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B. Full Novartis CTRD Template

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

CRIT124D2302

Title

A 40-week, randomized, double-blind, placebo-controlled, multicenter efficacy and safety study of methylphenidate hydrochloride extended release in the treatment of adult patients with childhood-onset of attention deficit hyperactivity disorder (ADHD)

Study Phase

Phase IIIb

Study Start/End Dates

Study Start: 24 Nov 2010 (first patient first visit)

Study Completion: 07 Aug 2012 (last patient last visit)

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, multicenter efficacy and safety study in adult patients with ADHD with the following treatment periods: pre-randomization period, treatment Period 1 (3 weeks titration followed by 6 weeks fixed-dose), treatment Period 2 (5 weeks titration to individual optimal dose) and treatment Period 3 (6 months withdrawal).

Centers

67 centers in 9 countries: Belgium (5), Colombia (3), Denmark (1), Germany (28), Norway (2), Singapore (1), South Africa (3), Sweden (3), United States (21)

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Publication

1. V. Kumar, Y. Ginsberg, T. Tvedten, T. Arngrim, A. Philipsen, P. Gandhi, CW. Chen, M. Huss. RIT-AB-40527 RIT-AB-40450 Methylphenidate hydrochloride modified release (MPH-LA) in adults with attention deficit hyperactivity disorder (ADHD): Safety. ADHD Atten Def Hyp Disord. 2013; (5): 111-247.
2. Y. Ginsberg, M. Huss, A. Philipsen, T. Tvedten, T. Arngrim, D. Gruener, K. Carter, CW. Chen, P. Gandhi, V. Kumar. Methylphenidate hydrochloride modified release (MPH-LA) in adults with attention deficit hyperactivity disorder (ADHD): self-rated, observer-rated and physician-rated assessments show consistently significant improvement compared to placebo. ADHD Atten Def Hyp Disord. 2013; (5): 111-247.
3. V. Kumar, Y. Ginsberg, T. Tvedten, T. Arngrim, D. Gruener, A. Philipsen, K. Carter, CW. Chen, M. Huss. RIT-AB-38509 40 week, double-blind, placebo-controlled, efficacy and safety study of methylphenidate hydrochloride modified release (MPH-LA) in adult ADHD: study design. ADHD Atten Def Hyp Disord. 2013; (5): 111-247.
4. M. Huss, Y. Ginsberg, A. Philipsen, T. Tvedten, T. Arngrim, D. Gruener, K. Carter, CW. Chen, V. Kumar. RIT-AB-38509 40 week, double-blind, placebo-controlled, efficacy and safety study of methylphenidate hydrochloride modified release (MPH-LA) in adult ADHD. ADHD Atten Def Hyp Disord. 2013; (5): 111-247.

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

Investigational therapy was methylphenidate hydrochloride, modified release hard capsules taken once daily in doses of 40, 60, or 80 mg

Statistical Methods

Statistical methods: Evaluation of the change from baseline to the end of Period 1 (Week 9) treatment in the total score of the DSM-IV ADHD RS was performed using an analysis of covariance (ANCOVA) model with treatment group and center as factors, and baseline DSM-IV ADHD RS total score as covariate. For the SDS, the same ANCOVA model was utilized with treatment group and center as factors, and baseline SDS total score as covariate.
For treatment failure during Period 3, a logistic-regression analysis using treatment as factor and DSM-IV ADHD RS total score at baseline 1 and baseline 2 as covariates was performed. Any missing DSM-IV ADHD RS scores were imputed based on the Multiple Imputation (MI) approach and the dichotomized responses (failure/non-failure) were created according to the treatment failure definition.
A logistic regression model with treatment as factor and baseline (visit 3 value) as covariate was performed to analyze the proportion of patients with clinical improvement on the CGI-I scale. The same logistic model was performed for CGI-S scale.
The same ANCOVA models were utilized for CAARS and ASRS rating scales.

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Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Diagnosis of attention deficit/hyperactivity disorder (ADHD) with a confirmed onset in childhood according to DSM-IV criteria
- Female patients of childbearing potential must be practicing an acceptable method of contraception

Exclusion Criteria

- Patients with body mass index (BMI) less than 18.5 kg/m^2 or more than 35 kg/m^2
- History of alcohol or substance abuse within the last six months
- History of seizures or use of anticonvulsant medication
- Any psychiatric condition that requires medication or may interfere with study participation
- Pre-existing cardiovascular disorders including severe hypertension, heart failure, myocardial infarction, etc.
- Significant respiratory, hepatic, gastrointestinal, renal, hematological or oncologic disorder
- Diagnosis of glaucoma, hyperthyroidism, pheochromocytoma
- Diagnosis of family history of Tourette's syndrome
- Pre-existing cerebrovascular disorders such as cerebral aneurysm, vascular abnormalities including vasculitis or stroke

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Participant Flow

Patient disposition for Period 1 (All patients)

Disposition/reason	Ritalin LA 40 mg N=181 n(%)	Ritalin LA 60 mg N=182 n(%)	Ritalin LA 80 mg N=181 n(%)	All Ritalin LA N=544 n(%)	Placebo N=181 n(%)	All N=725 n(%)
Screened	NA	NA	NA	NA	NA	863
Randomized	181	182	181	544	181	725
Completed all Period 1 visits*	156 (86.2)	147 (80.8)	145 (80.1)	448 (82.4)	155 (85.6)	603 (83.2)
Completed and Entered Period 2	152 (84.0)	141 (77.5)	138 (76.2)	431 (79.2)	153 (84.5)	584 (80.6)
Discontinued						
Total	29 (16.0)	41 (22.5)	43 (23.8)	113 (20.8)	28 (15.5)	141 (19.4)
Adverse event(s)	13 (7.2)	18 (9.9)	26 (14.4)	57 (10.5)	3 (1.7)	60 (8.3)
Unsatisfactory therapeutic effect	2 (1.1)	2 (1.1)	4 (2.2)	8 (1.5)	11 (6.1)	19 (2.6)
Patient withdrew consent	5 (2.8)	8 (4.4)	6 (3.3)	19 (3.5)	7 (3.9)	26 (3.6)
Lost to follow-up	4 (2.2)	6 (3.3)	3 (1.7)	13 (2.4)	4 (2.2)	17 (2.3)
Administrative problems	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.4)	2 (1.1)	4 (0.6)
Protocol deviation	5 (2.8)	6 (3.3)	3 (1.7)	14 (2.6)	1 (0.6)	15 (2.1)

* Includes patients who discontinued the study for any reason at Visit 8 and did not continue into Period 2.
Denominator used in the percentage calculations: randomized patients.
NA=not applicable

Patient disposition for Period 2 (All Randomized patients in Period 1)

Disposition reason	All Ritalin LA N=725 n(%)
Entered Period 2	584 (100.0)
Completed all Period 2 visits*	537 (92.0)
Completed and Entered Period 3	489 (83.7)
Discontinued	
Total	95 (16.3)
Adverse Event(s)	22 (3.8)
Unsatisfactory therapeutic effect	40 (6.8)
Subject withdrew consent	20 (3.4)
Lost to follow-up	10 (1.7)
Protocol deviation	3 (0.5)

Percentages for completing/discontinuing in Period 2 are based on the number of patients entered in Period 2.
* Includes patients who discontinued the study for any reason at Visit 13 and did not continue into Period 3.

