate, modified-release hard capsules) taken orally once daily in doses of 20, 40, 60 or 80 mg by all extension patients. Ritalin LA was provided at strengths of 20 mg and 30 mg, each bottle containing 30 capsules. A combination of bottles was used to make up the daily dose to ensure that the patient always took 1 capsule from each bottle dispensed.

Statistical Methods

A total of 298 patients entered the extension study and received treatment with Ritalin LA. The study population included patients who had completed the core study, as well as patients who had discontinued in Period 3 of the core study due to lack of therapeutic effect but were eligible for treatment with Ritalin LA according to the inclusion and exclusion criteria of the extension protocol. In addition, some patients enrolled in the extension study, were discontinued in Period 3 of the core study prior to implementation of Amendment 2. These patients could not be classified as Period 3 treatment failures and were therefore excluded from the efficacy sub-analysis of all extension patients based on their completion and treatment failure status in Period 3.

Two data analysis sets were prepared, one for the efficacy and safety analysis of the extension study and the other for the analyses of the duration of maximum continuous exposure and the relative incidence of AEs during the entire period of the core and the extension study.

- The "All Extension Patients" (AEP) analysis set was used for all efficacy and safety analyses of the extension study. The AEP was defined as all patients who had entered the open-label extension study and received at least one dose of Ritalin LA during the extension study.
- The "Safety analysis set for Period 1", was used for the analysis of maximum continuous exposure for the entire period of the core and the extension study and for analysis of AEs combined from the core and the extension study by maximum continuous exposure ($\leq$ 6 months, >6 months, $\leq$ 12 months and >12 months). This included all treated patients who were randomized at the start of core study. If a patient took both Ritalin LA and Placebo during different periods of the core study or extension, the patient was included in both treatment groups.

Major protocol deviations that excluded the patients from the analysis set have been listed in the table below:

Table Error! No text of specified style in document.**-1** **Major protocol deviations**

Deviation code	Description of deviation
I07_E1	Informed consent not signed prior to study assessment

Deviation code	Description of deviation
S27_E1	Patient entered study but did not receive study drug

Patient demographics and other baseline characteristics

All data for background and demographic variables were listed by subject. Demographics and other background variables were presented by treatment received in Period 3 of the core study for all Ritalin LA patients and for AEP combined by means of descriptive statistics (n, mean, standard deviation, minimum, median, maximum) for continuous variables, and by contingency tables (n, %) for discrete variables. With the exception of weight and smoking history that were collected at Visit 20 (week 40), all background and demographic variables were collected during screening phase of the core study.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information were listed by subject.

Age in the extension analyses was the age at first randomization, derived as follows:

Age (years) = (date of randomization – date of birth) / (365.25).

Summary of height in centimeters (cm) collected at screening was also reported.

Analysis was presented by treatment received in Period 3 of the core study and for AEP combined.

Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug administration has been summarized for each patient and listed by start date. Exposure to study medication in terms of days was summarized for extension study, and for Period 3 of core study plus extension study. Combined exposure for the core study plus extension was also presented with ‘All Ritalin LA’ and ‘Placebo’ groups for ‘Safety analysis set in Period 1’. Treatment group ‘All Ritalin LA’ was defined as patients taking Ritalin LA in any period during the core study and extension. It was possible that a patient could be counted under both ‘All Ritalin LA’ and ‘Placebo’ group. The longest continuous duration for which any patient had been on Ritalin LA or placebo was used for the output of the entire core study and extension.

The last daily dose by weight (mg/kg/day) has also been summarized and listed by patient.

The number and percentage of patients taking concomitant medications and non-drug therapies during the Period 3 and the extension study, and the number and percentage of patients who had received concomitant medications and non-drug therapies prior to extension (Week 40/Visit 20) and continued into the extension or received during extension, were summarized separately by preferred term (PT) according to the latest version of WHO Drug Reference List dictionary (which employs the Anatomical Therapeutic Chemical classification system).

Analysis of the primary variable(s)

In the extension study, no primary variables had been defined since the main objective was to collect and analyze long-term safety of Ritalin LA administered once daily for six months in adults with ADHD.

Statistical hypothesis, model, and method of analysis

There were no specified statistical hypotheses and models for safety variables. All safety summaries have been presented by mean daily dose (≤ 40, > 40-60, and > 60 mg/day). Adverse events have been coded using the MedDRA version 15.0 coding dictionary.

The incidence of AEs has been summarized by system organ class and PT. Separate summaries have been produced for all events, events by maximum severity, those suspected to be related to study drug, events leading to study drug discontinuation and events leading to study drug dose adjustment or interruption.

Deaths and serious adverse events have been summarized separately. Apart from the above, AEs were reported separately with following information:

- Severity grade (mild, moderate, severe),
- Relationship to the study drug(s) (suspected/not suspected),
- Duration (start and end dates or if continuing at final exam),
- Whether it constituted an SAE,
- Time of onset relative to start of core and extension study.

Safety analysis

All safety parameters were presented by mean daily dose (≤ 40 mg, > 40-60 mg, > 60 mg) for the extension study and by treatment received in Period 3 of the core study for 'Safety analysis set for Period 1'. In addition, all outputs were presented by gender and age group (18-30, 31-40, 41-50, and 51-60 years).

1. Adverse events

Adverse events were considered the primary variables for the study. The number and percentage of patients experiencing AEs was summarized by primary System Organ Class (SOC) and preferred term (PT). All AEs were coded using the latest version of MedDRA (version 15.0).

Adverse events were summarized as:

- Starting (or worsening) in the extension study
- Starting (or worsening) in Period 3 of the core and extension study (by treatment with Ritalin LA or Placebo in Period 3)

- AEs recorded during the core and the extension study by maximum continuous exposure (≤ 6 months, >6 months, ≤ 12 months and >12 months). If a patient took both Ritalin LA and placebo during different periods of the core study, the patient was included in both treatment groups (All Ritalin LA and Placebo) and the AEs occurring during the maximum continuous exposure period in a treatment group were included for analysis under the same treatment group.

2. Laboratory parameters

Summary statistics for Period 3 (of the core study) baseline (Week 14/Visit 13), extension baseline (Week 40/Visit 20), end of extension (Week 66/Visit 30), and changes from both baselines have been presented for each laboratory parameter.

Shift tables from both baselines to the end of extension visit have been presented with the number and percentage of patients with abnormalities according to normal ranges. Number and percent of patients with values outside the clinically notable ranges for extension and Period 3 plus extension have been reported.

Clinically notable laboratory results were presented as defined in the protocol.

3. Vital signs and weight

Vital signs assessments were performed at each visit and upon premature discontinuation in the extension study. Vital signs included blood pressure and pulse measurements. As systolic and diastolic blood pressures were measured three times for each visit, mean of three records was reported for each visit. Clinically notable vital signs were presented as defined in the protocol.

Summary statistics for vital signs based on average value at Period 3 baseline (Week 14/Visit 13) and extension baseline (Week 40/Visit 20), each post-baseline visit and change from both baselines have been provided. Clinically notable values and changes for extension and Period 3 plus extension have also been presented separately. The clinically notable values were listed by patient as described in the protocol.

Summary of body weight (to the nearest 0.1 kilogram [kg]) had been reported for Week 40/Visit 20, Week 54/Visit 27 and Week 66/Visit 30.

4. ECG

A standard 12-lead ECG was performed at Week 40/Visit 20 (extension baseline), and Week 66/Visit 30 (End of extension) or premature discontinuation visit.

Summary statistics for all ECG parameters at Period 3 baseline of the core study, extension baseline, at end of extension, and change from both baselines were presented. Clinically notable values and changes for extension and Period 3 plus extension have been summarized. Clinically notable ECGs were defined in the protocol.

Handling of missing values/censoring/discontinuations

As the primary objective was to evaluate the long-term safety of Ritalin LA, the safety profiles were presented up to study completion or early discontinuation; missing safety values were not imputed.

Supportive analyses

Not applicable.

Analysis of secondary variable(s)

1. Efficacy

The following efficacy variables have been summarized by the treatment received in Period 3 of the double-blind core study:

- DSM-IV ADHD RS total score and inattention and hyperactivity/impulsivity sub-scores: change from Period 3 baseline and end of Period 3 (extension baseline) to the end of extension study
- SDS total score and work life, social life and family life sub-scores: change from Period 3 baseline and end of Period 3 (extension baseline) to end of extension study
- CGI-I: proportion of patients with an improvement (defined as a rating of 1 "very much improved" or 2 "much improved") at the end of extension study.
- CGI-S: proportion of patients with an improvement (decrease) on the scale from Period 3 baseline and extension baseline to the end of the extension.

An additional efficacy sub-analysis of the DSM-IV ADHD RS and SDS total scores for Period 3 completers and Period 3 treatment failures has been summarized by the treatment received in Period 3 of the core study. In addition, some patients enrolled in the extension study, were discontinued in Period 3 of the core study prior to implementation of Amendment 2. These patients could not be classified as Period 3 treatment failures and were therefore excluded from the efficacy sub-analysis of all extension patients based on their completion and treatment failure status in Period 3.

In addition to overall summaries by treatment (and visit), all efficacy variables were summarized by gender and age category (18-30, 31-40, 41-50, 51-60 years).

For efficacy variables, last observation carried forward (LOCF) was applied, if the end of extension values were missing. If there was no available post-baseline value, end of extension value was set to missing.

Only those patients having non-missing baseline and at least one non-missing post-baseline value were considered for change from baseline.

Resource utilization

Not applicable.

Health-related quality of life

Not applicable.

Pharmacokinetics

Not applicable.

Sample size calculation

Under the assumptions of completion rate in the core study, 230 patients were expected to complete the core and 100 patients or more were expected to withdraw/discontinue from Period 3 of the core study due to treatment failure.

To ensure that a minimum of 300 patients were exposed to active treatment for 6 months and 100 patients for 12 months (requirement of ICH E1 guideline), using a combination of core and extension data, it was estimated that 180 patients who were core completers and 110 patients who were treatment failures were required to enter the extension study, assuming a dropout rate of 25% at 12 weeks and of 40% at 26 weeks during the extension (as observed in the core study CRIT124D2302).

Power for analysis of key secondary variables

Not applicable.

Interim analysis

No interim analyses were planned.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients eligible for inclusion in the extension study had to fulfill the following key inclusion criteria:

1. Patients should have completed the 40-week core study CRIT124D2302 and Week 40 (End of Study) assessments, or
2. Patients should have met the predefined criteria for lack of therapeutic effect during Period 3 of the core study (≥30% worsening on DSM-IV ADHD RS from Period 3 baseline and less than 30% remaining improvement from the Period 1 baseline score on the DSM-IV ADHD RS), and withdrawn from the core study, after completing core-study Week 40 assessments (Premature Discontinuation Visit).
3. Written informed consent was obtained before any study related activity from the extension protocol was performed.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use an effective method of contraception during dosing of study treatment. Effective contraception methods include:
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception],
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment,
- Male sterilization (at least 6 months prior to screening)

Exclusion criteria

Patients fulfilling any of the following criteria were not eligible for inclusion in this extension study:

1. Patients who, during the core study developed any psychiatric conditions, including anxiety, tension, agitation, aggressive behavior, psychotic symptoms and suicidal tendency that required treatment with medications, or developed conditions that, in the judgment of the investigator, may interfere with study participation and/or study assessments.
2. Patients who, during the core study developed cardiovascular disorders including severe hypertension, angina, arterial occlusive disease, heart failure, hemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
3. Patients who, during the core study developed cerebrovascular disorders such as cerebral aneurysm, vascular abnormalities including vasculitis or stroke.
4. Evidence upon physical examination during the core study of any clinically significant respiratory, hepatic, gastrointestinal, renal, hematological, or neoplastic disorder requiring current medical intervention/therapy or likely to have a significant impact on the outcome of this study.
5. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. Patients with a positive urine drug test at the End of Core Study (Week 40/Visit 20)/Premature discontinuation visit.
7. Patients with an abnormal electrocardiogram (ECG) at the End of Core Study (Week 40/Visit 20)/Premature discontinuation visit.
8. Patients who developed any seizure condition during the core study.
9. Diagnosis of glaucoma, hyperthyroidism, pheochromocytoma.
10. Diagnosis or family history of Tourette’s syndrome.

- **Participant Flow**

Patient disposition for extension by treatment received in Period 3 (All extension patients)

Disposition reason	All Ritalin LA in Period 3 N=216 n (%)	Placebo in Period 3 N=82 n (%)	All extension patients N=298 n (%)
Entered extension*	216 (100.0)	82 (100.0)	298**(100.0)
Completed extension	191 (88.4)	71 (86.6)	262 (87.9)
Total Discontinued	25 (11.6)	11 (13.4)	36 (12.1)
Adverse Event(s)	5 (2.3)	3 (3.7)	8 (2.7)
Unsatisfactory therapeutic effect	5 (2.3)	0	5 (1.7)
Subject's condition no longer requires study drug	1 (0.5)	0	1 (0.3)
Subject withdrew consent	6 (2.8)	5 (6.1)	11 (3.7)
Lost to follow-up	1 (0.5)	3 (3.7)	4 (1.3)
Administrative problems	3 (1.4)	0	3 (1.0)
Protocol deviation	4 (1.9)	0	4 (1.3)

* Includes patients who were classified as Period 3 completers, Period 3 treatment failures and Period 3 missing treatment failure (discontinued in the Period 3 of the core study prior to protocol amendment without meeting the revised treatment failure definition)
Denominator used in the percentage calculations: randomized patients.
** One additional patient (D2302E1-0504-00019) entered the extension, but did not receive a single dose of the study medication, and was subsequently excluded from the All extension patients population.