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Patient disposition for Period 2 by treatment group in Period 1
Randomized set for Period 1

Disposition/reason	Ritalin LA 40 mg N*=181 n(%)	Ritalin LA 60 mg N*=182 n(%)	Ritalin LA 80 mg N*=181 n(%)	All Ritalin LA N*=544 n(%)	Placebo N*=181 n(%)
Entered Period 2	152 (100.0)	141 (100.0)	138 (100.0)	431 (100.0)	153 (100.0)
Completed all period 2 visits	141 (92.8)	132 (93.6)	125 (90.6)	398 (92.3)	139 (90.8)
Completed and entered period 3	127 (83.6)	123 (87.2)	114 (82.6)	364 (84.5)	125 (81.7)
ADHD RS>=30% improvement in period 2	140 (92.1)	133 (94.3)	128 (92.8)	401 (93.0)	138 (90.2)
Discontinued					
Total	25 (16.4)	18 (12.8)	24 (17.4)	67 (15.5)	28 (18.3)
Adverse Event(s)	3 (2.0)	4 (2.8)	7 (5.1)	14 (3.2)	8 (5.2)
Unsatisfactory therapeutic effect	13 (8.6)	7 (5.0)	7 (5.1)	27 (6.3)	13 (8.5)
Subject withdrew consent	6 (3.9)	2 (1.4)	8 (5.8)	16 (3.7)	4 (2.6)
Lost to follow-up	3 (2.0)	3 (2.1)	1 (0.7)	7 (1.6)	3 (2.0)
Protocol deviation	0 (0.0)	2 (1.4)	1 (0.7)	3 (0.7)	0 (0.0)

Patient disposition for Period 3 (Randomized Set for Period 3)

Disposition/reason	**Ritalin LA 40 mg N=114 n(%)**	**Ritalin LA 60 mg N=132 n(%)**	**Ritalin LA 80 mg N=120 n(%)**	**All Ritalin LA N=366 n(%)**	**Placebo N=123 n(%)**	**All N=489 n(%)**
Randomized in Period 1*	181	182	181	544	181	725
Completed Period 1*	156	147	145	448	155	603
Completed Period 2*	141	132	125	398	139	537
Randomized at end of Period 2	114	132	120	366	123	489
Completed	60(52.6)	63(47.7)	70(58.3)	193(52.7)	42(34.1)	235(48.1)
Discontinued						
Total	54(47.4)	69(52.3)	50(41.7)	173(47.3)	81(65.9)	254(51.9)
Adverse event(s)	5(4.4)	11(8.3)	6(5.0)	22(6.0)	5(4.1)	27(5.5)
Abnormal laboratory value(s)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.8)	1(0.2)
Abnormal test procedure result(s)	0(0.0)	0(0.0)	1(0.8)	1(0.3)	0(0.0)	1(0.2)
Unsatisfactory therapeutic effect	28(24.6)	42(31.8)	29(24.2)	99(27.0)	62(50.4)	161(32.9)
Patient's condition no longer requires study drug	1(0.9)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	1(0.2)
Patient withdrew consent	12(10.5)	6(4.5)	4(3.3)	22(6.0)	3(2.4)	25(5.1)
Lost to follow-up	3(2.6)	4(3.0)	6(5.0)	13(3.6)	3(2.4)	16(3.3)
Administrative problems	0(0.0)	0(0.0)	1(0.8)	1(0.3)	0(0.0)	1(0.2)
Protocol deviation	5(4.4)	6(4.5)	3(2.5)	14(3.8)	7(5.7)	21(4.3)

* Randomized set for Period 1.
Denominator used in the percentage calculations: randomized patients in Period 3.

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Baseline Characteristics

Demographic and background characteristics by treatment (Randomized Set for Period 1)

	Ritalin LA 40mg (N=181)		Ritalin LA 60mg (N=182)		Ritalin LA 80mg (N=181)		All Ritalin LA (N=544)		Placebo (N=181)		All (N=725)	
Age (years)												
n	181		182		181		544		181		725	
Mean	35.1		34.8		34.9		34.9		36.8		35.4	
Median	35.0		34.0		34.0		34.5		38.0		35.0	
SD	11.37		10.79		11.13		11.08		12.15		11.38	
Min	18		18		18		18		18		18	
Max	60		60		57		60		60		60	
Age group -n(%)												
18-30	72	(39.8)	78	(42.9)	71	(39.2)	221	(40.6)	66	(36.5)	287	(39.6)
31-40	39	(21.5)	45	(24.7)	40	(22.1)	124	(22.8)	38	(21.0)	162	(22.3)
41-50	56	(30.9)	45	(24.7)	57	(31.5)	158	(29.0)	47	(26.0)	205	(28.3)
51-60	14	(7.7)	14	(7.7)	13	(7.2)	41	(7.5)	30	(16.6)	71	(9.8)
Sex - n(%)												
Male	94	(51.9)	105	(57.7)	95	(52.5)	294	(54.0)	101	(55.8)	395	(54.5)
Female	87	(48.1)	77	(42.3)	86	(47.5)	250	(46.0)	80	(44.2)	330	(45.5)
Race - n(%)												
Caucasian	160	(88.4)	155	(85.2)	165	(91.2)	480	(88.2)	169	(93.4)	649	(89.5)
Black	5	(2.8)	7	(3.8)	4	(2.2)	16	(2.9)	4	(2.2)	20	(2.8)
Asian	6	(3.3)	7	(3.8)	4	(2.2)	17	(3.1)	1	(0.6)	18	(2.5)
Native American	0	(0.0)	1	(0.5)	1	(0.6)	2	(0.4)	0	(0.0)	2	(0.3)
Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Other	10	(5.5)	12	(6.6)	7	(3.9)	29	(5.3)	7	(3.9)	36	(5.0)

	Ritalin LA 40mg (N=181)		Ritalin LA 60mg (N=182)		Ritalin LA 80mg (N=181)		All Ritalin LA (N=544)		Placebo (N=181)		All (N=725)	
Ethnicity - n(%)												
Hispanic /Latino	21	(11.6)	19	(10.4)	12	(6.6)	52	(9.6)	15	(8.3)	67	(9.2)
Chinese	1	(0.6)	1	(0.5)	1	(0.6)	3	(0.6)	2	(1.1)	5	(0.7)
Indian	4	(2.2)	4	(2.2)	0	(0.0)	8	(1.5)	0	(0.0)	8	(1.1)
Japanese	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Mixed ethnicity	3	(1.7)	2	(1.1)	1	(0.6)	6	(1.1)	1	(0.6)	7	(1.0)
Other	151	(83.4)	156	(85.7)	167	(92.3)	474	(87.1)	163	(90.1)	637	(87.9)
Height (cm)												
n	181		182		181		544		181		725	
Mean	172.6		173.7		173.6		173.3		172.8		173.2	
Median	172.0		174.0		175.0		174.0		173.0		174.0	
SD	9.66		9.36		9.68		9.56		9.87		9.64	
Min	146		147		145		145		147		145	
Max	202		199		195		202		205		205	
Weight (kg)												
n	181		182		181		544		181		725	
Mean	76.5		77.1		76.8		76.8		77.8		77.0	
Median	74.0		76.2		77.9		76.0		75.4		76.0	
SD	15.35		14.92		14.82		15.01		16.64		15.42	
Min	47		43		47		43		44		43	
Max	143		145		118		145		133		145	
Smoking status												
Current smoker (yes)	55	(30.4)	66	(36.3)	50	(27.6)	171	(31.4)	56	(30.9)	227	(31.3)
Cigarettes	52	(28.7)	65	(35.7)	49	(27.1)	166	(30.5)	54	(29.8)	220	(30.3)
Cigars	1	(0.6)	2	(1.1)	1	(0.6)	4	(0.7)	1	(0.6)	5	(0.7)
Pipe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.1)
Other	3	(1.7)	1	(0.5)	0	(0.0)	4	(0.7)	1	(0.6)	5	(0.7)

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Demographic for patients in Period 3 by treatment
Randomized set for Period 3

		Ritalin LA 40mg (N=114)		Ritalin LA 60mg (N=132)		Ritalin LA 80mg (N=120)		All Ritalin LA (N=366)		Placebo (N=123)		All (N=489)	
Age (years)													
	n	114		132		120		366		123		489	
	Mean	34.6		35.9		37.8		36.1		34.8		35.8	
	Median	31.5		36.0		40.0		38.0		34.0		37.0	
	SD	11.65		11.57		10.89		11.42		11.51		11.44	
	Min	18		18		18		18		18		18	
	Max	58		60		60		60		60		60	
Age group -n(%)													
	18-30	53	(46.5)	46	(34.8)	34	(28.3)	133	(36.3)	52	(42.3)	185	(37.8)
	31-40	19	(16.7)	32	(24.2)	27	(22.5)	78	(21.3)	27	(22.0)	105	(21.5)
	41-50	32	(28.1)	41	(31.1)	45	(37.5)	118	(32.2)	31	(25.2)	149	(30.5)
	51-60	10	(8.8)	13	(9.8)	14	(11.7)	37	(10.1)	13	(10.6)	50	(10.2)
Sex - n(%)													
	Male	54	(47.4)	74	(56.1)	74	(61.7)	202	(55.2)	71	(57.7)	273	(55.8)
	Female	60	(52.6)	58	(43.9)	46	(38.3)	164	(44.8)	52	(42.3)	216	(44.2)
Race - n(%)													
	Caucasian	100	(87.7)	120	(90.9)	113	(94.2)	333	(91.0)	107	(87.0)	440	(90.0)
	Black	2	(1.8)	1	(0.8)	4	(3.3)	7	(1.9)	7	(5.7)	14	(2.9)
	Asian	2	(1.8)	2	(1.5)	1	(0.8)	5	(1.4)	3	(2.4)	8	(1.6)
	Native American	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	1	(0.8)	2	(0.4)
	Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Other	10	(8.8)	9	(6.8)	1	(0.8)	20	(5.5)	5	(4.1)	25	(5.1)

Age (years) is at Period 1 baseline and Height (cm) is at screening.

Demographic for patients in Period 3 by treatment
Randomized set for Period 3

		Ritalin LA 40mg (N=114)		Ritalin LA 60mg (N=132)		Ritalin LA 80mg (N=120)		All Ritalin LA (N=366)		Placebo (N=123)		All (N=489)	
Ethnicity - n(%)													
	Hispanic/Latino	17	(14.9)	14	(10.6)	6	(5.0)	37	(10.1)	10	(8.1)	47	(9.6)
	Chinese	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	2	(1.6)	3	(0.6)
	Indian (Indian subcontinent)	1	(0.9)	3	(2.3)	1	(0.8)	5	(1.4)	0	(0.0)	5	(1.0)
	Japanese	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.2)
	Mixed Ethnicity	0	(0.0)	0	(0.0)	2	(1.7)	2	(0.5)	2	(1.6)	4	(0.8)
	Other	96	(84.2)	113	(85.6)	111	(92.5)	320	(87.4)	109	(88.6)	429	(87.7)
Height (cm)													
	n	114		132		120		366		123		489	
	Mean	171.3		173.9		175.2		173.5		173.5		173.5	
	Median	170.0		175.0		175.0		174.0		175.0		174.0	
	SD	9.73		9.13		9.25		9.47		9.37		9.43	
	Min	146		155		150		146		147		146	
	Max	193		199		205		205		190		205	
Weight (kg)													
	n	114		132		120		366		123		489	
	Mean	72.9		77.0		82.8		77.6		78.4		77.8	
	Median	71.6		75.0		82.9		75.9		78.4		76.2	
	SD	13.76		13.42		16.09		14.95		16.20		15.26	
	Min	48		52		45		45		44		44	
	Max	120		115		128		128		145		145	

Age (years) is at Period 1 baseline and Height (cm) is at screening.