Baseline Characteristics

Demographic characteristics by Period 3 treatment (All extension patients)

	All Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
Age (years)			
N	216	82	298
Mean	36.6	35.4	36.3
Median	38.0	36.0	38.0
SD	11.39	11.45	11.40
Min	18.0	18.0	18.0
Max	60.0	60.0	60.0
Age group (years)-n (%)			
18-30	73 (33.8)	34 (41.5)	107 (35.9)
31-40	47 (21.8)	15 (18.3)	62 (20.8)
41-50	74 (34.3)	25 (30.5)	99 (33.2)
51-60	22 (10.2)	8 (9.8)	30 (10.1)
Sex - n (%)			
Male	115 (53.2)	45 (54.9)	160 (53.7)
Female	101 (46.8)	37 (45.1)	138 (46.3)
Race – n (%)			
Caucasian	200 (92.6)	72 (87.8)	272 (91.3)
Black	3 (1.4)	4 (4.9)	7 (2.3)

	All Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
Asian	2 (0.9)	1 (1.2)	3 (1.0)
Native American	1 (0.5)	0	1 (0.3)
Other	10 (4.6)	5 (6.1)	15 (5.0)
Ethnicity - n (%)			
Hispanic/Latino	19 (8.8)	6 (7.3)	25 (8.4)
Chinese	0	1 (1.2)	1 (0.3)
Indian (Indian subcontinent)	2 (0.9)	0	2 (0.7)
Japanese	1 (0.5)	0	1 (0.3)
Mixed Ethnicity	1 (0.5)	0	1 (0.3)
Other	193 (89.4)	75 (91.5)	268 (89.9)
Height (cm)			
N	216	82	298
Mean	173.6	173.5	173.6
Median	174.0	175.0	174.0
SD	9.35	8.78	9.18
Min	146.0	150.0	146.0
Max	205.0	189.0	205.0
Weight (kg)			
N	216	82	298
Mean	75.7	78.3	76.4
Median	73.9	79.5	74.8
SD	15.69	15.50	15.65
Min	46.0	42.0	42.0
Max	127.0	115.2	127.0
BMI (kg/m2)			
N	216	82	298
Mean	25.0	25.9	25.2
Median	24.7	25.3	24.9
SD	3.88	4.40	4.04
Min	17.3	17.3	17.3
Max	38.3	36.0	38.3
Smoking status			
Current smoker (yes)	59 (27.3)	24 (29.3)	83 (27.9)
Cigarettes	57 (26.4)	24 (29.3)	81 (27.2)
Period 3 treatment failures*	46 (21.3)	45 (54.9)	91 (30.5)
Period 3 completers	134 (62.0)	26 (31.7)	160 (53.7)

Age calculation is based on the randomization date of core study Period 1.
Height in centimeters was collected at screening (core study).Weight and smoking status collected at extension baseline.
BMI = body mass index.
A treatment failure is defined as at least 30% or more worsening on DSM-IV ADHD RS rating scale score from Period 3 baseline and a less than 30% remaining improvement from the Period 1 baseline on the same scale.
* Patients discontinued in Period 3 of the core study prior to implementation of Amendment 2, without meeting the revised treatment failure definition were not classified as treatment failure and are not included in this table.

Outcome measures

The primary objective of this extension study was to evaluate long term safety in patients with ADHD and thus the safety results are presented as primary outcome measures.

Primary Outcome Result(s)

Safety Results

Number (%) of patients with AEs starting in extension regardless of study drug relationship by primary system organ class and extension mean daily dose (All extension patients)

Primary System Organ Class	Ritalin LA mean daily dose in extension <=40 mg N=85 n (%)		>40-60 mg N=104 n (%)		>60 mg N=109 n (%)		All Extension patients N=298 n (%)	
Any primary system organ class	59	(69.4)	78	(75.0)	71	(65.1)	208	(69.8)
Cardiac Disorders	4	(4.7)	7	(6.7)	4	(3.7)	15	(5.0)
Ear and Labyrinth Disorders	1	(1.2)	3	(2.9)	2	(1.8)	6	(2.0)
Eye Disorders	1	(1.2)	3	(2.9)	3	(2.8)	7	(2.3)
Gastrointestinal Disorders	20	(23.5)	21	(20.2)	16	(14.7)	57	(19.1)
General Disorders and Administration Site Condition	11	(12.9)	8	(7.7)	4	(3.7)	23	(7.7)
Immune System Disorders	3	(3.5)	1	(1.0)	2	(1.8)	6	(2.0)
Infections and Infestations	29	(34.1)	47	(45.2)	38	(34.9)	114	(38.3)
Injury, Poisoning and Procedural Complications	2	(2.4)	3	(2.9)	5	(4.6)	10	(3.4)
Investigations	0	(0.0)	6	(5.8)	6	(5.5)	12	(4.0)
Metabolism and Nutrition Disorders	4	(4.7)	12	(11.5)	8	(7.3)	24	(8.1)
Musculoskeletal and Connective Tissue Disorders	5	(5.9)	15	(14.4)	7	(6.4)	27	(9.1)
Neoplasms Benign, malignant and Unspecified (Incl Cysts and Polyps)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Nervous System Disorders	20	(23.5)	23	(22.1)	21	(19.3)	64	(21.5)
Psychiatric Disorders	19	(22.4)	29	(27.9)	14	(12.8)	62	(20.8)
Renal and Urinary Disorders	0	(0.0)	1	(1.0)	1	(0.9)	2	(0.7)
Reproductive System and Breast Disorders	3	(3.5)	3	(2.9)	3	(2.8)	9	(3.0)
Respiratory, Thoracic and Mediastinal Disorders	6	(7.1)	11	(10.6)	6	(5.5)	23	(7.7)
Skin and Subcutaneous Tissue Disorders	5	(5.9)	5	(4.8)	5	(4.6)	15	(5.0)
Surgical and Medical Procedures	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Vascular Disorders	4	(4.7)	3	(2.9)	5	(4.6)	12	(4.0)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in total row.