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Demographic for patients in Period 3 by treatment
Randomized set for Period 3

		Ritalin LA 40mg (N=114)		Ritalin LA 60mg (N=132)		Ritalin LA 80mg (N=120)		All Ritalin LA (N=366)		Placebo (N=123)		All (N=489)	
BMI (kg/m**2)													
	n	114		132		120		366		123		489	
	Mean	24.8		25.5		26.8		25.7		25.9		25.7	
	Median	24.4		24.9		26.7		25.2		25.7		25.3	
	SD	3.75		3.81		3.87		3.89		4.24		3.98	
	Min	18		18		19		18		18		18	
	Max	35		35		35		35		44		44	
Smoking status													
	Current smoker (yes)	35	(30.7)	37	(28.0)	36	(30.0)	108	(29.5)	38	(30.9)	146	(29.9)
	Cigarettes	34	(29.8)	36	(27.3)	36	(30.0)	106	(29.0)	37	(30.1)	143	(29.2)
	Cigars	2	(1.8)	1	(0.8)	0	(0.0)	3	(0.8)	0	(0.0)	3	(0.6)
	Pipe	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.2)
	Other	0	(0.0)	1	(0.8)	1	(0.8)	2	(0.5)	0	(0.0)	2	(0.4)

Outcome Measures

Primary Outcome Result(s)

Analysis of improvement from baseline 1 to end of Period 1 on DSM-IV ADHD RS total score by treatment / LOCF (Full Analysis Set for Period 1) - Primary endpoint

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit 2 (Baseline 1)	N	174	175	179	172
	Mean	39.6	38.9	39.4	39.1
	Median	39.0	38.0	40.0	38.0
	SD	6.19	5.57	5.55	5.95
	Min	30	30	29	21
	Max	54	54	53	54
Final visit*	N	160	155	156	161
	Mean	23.7	24.0	22.5	29.5
	Median	22.5	24.0	21.0	31.0
	SD	12.62	11.30	11.53	11.64
	Min	0	4	0	2
	Max	54	50	54	54
Improvement from Baseline 1	N	160	155	156	161
	Mean	16.0	14.7	16.8	9.7
	SD	12.18	10.12	11.36	11.05
	LS mean	15.45	14.71	16.36	9.35
	LS mean difference from placebo(95% CI)	6.10 (3.68, 8.53)	5.36 (2.92, 7.79)	7.01 (4.59, 9.42)	
	p-value**	<0.0001	<0.0001	<0.0001	
	significance level***	0.0167	0.0208	0.0313	

Improvement is a decrease and is calculated as baseline 1 - Final Visit value.
LS mean = Least squares mean changes from the Analysis of Covariance (ANCOVA) model with treatment group, center as factors and baseline DSM-IV ADHD RS total score as covariate.
*LOCF using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1.
**Two-sided p-value based on the difference between each Ritalin LA group and Placebo.
***Significance level =the final two-sided level of significance(alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.

Analysis of improvement from baseline 1 to end of Period 1 on SDS total score by treatment / LOCF (FAS for Period 1) - Primary endpoint

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit 2 (Baseline 1)	N	172	171	176	166
	Mean	20.7	19.2	19.6	19.9
	Median	21.0	20.0	20.0	20.0
	SD	5.77	6.14	5.88	5.17
	Min	1	0	0	2
	Max	30	30	30	30
Final visit*	N	151	149	149	154
	Mean	14.5	14.9	13.8	16.9
	Median	15.0	15.0	13.0	18.0
	SD	7.39	7.25	7.18	7.11
	Min	0	0	0	0
	Max	30	30	30	30
Improvement from baseline 1	N	151	146	148	152
	Mean	6.4	4.7	6.1	2.9
	SD	7.54	7.08	7.31	7.47
	LS mean	5.89	4.90	6.47	3.03
	LS mean difference from placebo(95% CI)	2.86 (1.33, 4.39)	1.87 (0.33, 3.41)	3.44 (1.91, 4.97)	
	p-value**	0.0003	0.0176	<0.0001	
	significance level***	0.0167	0.0208	0.0313	

Improvement is a decrease and is calculated as baseline 1 - Final Visit value.
LS mean = Least squares mean changes from the Analysis of Covariance (ANCOVA) model with treatment group, center as factors and baseline SDS total score as covariate.
*LOCF using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1.
**Two-sided p-value based on the difference between each Ritalin LA group and Placebo.
***Significance level =the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.

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Percentage of treatment failures during Period 3 (Full Analysis Set for Period 3) - Primary endpoint

	All Ritalin LA N=352 n (%)	Placebo N=115 n (%)	All Ritalin LA vs Placebo Odds ratio (95% CI)	All Ritalin LA vs Placebo P-value** (significance level***)
Without imputation				
Treatment failure	59 (16.8)	50 (43.5)		
Not treatment failure	188 (53.4)	36 (31.3)		
Missing treatment failure status #	104 (29.5)	29 (25.2)		
With imputation				
Treatment failure *	75 (21.3)	57 (49.6)	0.3 (0.2, 0.4)	<0.0001(0.0500)
Not treatment failure	277 (78.7)	58 (50.4)		

One patient in Ritalin LA 80mg does not have post baseline 2 measurements.
Where the treatment failure status was missing and therefore requiring imputation, the missing DSM-IV ADHD RS scores were derived using the Multiple Imputation approach.
* A treatment failure during Period 3 is defined as: 30% or more worsening on DSM-IV ADHD RS rating scale score from Period 3 baseline at Visit 13 (randomization 2) AND less than 30% remaining improvement from Period 1 baseline score (visit 2) on DSM-IV ADHD RS rating scale.
** Based on comparison between the proportion of treatment failures each Ritalin LA group and Placebo from the logistic regression model using treatment, center as factors, and ADHD RS total score at re-randomization baseline for period 3 as covariate.
*** Significance level = the final two-sided alpha for the test following extended gatekeeping procedure.

Percentage of treatment failures during Period 3 by dose group
Full analysis set for Period 3

	Ritalin LA 40mg N=110 n (%)	Ritalin LA 60mg N=128 n (%)	Ritalin LA 80mg N=114 n (%)	Placebo N=115 n (%)
Without imputation				
Treatment failure	13(11.8)	26(20.3)	20(17.5)	50(43.5)
Not treatment failure	60(54.5)	64(50.0)	64(56.1)	36(31.3)
Missing Treatment failure status	37(33.6)	38(29.7)	29(25.4)	29(25.2)
With imputation				
Treatment failure *	18(16.4)	34(26.6)	23(20.2)	57(49.6)
Not treatment failure	92(83.6)	94(73.4)	91(79.8)	58(50.4)
Odds ratio (95% CI)[Ritalin LA vs Placebo]	0.2(0.1, 0.4)	0.4(0.2, 0.7)	0.3(0.1, 0.5)	
p-value **	<0.0001	0.0008	<0.0001	

One patient in Ritalin LA 80 mg group does not have any period 3 visit.
The missing DSM-IV ADHD RS scores are imputed based on the Multiple Imputation
*Treatment failure is defined as: 100×(DSM-IV ADHD RS total score during Period 3 - DSM-IV ADHD RS total score at re-randomization (visit 13))/DSM-IV ADHD RS total score at re-randomization (visit 13) >= 30% AND 100×(DSM-IV ADHD RS total score during Period 3 - DSM-IV ADHD RS total score at randomization (visit 2))/DSM-IV ADHD RS total score at randomization (visit 2) > - 30%.
**Based on comparison between the proportion of treatment failures each Ritalin LA group and Placebo from the logistic regression model using treatment,and both baseline scores as covariates.

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Secondary Outcome Result(s)

Proportion of patients with improvement on CGI-I scale from baseline 1 to end of Period 1 by treatment / LOCF (Full Analysis Set for Period 1) – Key Secondary Endpoint

	Ritalin LA 40 mg N=174	Ritalin LA 60 mg N=175	Ritalin LA 80 mg N=179	Placebo N=172
n (%)	90 (56.3)	85 (54.8)	89 (57.1)	51 (31.7)
Odds-ratio*	2.44	2.25	2.51	
95% CI for odds-ratio	(1.52, 3.93)	(1.40, 3.64)	(1.56, 4.05)	
p-value**	0.0002	0.0009	0.0002	
significance level***	0.0167	0.0250	0.0500	

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.
*The odds of Ritalin LA-treated patient having improvement on the CGI-I scale relative to the odds of a Placebo treated patient based on the logistic regression model using treatment, and baseline (Visit 3 value) as covariate.
*LOCF using the last visit for the patient in the 6-week fixed-dose phase of Period 1.
** Two-sided p-value based on comparison between each Ritalin LA group and Placebo using the logistic regression model.
***Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.

n (%) is based on evaluable patients.

Analysis of the proportion of patients with improvement on CGI-I scale in Period 1
by treatment and visit/ LOCF
Full analysis set for Period 1

Visit	Statistics	Ritalin LA 40 mg N=174	Ritalin LA 60 mg N=175	Ritalin LA 80 mg N=179	Placebo N=172
Visit 3	n (%)	40 (23.7)	30 (17.9)	40 (23.1)	13 (7.8)
Visit 4	n (%)	65 (39.4)	52 (31.3)	63 (37.7)	30 (18.2)
Visit 5	n (%)	72 (45.6)	73 (46.8)	73 (47.1)	48 (29.6)
Visit 6	n (%)	83 (55.0)	82 (58.2)	84 (57.5)	49 (32.9)
Visit 7	n (%)	90 (59.6)	86 (60.1)	87 (60.8)	42 (28.4)
Final visit	n (%)	90 (56.3)	85 (54.8)	89 (57.1)	51 (31.7)
	Odds-ratio*	2.44	2.25	2.51	
	95% CI for odds-ratio	(1.52, 3.93)	(1.40, 3.64)	(1.56, 4.05)	
	p-value**	0.0002	0.0009	0.0002	
	significance level***	0.0167	0.0250	0.0500	

n (%) is based on evaluable patients.
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.
*The odds of Ritalin LA-treated patient having improvement on the CGI-I scale relative to the odds of a Placebo treated patient based on the logistic regression model using treatment, and baseline as covariate.
*LOCF using the final visit for the patient in the 6-week fixed-dose phase of Period 1.
** Two-sided p-value based on comparison between each Ritalin LA group and Placebo using the logistic regression model.
***Significance level = the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.

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Improvement from baseline 1 in DSM-IV ADHD RS total score, SDS total score, CAARS-O:S total score and ASRS total score at the end of Period 2 (Visit 13/ Week 14) (Full Analysis Set for Period 2)

	All Ritalin LA Group (Total N=563)		
Efficacy Assessment at Visit 13/ Week 14	**N***	**Mean**	**SD**
DSM-IV ADHD total score	494	24.8	8.97
SDS total score	480	10.1	7.25
CAARS-O:S total score	411	15.5	15.25
ASRS total score	490	23.2	14.16

* The majority of patients had attained their individual optimal dose at Visit 13/ Week 14

CGI-I rating at the end of Period 2 (Visit 13/ Week 14) (Full Analysis Set for Period 2)

	All Ritalin LA Group (N=563)			
	1 – Very much improved		2- Much improved	
	n*	%**	n*	%**
CGI-I rating at Visit 13/ Week 14	195	39.6	230	46.7

* The majority of patients had attained their individual optimal dose at Visit 13/ Week 14.
** Based on patients with available data (492)

	Gender/Age Group (in years)		All Ritalin LA N=563 n (%)
Visit 13 (Week 14)	Overall	1 (Very much improved)	195(34.6)
		2 (Much improved)	230(40.9)
		3 (Minimally improved)	42(7.5)
		4 (No change)	16(2.8)
		5 (Minimally worse)	7(1.2)
		6 (Much worse)	2(0.4)
		7 (Very much worse)	0

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CGI-S rating at the end of Period 2 (Visit 13/ Week 14) (Full Analysis Set for Period 2)

	All Ritalin LA Group (N=563)			
	1 – Normal, not ill at all		2- Boderline mentally ill	
	n *	% **	n *	% **
CGI-S rating at Visit 13/ Week 14	91	18.5	151	30.7

* The majority of patients had attained their individual optimal dose at Visit 13/ Week 14.
** Based on patients with available data (492)

	Gender/Age Group (in years)		All Ritalin LA N=563 n (%)
Visit 13 (Week 14)	Overall	1 (Normal, not ill at all)	91(16.2)
		2 (Borderline mentally ill)	151(26.8)
		3 (Mildly ill)	193(34.3)
		4 (Moderately ill)	50(8.9)
		5 (Markedly ill)	7(1.2)
		6 (Severely ill)	0
		7 (Among the most extremely ill patients)	0

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Analysis of change from baseline 2 to end of Period 3 on DSM-IV ADHD RS total score by treatment / MMRM analysis (Full Analysis Set for Period 3)