Number (%) of patients with most frequent AEs (>=2% for any group) starting in extension regardless of study drug relationship by preferred term and extension mean daily dose (All extension patients)

	Ritalin LA mean daily dose in extension	All Extension

Preferred Term	<=40 mg N=85 n (%)		>40-60 mg N=104 n (%)		>60 mg N=109 n (%)		patients N=298 n (%)	
Total no. of patients with AEs	59	(69.4)	78	(75.0)	71	(65.1)	208	(69.8)
Nasopharyngitis	15	(17.6)	29	(27.9)	13	(11.9)	57	(19.1)
Headache	15	(17.6)	12	(11.5)	15	(13.8)	42	(14.1)
Decreased appetite	4	(4.7)	12	(11.5)	7	(6.4)	23	(7.7)
Dry mouth	4	(4.7)	12	(11.5)	4	(3.7)	20	(6.7)
Nausea	7	(8.2)	4	(3.8)	4	(3.7)	15	(5.0)
Upper respiratory tract infection	1	(1.2)	4	(3.8)	9	(8.3)	14	(4.7)
Anxiety	3	(3.5)	5	(4.8)	3	(2.8)	11	(3.7)
Insomnia	2	(2.4)	7	(6.7)	2	(1.8)	11	(3.7)
Sinusitis	2	(2.4)	6	(5.8)	3	(2.8)	11	(3.7)
Gastroenteritis	0	(0.0)	3	(2.9)	7	(6.4)	10	(3.4)
Fatigue	5	(5.9)	3	(2.9)	1	(0.9)	9	(3.0)
Initial insomnia	3	(3.5)	4	(3.8)	1	(0.9)	8	(2.7)
Oropharyngeal pain	2	(2.4)	4	(3.8)	2	(1.8)	8	(2.7)
Tachycardia	2	(2.4)	3	(2.9)	3	(2.8)	8	(2.7)
Agitation	2	(2.4)	5	(4.8)	0	(0.0)	7	(2.3)
Hyperhidrosis	1	(1.2)	2	(1.9)	4	(3.7)	7	(2.3)
Sleep disorder	3	(3.5)	2	(1.9)	2	(1.8)	7	(2.3)
Depressed mood	3	(3.5)	1	(1.0)	2	(1.8)	6	(2.0)
Diarrhoea	4	(4.7)	1	(1.0)	1	(0.9)	6	(2.0)
Dysmenorrhoea	1	(1.2)	3	(2.9)	2	(1.8)	6	(2.0)
Palpitations	1	(1.2)	4	(3.8)	1	(0.9)	6	(2.0)
Weight decreased	0	(0.0)	2	(1.9)	4	(3.7)	6	(2.0)
Back pain	0	(0.0)	5	(4.8)	0	(0.0)	5	(1.7)
Blood pressure increased	0	(0.0)	2	(1.9)	3	(2.8)	5	(1.7)
Hypertension	3	(3.5)	0	(0.0)	2	(1.8)	5	(1.7)
Influenza	0	(0.0)	5	(4.8)	0	(0.0)	5	(1.7)
Irritability	3	(3.5)	2	(1.9)	0	(0.0)	5	(1.7)
Migraine	3	(3.5)	1	(1.0)	1	(0.9)	5	(1.7)
Restlessness	2	(2.4)	1	(1.0)	2	(1.8)	5	(1.7)
Tremor	2	(2.4)	2	(1.9)	1	(0.9)	5	(1.7)
Cough	2	(2.4)	1	(1.0)	1	(0.9)	4	(1.3)
Dizziness	3	(3.5)	1	(1.0)	0	(0.0)	4	(1.3)
Gastroenteritis viral	2	(2.4)	2	(1.9)	0	(0.0)	4	(1.3)
Seasonal allergy	2	(2.4)	1	(1.0)	1	(0.9)	4	(1.3)
Vomiting	2	(2.4)	1	(1.0)	1	(0.9)	4	(1.3)
Asthenia	2	(2.4)	1	(1.0)	0	(0.0)	3	(1.0)
Dyspepsia	2	(2.4)	0	(0.0)	1	(0.9)	3	(1.0)
Nasal congestion	2	(2.4)	1	(1.0)	0	(0.0)	3	(1.0)
Tension headache	2	(2.4)	0	(0.0)	1	(0.9)	3	(1.0)
Menorrhagia	2	(2.4)	0	(0.0)	0	(0.0)	2	(0.7)
Musculoskeletal pain	2	(2.4)	0	(0.0)	0	(0.0)	2	(0.7)
Pharyngitis	2	(2.4)	0	(0.0)	0	(0.0)	2	(0.7)
Rash	2	(2.4)	0	(0.0)	0	(0.0)	2	(0.7)

Preferred Term	Ritalin LA mean daily dose in extension <=40 mg N=85 n (%)	>40-60 mg N=104 n (%)	>60 mg N=109 n (%)	All Extension patients N=298 n (%)

Preferred terms are sorted in descending frequency, as reported in the 'All extension patients' column.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.

Number (%) of patients with AEs starting in Period 3 of the core study or in extension regardless of study drug relationship by primary system organ class and Period 3 treatment (All extension patients)

Primary System Organ Class	Ritalin LA in Period 3 N=216 n (%)		Placebo in Period 3 N=82 n (%)		All Extension patients N=298 n (%)	
Any primary system organ class	175	(81.0)	65	(79.3)	240	(80.5)
Blood and Lymphatic System Disorders	3	(1.4)	0	(0.0)	3	(1.0)
Cardiac Disorders	12	(5.6)	10	(12.2)	22	(7.4)
Ear and Labyrinth Disorders	3	(1.4)	4	(4.9)	7	(2.3)
Endocrine Disorders	1	(0.5)	0	(0.0)	1	(0.3)
Eye Disorders	9	(4.2)	2	(2.4)	11	(3.7)
Gastrointestinal Disorders	56	(25.9)	23	(28.0)	79	(26.5)
General Disorders and Administration Site Condition	25	(11.6)	14	(17.1)	39	(13.1)
Immune System Disorders	7	(3.2)	2	(2.4)	9	(3.0)
Infections and Infestations	110	(50.9)	43	(52.4)	153	(51.3)
Injury, Poisoning and Procedural Complications	18	(8.3)	5	(6.1)	23	(7.7)
Investigations	11	(5.1)	9	(11.0)	20	(6.7)
Metabolism and Nutrition Disorders	17	(7.9)	12	(14.6)	29	(9.7)
Musculoskeletal and Connective Tissue Disorders	33	(15.3)	12	(14.6)	45	(15.1)
Neoplasms Benign, malignant and Unspecified (Incl Cysts and Polyps)	1	(0.5)	0	(0.0)	1	(0.3)
Nervous System Disorders	58	(26.9)	29	(35.4)	87	(29.2)
Psychiatric Disorders	53	(24.5)	24	(29.3)	77	(25.8)
Renal and Urinary Disorders	2	(0.9)	1	(1.2)	3	(1.0)
Reproductive System and Breast Disorders	10	(4.6)	2	(2.4)	12	(4.0)
Respiratory, Thoracic and Mediastinal Disorders	23	(10.6)	9	(11.0)	32	(10.7)
Skin and Subcutaneous Tissue Disorders	19	(8.8)	6	(7.3)	25	(8.4)
Surgical and Medical Procedures	1	(0.5)	0	(0.0)	1	(0.3)
Vascular Disorders	14	(6.5)	3	(3.7)	17	(5.7)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in total row.