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit 13 (Baseline 2)	N	110	128	114	352	115
	Mean	12.3	13.1	14.9	13.4	14.0
	Median	11.0	13.0	15.0	13.0	14.0
	SD	7.07	6.06	7.55	6.95	7.54
	Min	0	0	0	0	0
	Max	28	29	30	30	33
Final visit*	N	101	121	106	328	106
	Mean	15.4	18.3	17.2	17.1	23.5
	Median	14.0	17.0	17.0	15.0	24.0
	SD	11.39	10.91	10.21	10.87	12.87
	Min	0	0	0	0	0
	Max	54	51	47	54	47
Final score change from Baseline 2	N	101	121	106	328	106
	Mean	3.0	5.1	2.6	3.6	9.3
	SD	10.07	10.85	8.67	9.98	11.95
	LS mean	0.40	2.41	1.16	1.37	6.30
	LS mean difference from placebo(95% CI)	-5.90 (-7.88,-3.92)	-3.89 (-5.81,-1.97)	-5.14 (-7.10,-3.18)	-4.94 (-6.56,-3.32)	
	p-value**	<0.0001	<0.0001	<0.0001	<0.0001	

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Worsening from Baseline 2 is calculated as Final Visit value - Visit 13 value.
MMRM (mixed-effect models for repeated measures): DSM-IV ADHD RS total score change from baseline = treatment, center, visit (categorical), treatment by visit interaction, baseline score and baseline score by visit interaction.
*No multiple imputation approach was applied.
**Two-sided p-value based on the difference between each Ritalin LA group and Placebo.

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Analysis of change from baseline 2 to end of Period 3 on SDS total score by treatment / LOCF/Multiple Imputation (Full Analysis Set for Period 3)

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit13 (Baseline 2)	N	110	128	112	350	115
	Mean	8.7	9.8	11.2	9.9	9.3
	Median	9.0	9.0	10.0	9.0	9.0
	SD	5.34	6.38	6.40	6.14	5.66
	Min	0	0	0	0	0
	Max	21	30	25	30	29
Final visit	N	100	118	103	321	102
	Mean	10.8	11.9	13.2	12.0	14.3
	Median	11.0	11.0	13.0	11.0	14.5
	SD	7.03	7.11	6.60	6.97	7.97
	Min	0	0	0	0	0
	Max	30	30	30	30	28
Final score change from baseline 2	N	100	118	101	319	102
	Mean	2.1	2.3	2.0	2.1	5.0
	SD	6.34	7.19	6.81	6.79	8.15
	LS mean *	1.30	1.86	2.82	1.98	5.48
	LS mean difference from placebo (95% CI) *	-4.18 (-6.03,-2.33)	-3.62 (-5.38,-1.85)	-2.66 (-4.56,-0.77)	-3.52 (-5.03,-2.02)	
	p-value**	<0.0001	<0.0001	0.0058	<0.0001	

Final visit only includes non-missing end visit values.
Change from baseline is calculated as Final Visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) SDS total score as covariate.
Final visit only includes non-missing end visit values
* For missing SDS total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing SDS total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

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Analysis of the proportion of patients with worsening from baseline 2 on CGI-I scale in Period 3
by treatment / LOCF
Full analysis set for Period 3

Statistics	Ritalin LA 40 mg N=110	Ritalin LA 60 mg N=128	Ritalin LA 80 mg N=114	All Ritalin LA N=352	Placebo N=115
n (%)	6 (5.9)	13 (10.8)	5 (4.6)	24 (7.3)	21 (19.4)
Odds-ratio*	0.26	0.50	0.20	0.32	
95% CI for odds-ratio	(0.10, 0.66)	(0.24, 1.05)	(0.07, 0.55)	(0.17, 0.61)	
p-value**	0.0050	0.0688	0.0020	0.0005	

Worsening in CGI-I is a score of 6 or 7. n (%) is based on evaluable patients.
*The odds of Ritalin LA-treated patient having worsening on CGI-I scale relative to the odds of a Placebo-treated patient based on the logistic regression model using treatment, and baseline 1 as covariate.
** Two-sided p-value based on comparison between each Ritalin LA group and Placebo using the logistic regression model. Statistical signficance is indicated if $p < 0.05$

Proportion of patients with worsening on CGI-S scale from baseline 2 to end of Period 3 by treatment / LOCF/Multiple Imputation (Full Analysis Set for Period 3)

Statistics	Ritalin LA 40 mg N=110	Ritalin LA 60 mg N=128	Ritalin LA 80 mg N=113	All Ritalin LA N=351	Placebo N=114
n (%)	39 (38.2)	50 (41.7)	35 (32.7)	124 (37.7)	72 (65.5)
Odds-ratio*	0.32	0.35	0.25	0.31	
95% CI for odds-ratio	(0.18, 0.55)	(0.21, 0.60)	(0.14, 0.45)	(0.19, 0.48)	
p-value**	<0.0001	0.0001	<0.0001	<0.0001	

n(%) based on evaluable patients. Worsening from baseline 2 to end of Period 3 defined as increase on CGI-S. For missing CGI-S score at week 40, last available post-baseline score at early discontinuation is carried forward.
If no post-baseline score is available, missing CGI-S score at week 40 is imputed based on the Multiple Imputation approach within each treatment arm.
*The odds of Ritalin LA-treated patient having worsening on CGI-S scale relative to the odds of a Placebo-treated patient based on the logistic regression model using treatment, center as factors, and baseline 1 as covariate.
** Two-sided p-value based on comparison between each Ritalin LA group and Placebo using the logistic regression model. Statistical significance is indicated if $p < 0.05$.

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Analysis of the proportion of patients with worsening from baseline 2 on CGI-S scale in Period 3
by treatment / LOCF/Multiple Imputation
Full analysis set for Period 3

Statistics	Ritalin LA 40 mg N=110	Ritalin LA 60 mg N=128	Ritalin LA 80 mg N=114	All Ritalin LA N=352	Placebo N=115
n (%)	39 (38.2)	50 (41.7)	35 (32.7)	124 (37.7)	72 (65.5)
Odds-ratio*	0.32	0.35	0.25	0.31	
95% CI for odds-ratio	(0.18, 0.55)	(0.21, 0.60)	(0.14, 0.45)	(0.19, 0.48)	
p-value**	<0.0001	0.0001	<0.0001	<0.0001	

n (%) based on evaluable patients. Worsening from baseline 2 to end of Period 3 defined as increase on CGI-S.
*The odds of Ritalin LA-treated patient having worsening on CGI-S scale relative to the odds of a Placebo-treated patient based on the logistic regression model using treatment, and baseline 1 as covariate.
For missing CGI-S score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing CGI-S score at week 40 is imputed based on the Multiple Imputation approach within each treatment arm.
** Two-sided p-value based on comparison between each Ritalin LA group and Placebo using the logistic regression model. Statistical signficance is indicated if p < 0.05