Number (%) of patients with most frequent AEs (>=2% for any group) starting in Period 3 or in extension regardless of study drug relationship by preferred term and Period 3 treatment (All extension patients)

Preferred Term	Ritalin LA in Period 3 N=216 n	(%)	Placebo in Period 3 N=82 n	(%)	All Extension patients N=298 n	(%)
Total no. of patients with AEs	175	(81.0)	65	(79.3)	240	(80.5)
Nasopharyngitis	59	(27.3)	20	(24.4)	79	(26.5)
Headache	41	(19.0)	21	(25.6)	62	(20.8)
Decreased appetite	15	(6.9)	11	(13.4)	26	(8.7)
Dry mouth	15	(6.9)	9	(11.0)	24	(8.1)
Nausea	15	(6.9)	3	(3.7)	18	(6.0)
Upper respiratory tract infection	13	(6.0)	4	(4.9)	17	(5.7)
Diarrhoea	9	(4.2)	6	(7.3)	15	(5.0)
Back pain	9	(4.2)	5	(6.1)	14	(4.7)
Fatigue	11	(5.1)	3	(3.7)	14	(4.7)
Insomnia	10	(4.6)	4	(4.9)	14	(4.7)
Anxiety	7	(3.2)	6	(7.3)	13	(4.4)
Gastroenteritis	8	(3.7)	5	(6.1)	13	(4.4)
Sinusitis	10	(4.6)	3	(3.7)	13	(4.4)
Initial insomnia	7	(3.2)	4	(4.9)	11	(3.7)
Oropharyngeal pain	6	(2.8)	5	(6.1)	11	(3.7)
Tachycardia	5	(2.3)	6	(7.3)	11	(3.7)
Hyperhidrosis	9	(4.2)	1	(1.2)	10	(3.4)
Irritability	8	(3.7)	2	(2.4)	10	(3.4)
Blood pressure increased	6	(2.8)	3	(3.7)	9	(3.0)
Cough	8	(3.7)	1	(1.2)	9	(3.0)
Restlessness	6	(2.8)	3	(3.7)	9	(3.0)
Arthralgia	6	(2.8)	2	(2.4)	8	(2.7)
Bronchitis	6	(2.8)	2	(2.4)	8	(2.7)
Depressed mood	8	(3.7)	0	(0.0)	8	(2.7)
Hypertension	6	(2.8)	2	(2.4)	8	(2.7)
Influenza	3	(1.4)	5	(6.1)	8	(2.7)
Palpitations	4	(1.9)	4	(4.9)	8	(2.7)
Weight decreased	5	(2.3)	3	(3.7)	8	(2.7)
Agitation	3	(1.4)	4	(4.9)	7	(2.3)
Dizziness	6	(2.8)	1	(1.2)	7	(2.3)
Dysmenorrhoea	5	(2.3)	2	(2.4)	7	(2.3)
Gastroenteritis viral	3	(1.4)	4	(4.9)	7	(2.3)
Sleep disorder	5	(2.3)	2	(2.4)	7	(2.3)
Tremor	6	(2.8)	1	(1.2)	7	(2.3)
Seasonal allergy	5	(2.3)	1	(1.2)	6	(2.0)
Vomiting	3	(1.4)	3	(3.7)	6	(2.0)
Dyspepsia	5	(2.3)	0	(0.0)	5	(1.7)
Migraine	5	(2.3)	0	(0.0)	5	(1.7)
Pain in extremity	5	(2.3)	0	(0.0)	5	(1.7)
Pyrexia	2	(0.9)	2	(2.4)	4	(1.3)

Preferred Term	Ritalin LA in Period 3 N=216 n (%)		Placebo in Period 3 N=82 n (%)		All Extension patients N=298 n (%)	
Vertigo	2	(0.9)	2	(2.4)	4	(1.3)
Abdominal pain	1	(0.5)	2	(2.4)	3	(1.0)
Feeling jittery	1	(0.5)	2	(2.4)	3	(1.0)
Muscle spasms	1	(0.5)	2	(2.4)	3	(1.0)
Nasal congestion	1	(0.5)	2	(2.4)	3	(1.0)
Tension headache	1	(0.5)	2	(2.4)	3	(1.0)
Urinary tract infection	0	(0.0)	2	(2.4)	2	(0.7)

Preferred terms are sorted in descending frequency, as reported in the 'All extension patients' column.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.

Number (%) of patients with AEs, and AEs adjusted for exposure time during extension by primary system organ class, preferred term, and extension mean daily dose (IDR >=1 per 1000 person weeks in All extension patients group) All extension patients

Primary System Organ Class Preferred Term	Ritalin LA mean daily dose in extension <=40 mg N=85 FT=1884.6 n (%) IDR			>40-60 mg N=104 FT=2569.1 n (%) IDR			>60 mg N=109 FT=2803.3 n (%) IDR			All Extension patients N=298 FT=7257.0 n (%) IDR			Frequency range for Mean daily dose <=40 mg
Cardiac Disorders													
Tachycardia	2	(2.4)	1.1	3	(2.9)	1.2	3	(2.8)	1.1	8	(2.7)	1.1	common
Gastrointestinal Disorders													
Dry mouth	4	(4.7)	2.1	12	(11.5)	4.7	4	(3.7)	1.4	20	(6.7)	2.8	common
Nausea	7	(8.2)	3.7	4	(3.8)	1.6	4	(3.7)	1.4	15	(5.0)	2.1	common
General Disorders and Administration Site Condition													
Fatigue	5	(5.9)	2.7	3	(2.9)	1.2	1	(0.9)	0.4	9	(3.0)	1.2	common
Infections and Infestations													
Nasopharyngitis	15	(17.6)	8.0	29	(27.9)	11.3	13	(11.9)	4.6	57	(19.1)	7.9	very common
Upper respiratory tract infection	1	(1.2)	0.5	4	(3.8)	1.6	9	(8.3)	3.2	14	(4.7)	1.9	common
Sinusitis	2	(2.4)	1.1	6	(5.8)	2.3	3	(2.8)	1.1	11	(3.7)	1.5	common
Gastroenteritis	0	(0.0)	0.0	3	(2.9)	1.2	7	(6.4)	2.5	10	(3.4)	1.4	
Metabolism and Nutrition Disorders													
Decreased appetite	4	(4.7)	2.1	12	(11.5)	4.7	7	(6.4)	2.5	23	(7.7)	3.2	common
Nervous System Disorders													
Headache	15	(17.6)	8.0	12	(11.5)	4.7	15	(13.8)	5.4	42	(14.1)	5.8	very common
Psychiatric Disorders													
Anxiety	3	(3.5)	1.6	5	(4.8)	1.9	3	(2.8)	1.1	11	(3.7)	1.5	common
Insomnia	2	(2.4)	1.1	7	(6.7)	2.7	2	(1.8)	0.7	11	(3.7)	1.5	common
Initial insomnia	3	(3.5)	1.6	4	(3.8)	1.6	1	(0.9)	0.4	8	(2.7)	1.1	common
Respiratory, Thoracic and Mediastinal Disorders													
Oropharyngeal pain	2	(2.4)	1.1	4	(3.8)	1.6	2	(1.8)	0.7	8	(2.7)	1.1	common

Primary System Organ Class Preferred Term	Ritalin LA mean daily dose in extension <=40 mg N=85 FT=1884.6 n (%) IDR	 >40-60 mg N=104 FT=2569.1 n (%) IDR	 >60 mg N=109 FT=2803.3 n (%) IDR	All Extension patients N=298 FT=7257.0 n (%) IDR	Frequency range for Mean daily dose <=40 mg
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the All extension patients column. A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment. Frequencies are defined as follows: very common (>=1/10); common (>=1/100 to <1/10); uncommon(>=1/1000 to <1/100); FT = follow-up time in weeks IDR = incidence density rate per 1000 person weeks, calculated as 1000*n/FT					

Number (%) of patients with adverse events starting in periods where maximum continuous exposure achieved by primary system organ class and maximum continuous exposure (Safety analysis set in Period 1)

Primary System Organ Class	Ritalin LA maximum continuous exposure <= 6 months N=341 n (%)		 > 6 months N=354 n (%)		 ≤ 12 months N=559 n (%)		 > 12 months N=136 n (%)	
Any primary system organ class	**275**	**(80.6)**	**302**	**(85.3)**	**457**	**(81.8)**	**120**	**(88.2)**
Blood and Lymphatic System Disorders	0	(0.0)	5	(1.4)	4	(0.7)	1	(0.7)
Cardiac Disorders	53	(15.5)	62	(17.5)	91	(16.3)	24	(17.6)
Congenital, Familial and Genetic Disorders	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)
Ear and Labyrinth Disorders	19	(5.6)	21	(5.9)	34	(6.1)	6	(4.4)
Endocrine Disorders	1	(0.3)	2	(0.6)	3	(0.5)	0	(0.0)
Eye Disorders	12	(3.5)	20	(5.6)	24	(4.3)	8	(5.9)
Gastrointestinal Disorders	126	(37.0)	153	(43.2)	209	(37.4)	70	(51.5)
General Disorders and Administration Site Condition	77	(22.6)	86	(24.3)	126	(22.5)	37	(27.2)
Hepatobiliary Disorders	1	(0.3)	0	(0.0)	1	(0.2)	0	(0.0)
Immune System Disorders	3	(0.9)	10	(2.8)	7	(1.3)	6	(4.4)
Infections and Infestations	79	(23.2)	188	(53.1)	181	(32.4)	86	(63.2)
Injury, Poisoning and Procedural Complications	14	(4.1)	35	(9.9)	32	(5.7)	17	(12.5)
Investigations	40	(11.7)	42	(11.9)	63	(11.3)	19	(14.0)
Metabolism and Nutrition Disorders	80	(23.5)	102	(28.8)	135	(24.2)	47	(34.6)
Musculoskeletal and Connective Tissue Disorders	28	(8.2)	62	(17.5)	61	(10.9)	29	(21.3)
Neoplasms Benign, malignant & Unspecified (Incl Cysts & Polyps)	0	(0.0)	1	(0.3)	0	0	1	(0.7)
Nervous System Disorders	127	(37.2)	154	(43.5)	219	(39.2)	62	(45.6)
Psychiatric Disorders	163	(47.8)	147	(41.5)	255	(45.6)	55	(40.4)
Renal and Urinary Disorders	3	(0.9)	9	(2.5)	9	(1.6)	3	(2.2)
Reproductive System and Breast Disorders	7	(2.1)	19	(5.4)	20	(3.6)	6	(4.4)

Primary System Organ Class	Ritalin LA maximum continuous exposure <= 6 months N=341 n (%)		> 6 months N=354 n (%)		≤ 12 months N=559 n (%)		> 12 months N=136 n (%)	
Respiratory, Thoracic and Mediastinal Disorders	28	(8.2)	43	(12.1)	50	(8.9)	21	(15.4)
Skin and Subcutaneous Tissue Disorders	44	(12.9)	47	(13.3)	68	(12.2)	23	(16.9)
Surgical and Medical Procedures	0	(0.0)	1	(0.3)	0	0	1	(0.7)
Vascular Disorders	18	(5.3)	19	(5.4)	28	(5.0)	9	(6.6)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once.
Total N treated Ritalin LA in any period through the core and extension study is 695.

Number (%) of patients who died, had SAEs, or discontinued because of AEs/SAEs starting in extension by extension mean daily dose (All extension patients)

	Ritalin LA mean daily dose in extension <=40 mg N=85 n (%)		>40-60 mg N=104 n (%)		>60 mg N=109 n (%)		All Extension patients N=298 n (%)	
No. of patients who died, had SAE, discontinued due to SAE or significant AEs	5	(5.9)	1	(1.0)	3	(2.8)	9	(3.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
SAE(s)	0	(0.0)	0	(0.0)	2	(1.8)	2	(0.7)
Discontinued due to AE(s)	5	(5.9)	1	(1.0)	1	(0.9)	7	(2.3)
Discontinued due to SAE(s)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

AEs that occurred after patient's treatment end date are not included.

Number (%) of patients with SAEs starting during extension by primary system organ class, preferred term and extension mean daily dose (All extension patients)

Primary System Organ Class/ and Preferred Term	Ritalin LA mean daily dose in extension <=40 mg N=85 n (%)		>40-60 mg N=104 n (%)		>60 mg N=109 n (%)		All Extension patients N=298 n (%)	
Total	0	(0.0)	0	(0.0)	2	(1.8)	2	(0.7)
Gastrointestinal Disorders								
Total	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Pancreatitis	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Musculoskeletal and Connective Tissue Disorders								
Total	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Exostosis	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Neoplasms Benign, malignant and Unspecified (Incl Cysts and Polyps)								
Total	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)
Non-Hodgkin's lymphoma	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)

Number (%) of patients who died, had AEs, SAEs, or AEs suspected to be related to study drug in Period 3 or extension by Period 3 treatment (All extension patients)

	Ritalin LA in Period 3 N=216 n (%)		Placebo in Period 3 N=82 n (%)		All extension Patients N=298 n (%)	
Any adverse events	175	(81.0)	65	(79.3)	240	(80.5)
Any serious adverse events	2	(0.9)	0	(0.0)	2	(0.7)
Death	0	(0.0)	0	(0.0)	0	(0.0)
Any AEs suspected to be study drug related	90	(41.7)	35	(42.7)	125	(41.9)

Number (%) of patients with SAEs starting in Period 3 or extension by primary system organ class, preferred term and Period 3 treatment (All extension patients)

Primary System Organ Class/ and Preferred Term	Ritalin LA in Period 3 N=216 n (%)		Placebo in Period 3 N=82 n (%)		All Extension patients N=298 n (%)	
Total	2	(0.9)	0	(0.0)	2	(0.7)
Gastrointestinal Disorders						
-Total	1	(0.5)	0	(0.0)	1	(0.3)
Pancreatitis	1	(0.5)	0	(0.0)	1	(0.3)
Musculoskeletal and Connective Tissue Disorders						
-Total	1	(0.5)	0	(0.0)	1	(0.3)
Exostosis	1	(0.5)	0	(0.0)	1	(0.3)
Neoplasms Benign, malignant and Unspecified (Incl Cysts and Polyps)						
-Total	1	(0.5)	0	(0.0)	1	(0.3)
Non-Hodgkin's lymphoma	1	(0.5)	0	(0.0)	1	(0.3)