Analysis of change from baseline 2 to end of Period 3 in CAARS-O:S total score by treatment / LOCF/Multiple Imputation (Full Analysis Set for Period 3)

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit13 (Baseline 2)	N	109	126	113	348	115
	Mean	28.6	29.6	34.3	30.8	33.3
	Median	28.0	28.0	33.0	30.0	33.0
	SD	12.73	12.54	14.60	13.49	13.19
	Min	0	8	2	0	7
	Max	58	64	73	73	73
Final visit	N	76	92	83	251	78
	Mean	26.0	30.7	34.5	30.6	36.2
	Median	25.0	29.0	34.0	29.0	34.0
	SD	13.39	14.08	14.62	14.41	14.82
	Min	0	6	0	0	0
	Max	63	62	75	75	73
Final score change from baseline 2	N	76	92	83	251	78
	Mean	-2.7	1.7	-0.2	-0.3	2.9
	SD	11.74	12.00	14.23	12.78	15.26
	LS mean *	-2.89	1.49	2.86	0.53	6.40
	LS mean difference from placebo (95% CI) *	-9.29 (-13.4,-5.18)	-4.91 (-8.85,-0.97)	-3.54 (-7.58, 0.49)	-5.86 (-9.29,-2.44)	
	p-value**	<0.0001	0.0147	0.0855	0.0008	

Final Visit only includes non-missing end visit values.
Worsening is an increase and is calculated as Final Visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) total score as covariate.
* For missing total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

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Analysis of change from baseline 2 to end of Period 3 in ASRS total score by treatment / LOCF/Multiple Imputation (Full Analysis Set for Period 3)

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit13 (Baseline2)	N	110	128	113	351	115
	Mean	26.8	28.0	30.6	28.5	29.2
	Median	27.0	27.0	30.0	28.0	30.0
	SD	13.21	11.02	11.34	11.91	12.07
	Min	0	1	0	0	2
	Max	72	56	52	72	59
Final visit	N	99	119	105	323	103
	Mean	29.9	31.9	33.3	31.8	36.9
	Median	29.0	30.0	34.0	30.0	38.0
	SD	14.95	12.58	13.03	13.52	14.23
	Min	0	0	0	0	0
	Max	72	69	72	72	68
Final score change from baseline2	N	99	119	105	323	103
	Mean	3.0	3.8	3.0	3.3	8.0
	SD	12.64	12.66	11.54	12.27	16.39
	LS mean *	1.66	2.80	3.24	2.57	8.98
	LS mean difference from placebo (95% CI) *	-7.31 (-10.9,-3.76)	-6.18 (-9.55,-2.81)	-5.74 (-9.35,-2.13)	-6.41 (-9.30,-3.53)	
	p-value**	<0.0001	0.0003	0.0018	<0.0001	

Final Visit only includes non-missing end visit values.
Change from baseline is calculated as Final Visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) total score as covariate.
Final visit only includes non-missing end visit values.
* For missing total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

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Safety Results

Number (%) of patients with AEs during Period 1 by primary system organ class and treatment (Safety Analysis Set for Period 1)

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Primary system organ class										
Any primary system organ class	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Blood and Lymphatic System Disorders	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	0	(0.0)
Cardiac Disorders	15	(8.3)	24	(13.3)	24	(13.3)	63	(11.6)	1	(0.6)
Ear and Labyrinth Disorders	5	(2.8)	7	(3.9)	8	(4.4)	20	(3.7)	4	(2.2)
Endocrine Disorders	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Eye Disorders	4	(2.2)	5	(2.8)	6	(3.3)	15	(2.8)	4	(2.2)
Gastrointestinal Disorders	67	(37.2)	61	(33.7)	68	(37.6)	196	(36.2)	29	(16.1)
General Disorders and Administration Site Conditions	30	(16.7)	33	(18.2)	33	(18.2)	96	(17.7)	27	(15.0)
Immune System Disorders	1	(0.6)	0	(0.0)	2	(1.1)	3	(0.6)	0	(0.0)
Infections and Infestations	42	(23.3)	28	(15.5)	34	(18.8)	104	(19.2)	40	(22.2)
Injury, Poisoning and Procedural Complications	6	(3.3)	5	(2.8)	6	(3.3)	17	(3.1)	2	(1.1)
Investigations	12	(6.7)	10	(5.5)	24	(13.3)	46	(8.5)	6	(3.3)
Metabolism and Nutrition Disorders	40	(22.2)	49	(27.1)	49	(27.1)	138	(25.5)	13	(7.2)
Musculoskeletal and Connective Tissue Disorders	10	(5.6)	12	(6.6)	10	(5.5)	32	(5.9)	11	(6.1)
Nervous System Disorders	63	(35.0)	59	(32.6)	52	(28.7)	174	(32.1)	45	(25.0)
Psychiatric Disorders	58	(32.2)	63	(34.8)	67	(37.0)	188	(34.7)	25	(13.9)
Renal and Urinary Disorders	1	(0.6)	2	(1.1)	2	(1.1)	5	(0.9)	0	(0.0)
Reproductive System and Breast Disorders	3	(1.7)	5	(2.8)	6	(3.3)	14	(2.6)	2	(1.1)
Respiratory, Thoracic and Mediastinal Disorders	6	(3.3)	8	(4.4)	12	(6.6)	26	(4.8)	4	(2.2)
Skin and Subcutaneous Tissue Disorders	16	(8.9)	18	(9.9)	21	(11.6)	55	(10.1)	11	(6.1)
Vascular Disorders	6	(3.3)	6	(3.3)	5	(2.8)	17	(3.1)	1	(0.6)

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

NOVARTIS

Number (%) of patients with most frequent AEs during Period 1 by preferred term and treatment (>=5% for any group) (Safety Analysis Set for Period 1)