Secondary Outcome Result(s)

DSM-IV ADHD RS total score and change from baseline in extension by Period 3 treatment (All extension patients)

Visit (Week)	Statistics	Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
Visit 13 (Week 14/Period 3 baseline)	n	216	82	298
	Mean	12.9	12.9	12.9
	SD	6.68	6.93	6.74
	Median	12.0	13.0	13.0
	Min	0	0	0
	Max	30	32	32
Visit 20 (Week 40/extension baseline)	n	216	82	298
	Mean	16.9	25.1	19.2
	SD	11.13	12.28	12.00
	Median	15.0	26.0	17.0
	Min	0	0	0

Visit (Week)	Statistics	Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
	Max	54	47	54
Final visit*	n	216	81	297
	Mean	12.0	11.9	12.0
	SD	8.03	7.14	7.78
	Median	11.0	12.0	12.0
	Min	0	0	0
	Max	43	32	43
Change from Period 3 baseline	n	216	81	297
	Mean	-0.9	-0.9	-0.9
	SD	7.74	5.93	7.28
	Median	-2.0	-1.0	-1.0
	Min	-24	-20	-24
	Max	33	15	33
Change from extension baseline	n	216	81	297
	Mean	-5.0	-13.0	-7.2
	SD	10.10	11.20	11.00
	Median	-2.0	-13.0	-4.0
	Min	-44	-34	-44
	Max	35	12	35

Visit 13/20 indicate Period 3/extension baseline visits, not necessarily present the values at the visit.
*LOCF applied for each patient with data in extension period. If no post-baseline is available, it is considered as missing.

SDS total score and change from baseline in extension by Period 3 treatment (All extension patients)

Visit (Week)	Statistics	Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
Visit 13 (Week 14/Period 3 baseline)	n	214	82	296
	Mean	9.5	8.8	9.3
	SD	5.95	5.31	5.78
	Median	9.0	8.5	9.0
	Min	0	0	0
	Max	29	25	29
Visit 20 (Week 40/extension baseline)	n	216	82	298
	Mean	11.9	15.1	12.8
	SD	7.05	7.43	7.28
	Median	11.0	15.5	12.0
	Min	0	0	0
	Max	30	28	30
Final visit*	n	216	81	297
	Mean	8.2	7.3	8.0
	SD	5.63	4.96	5.46
	Median	7.0	7.0	7.0
	Min	0	0	0

Visit (Week)	Statistics	Ritalin LA in Period 3 N=216	Placebo in Period 3 N=82	All extension patients N=298
	Max	27	21	27
Change from Period 3 baseline	n	214	81	295
	Mean	-1.3	-1.5	-1.4
	SD	5.67	5.07	5.50
	Median	-1.0	-1.0	-1.0
	Min	-20	-19	-20
	Max	22	12	22
Change from extension baseline	n	216	81	297
	Mean	-3.7	-7.7	-4.8
	SD	6.27	7.64	6.88
	Median	-3.0	-6.0	-3.0
	Min	-20	-28	-28
	Max	18	5	18

Visit 13/20 indicate Period 3/extension baseline visits, not necessarily present the values at the visit.
* LOCF applied for each patient with data in extension period. If no post-baseline was available, it was considered as missing.

Other Relevant Findings

Proportion of patients with improvement in CGI-I scale in extension by Period 3 treatment (All extension patients)

		Ritalin LA in Period 3 N=216 Total n (%)		Placebo in Period 3 N=82 Total n (%)		All extension patients N=298 Total n (%)
Extension final visit	216	141 (65.3)	81	65 (80.2)	297	206 (69.4)

Improvement on the CGI-I scale is defined as a visit rating of 1 “very much improved” or 2 “much improved” on the CGI-I scale.
* LOCF applied for each patient in extension period.
% calculation is based on total number of patients with available data.

Proportion of patients with improvement in CGI-S scale in extension by Period 3 treatment (All extension patients)

		Ritalin LA in Period 3 N=216 Total n (%)		Placebo in Period 3 N=82 Total n (%)		All extension patients N=298 Total n (%)
From extension baseline to extension final visit	212	91 (42.9)	78	60 (76.9)	290	151 (52.1)
From Period 3 baseline to extension final visit	212	68 (32.1)	78	23 (29.5)	290	91 (31.4)

Improvement from baseline is defined as a decrease on the CGI-S scale.
* LOCF applied for each patient with data in extension period.
% calculation is based on total number of patients with available data.

Number (%) of patients with newly occurring clinically notable abnormalities in Hematology/Chemistry values during extension by extension mean daily dose (All extension patients)

		Ritalin LA mean daily dose in extension						All extension patients N=298	
		<=40 mg N=85		>40-60 mg N=104		>60 mg N=109			
Parameter	**Criterion**	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Eosinophils	> 10 %	78	0 (0.0)	97	1 (1.0)	100	1 (1.0)	275	2 (0.7)
Gamma Glutamyltransferase	> 120 U/L	78	0 (0.0)	97	0 (0.0)	104	1 (1.0)	279	1 (0.4)
Potassium	> 6 U/L	79	0 (0.0)	97	0 (0.0)	105	1 (1.0)	281	1 (0.4)

Total = Number of patients with evaluable criterion (whose baseline laboratory values are not outside the clinically notable limits and who have post-baseline laboratory values).
n = Number of patients meeting the criterion (whose post-baseline laboratory values are clinically notably abnormal).
Denominators for the percentage calculations are the number of patients with evaluable criterion

Number (%) of patients with newly occurring clinically notable abnormalities in Hematology/Chemistry values in Period 3 or in extension by Period 3 treatment (All extension patients)

		Ritalin LA in Period 3 N=216		Placebo in Period 3 N=82		All extension patients N=298	
Parameter	**Criterion**	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Bilirubin (total)	> 34.2 umol/L	213	1 (0.5)	79	0 (0.0)	292	1 (0.3)
Creatinine	> 176.8 umol/L	212	0 (0.0)	79	1 (1.3)	291	1 (0.3)
Eosinophils	> 10 %	210	2 (1.0)	77	1 (1.3)	287	3 (1.0)
Gamma Glutamyltransferase	> 120 U/L	212	2 (0.9)	78	0 (0.0)	290	2 (0.7)
Glucose	< 2.78 mmol/L	212	0 (0.0)	77	1 (1.3)	289	1 (0.3)
Potassium	> 6 U/L	212	1 (0.5)	78	0 (0.0)	290	1 (0.3)
SGOT (AST)	> 100 U/L	211	1 (0.5)	77	0 (0.0)	288	1 (0.3)
SGPT (ALT)	> 110 U/L	211	1 (0.5)	77	0 (0.0)	288	1 (0.3)
Uric Acid	> 594.8 mmol/L	213	1 (0.5)	78	0 (0.0)	291	1 (0.3)

Total = Number of patients with evaluable criterion (whose baseline laboratory values are not outside the clinically notable limits and who have post-baseline laboratory values).
n = Number of patients meeting the criterion (whose post-baseline laboratory values are clinically notably abnormal).
Denominators for the percentage calculations are the number of patients with evaluable criterion.

Number (%) of patients with clinically notable changes in vital signs and body weight during extension by extension mean daily dose (All extension patients)

		Ritalin LA mean daily dose in extension						All extension patients	
		<=40 mg N=85		>40-60 mg N=104		>60 mg N=109			
	Criterion	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Systolic Blood Pressure (mmHg)	High	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	Low	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	High & Low	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	Total	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
Diastolic Blood Pressure (mmHg)	High	84	0 (0.0)	104	0 (0.0)	109	2 (1.8)	297	2 (0.7)
	Low	84	0 (0.0)	104	1 (1.0)	109	0 (0.0)	297	1 (0.3)
	High & Low	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	Total	84	0 (0.0)	104	1 (1.0)	109	2 (1.8)	297	3 (1.0)
Heart rate (bpm)	High	84	0 (0.0)	104	0 (0.0)	109	3 (2.8)	297	3 (1.0)
	Low	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	High & Low	84	0 (0.0)	104	0 (0.0)	109	0 (0.0)	297	0 (0.0)
	Total	84	0 (0.0)	104	0 (0.0)	109	3 (2.8)	297	3 (1.0)
Weight (kg)	Decrease	83	1 (1.2)	101	9 (8.9)	106	10 (9.4)	290	20 (6.9)

Denominators for the percentage calculations are the number of patients with evaluable criterion. Criteria for clinically notable changes are compared to extension baseline.

Number (%) of patients with clinically notable changes in vital signs and body weight in Period 3 or extension by Period 3 treatment (All extension patients)

	Criterion	Ritalin LA in Period 3 N=216		Placebo in Period 3 N=82		All extension patients N=298	
		Total	n (%)	Total	n (%)	Total	n (%)
Systolic Blood Pressure (mmHg)	High	216	0	82	0	298	0
	Low	216	1 (0.5)	82	0	298	1 (0.3)
	High & Low	216	0	82	0	298	0
	Total	216	1 (0.5)	82	0	298	1 (0.3)
Diastolic Blood Pressure (mmHg)	High	216	2 (0.9)	82	2 (2.4)	298	4 (1.3)
	Low	216	1 (0.5)	82	0	298	1 (0.3)
	High & Low	216	0	82	0	298	0
	Total	216	3 (1.4)	82	2 (2.4)	298	5 (1.7)
Heart rate (bpm)	High	216	1 (0.5)	82	2 (2.4)	298	3 (1.0)
	Low	216	3 (1.4)	82	0	298	3 (1.0)
	High & Low	216	0	82	0	298	0
	Total	216	4 (1.9)	82	2 (2.4)	298	6 (2.0)
Weight (kg)	Decrease	214	18 (8.4)	80	11 (13.8)	294	29 (9.9)

Denominators for the percentage calculations are the number of patients with evaluable criterion.
Criteria for clinically notable changes are compared to Period 3 baseline for Period 3 and extension baseline for extension period.

Number (%) of patients with clinically notable changes in ECG during extension by extension mean daily dose (All extension patients)

	Ritalin LA mean daily dose in extension									All Extension patients N=298		
	<=40 mg N=85			>40-60 mg N=104			>60 mg N=109					
	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)
QT > 500 ms	76	0	(0.0)	96	0	(0.0)	101	0	(0.0)	273	0	(0.0)
QTcB > 500 ms	76	0	(0.0)	96	0	(0.0)	101	0	(0.0)	273	0	(0.0)
QTcF > 500 ms	76	0	(0.0)	96	0	(0.0)	101	0	(0.0)	273	0	(0.0)
QT inc from baseline >=30 ms	76	12	(15.8)	96	12	(12.5)	101	6	(5.9)	273	30	(11.0)
QTcB inc from baseline >=30 ms	76	4	(5.3)	96	8	(8.3)	101	10	(9.8)	273	22	(8.1)
QTcF inc from baseline >=30 ms	76	4	(5.3)	96	5	(5.2)	101	2	(2.0)	273	11	(4.0)
PR inc from baseline > 25% to a value >200 ms	76	0	(0.0)	96	0	(0.0)	101	0	(0.0)	273	0	(0.0)
QRS inc from baseline > 25% to a value >110 ms	76	0	(0.0)	96	0	(0.0)	101	1	(1.0)	273	1	(0.4)

n: the number of patients meeting the criterion.
% is calculated based on the number of patients with available baseline and post-baseline data. Denominators for the percentage calculations are the number of patients with evaluable criterion.
Criteria for clinically notable changes are compared to Period 3 baseline for Period 3 and extension baseline for extension period.
QTcB (Bazett's QTc) interval was calculated as QT/Square root of (RR/1000).
QTcF (Fridericia's QTc) interval was calculated as QT/Cube root of (RR/1000).

Number (%) of patients with clinically notable changes in ECG in Period 3 or extension by Period 3 treatment (All extension patients)

	Ritalin LA in Period 3 N=216			Placebo in Period 3 N=82			All Extension patients N=298		
	Total	n	(%)	Total	n	(%)	Total	n	(%)
QT > 500 ms	216	0	(0.0)	82	0	(0.0)	298	0	(0.0)
QTcB > 500 ms	216	0	(0.0)	82	0	(0.0)	298	0	(0.0)
QTcF > 500 ms	216	0	(0.0)	82	0	(0.0)	298	0	(0.0)
QT inc from baseline >=30 ms	216	54	(25.0)	82	26	(31.7)	298	80	(26.8)
QTcB inc from baseline >=30 ms	216	39	(18.1)	82	8	(9.8)	298	47	(15.8)
QTcF inc from baseline >=30 ms	216	16	(7.4)	82	6	(7.3)	298	22	(7.4)
PR inc from baseline > 25% to a value >200 ms	216	1	(0.5)	82	0	(0.0)	298	1	(0.3)
QRS inc from baseline > 25% to a value >110 ms	216	1	(0.5)	82	0	(0.0)	298	1	(0.3)

n: the number of patients meeting the criterion
% is calculated based on number of patients with available baseline and post-baseline data.
QTcB (Bazett's QTc) interval was calculated as QT/Square root of (RR/1000).
QTcF (Fridericia's QTc) interval was calculated as QT/Cube root of (RR/1000).

Date of Clinical Trial Report

28th June 2013

Date Inclusion on Novartis Clinical Trial Results Database

05-February- 2014

Date of Latest Update