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Total no. of patients with AEs	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Decreased appetite	39	(21.7)	49	(27.1)	48	(26.5)	136	(25.1)	8	(4.4)
Headache	39	(21.7)	42	(23.2)	30	(16.6)	111	(20.5)	30	(16.7)
Dry mouth	34	(18.9)	39	(21.5)	37	(20.4)	110	(20.3)	4	(2.2)
Nausea	15	(8.3)	20	(11.0)	23	(12.7)	58	(10.7)	9	(5.0)
Nasopharyngitis	22	(12.2)	15	(8.3)	17	(9.4)	54	(10.0)	17	(9.4)
Insomnia	13	(7.2)	18	(9.9)	13	(7.2)	44	(8.1)	7	(3.9)
Hyperhidrosis	12	(6.7)	14	(7.7)	17	(9.4)	43	(7.9)	5	(2.8)
Palpitations	8	(4.4)	15	(8.3)	16	(8.8)	39	(7.2)	1	(0.6)
Fatigue	11	(6.1)	16	(8.8)	11	(6.1)	38	(7.0)	11	(6.1)
Dizziness	12	(6.7)	9	(5.0)	11	(6.1)	32	(5.9)	5	(2.8)
Irritability	11	(6.1)	12	(6.6)	9	(5.0)	32	(5.9)	8	(4.4)
Anxiety	8	(4.4)	11	(6.1)	10	(5.5)	29	(5.4)	1	(0.6)
Initial insomnia	9	(5.0)	4	(2.2)	15	(8.3)	28	(5.2)	2	(1.1)
Restlessness	9	(5.0)	10	(5.5)	7	(3.9)	26	(4.8)	5	(2.8)
Tachycardia	6	(3.3)	10	(5.5)	10	(5.5)	26	(4.8)	0	(0.0)
Abdominal pain upper	6	(3.3)	3	(1.7)	13	(7.2)	22	(4.1)	7	(3.9)
Diarrhoea	4	(2.2)	4	(2.2)	9	(5.0)	17	(3.1)	12	(6.7)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with AEs during Period 2 by primary system organ class (Safety Analysis Set for Period 2)

	All Ritalin LA N=580 n(%)	
Primary system organ class		
Any primary system organ class	**378**	**(65.2)**
Blood and Lymphatic System Disorders	1	(0.2)
Cardiac Disorders	59	(10.2)
Congenital, Familial and Genetic Disorders	1	(0.2)
Ear and Labyrinth Disorders	11	(1.9)
Endocrine Disorders	1	(0.2)
Eye Disorders	6	(1.0)
Gastrointestinal Disorders	105	(18.1)
General Disorders and Administration Site Conditions	75	(12.9)
Immune System Disorders	4	(0.7)
Infections and Infestations	87	(15.0)
Injury, Poisoning and Procedural Complications	17	(2.9)
Investigations	29	(5.0)
Metabolism and Nutrition Disorders	64	(11.0)
Musculoskeletal and Connective Tissue Disorders	27	(4.7)
Nervous System Disorders	121	(20.9)
Psychiatric Disorders	145	(25.0)
Renal and Urinary Disorders	3	(0.5)
Reproductive System and Breast Disorders	6	(1.0)
Respiratory, Thoracic and Mediastinal Disorders	27	(4.7)
Skin and Subcutaneous Tissue Disorders	33	(5.7)
Vascular Disorders	7	(1.2)

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

NOVARTIS

Number (%) of patients with most frequent AEs during Period 2 by preferred term (>= 5%) (Safety Analysis Set for Period 2)

	All Ritalin LA N=580 n(%)	
Total no. of patients with AEs	**378**	**(65.2)**
Headache	78	(13.4)
Decreased appetite	62	(10.7)
Dry mouth	50	(8.6)
Nasopharyngitis	43	(7.4)
Nausea	37	(6.4)
Insomnia	34	(5.9)
Palpitations	29	(5.0)
Tachycardia	29	(5.0)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with AEs during Period 3 by primary system organ class and treatment (Safety Analysis Set for Period 3)

	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Primary system organ class										
Any primary system organ class	64	(56.6)	75	(57.7)	58	(49.2)	197	(54.6)	44	(36.4)
Blood and Lymphatic System Disorders	1	(0.9)	2	(1.5)	0	(0.0)	3	(0.8)	0	(0.0)
Cardiac Disorders	5	(4.4)	2	(1.5)	7	(5.9)	14	(3.9)	2	(1.7)
Congenital, Familial and Genetic Disorders	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)
Ear and Labyrinth Disorders	2	(1.8)	1	(0.8)	1	(0.8)	4	(1.1)	1	(0.8)
Endocrine Disorders	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)
Eye Disorders	2	(1.8)	4	(3.1)	3	(2.5)	9	(2.5)	0	(0.0)
Gastrointestinal Disorders	13	(11.5)	15	(11.5)	16	(13.6)	44	(12.2)	6	(5.0)
General Disorders and Administration Site Conditions	6	(5.3)	8	(6.2)	3	(2.5)	17	(4.7)	7	(5.8)
Hepatobiliary Disorders	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Immune System Disorders	1	(0.9)	0	(0.0)	1	(0.8)	2	(0.6)	0	(0.0)
Infections and Infestations	28	(24.8)	27	(20.8)	26	(22.0)	81	(22.4)	18	(14.9)
Injury, Poisoning and Procedural Complications	5	(4.4)	8	(6.2)	4	(3.4)	17	(4.7)	3	(2.5)
Investigations	4	(3.5)	4	(3.1)	4	(3.4)	12	(3.3)	4	(3.3)
Metabolism and Nutrition Disorders	4	(3.5)	6	(4.6)	4	(3.4)	14	(3.9)	2	(1.7)
Musculoskeletal and Connective Tissue Disorders	11	(9.7)	9	(6.9)	8	(6.8)	28	(7.8)	9	(7.4)
Nervous System Disorders	14	(12.4)	21	(16.2)	12	(10.2)	47	(13.0)	12	(9.9)
Psychiatric Disorders	12	(10.6)	15	(11.5)	14	(11.9)	41	(11.4)	12	(9.9)
Renal and Urinary Disorders	0	(0.0)	1	(0.8)	3	(2.5)	4	(1.1)	0	(0.0)
Reproductive System and Breast Disorders	4	(3.5)	0	(0.0)	0	(0.0)	4	(1.1)	1	(0.8)
Respiratory, Thoracic and Mediastinal Disorders	5	(4.4)	5	(3.8)	5	(4.2)	15	(4.2)	3	(2.5)
Skin and Subcutaneous Tissue Disorders	6	(5.3)	4	(3.1)	2	(1.7)	12	(3.3)	2	(1.7)
Vascular Disorders	2	(1.8)	3	(2.3)	3	(2.5)	8	(2.2)	1	(0.8)

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

NOVARTIS

Number (%) of patients with most frequent AEs during Period 3 by preferred term and treatment (>= 5% for any group) (Safety Analysis Set for Period 3)

	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Total no. of patients with AEs	**64**	**(56.6)**	**75**	**(57.7)**	**58**	**(49.2)**	**197**	**(54.6)**	**44**	**(36.4)**
Nasopharyngitis	11	(9.7)	18	(13.8)	15	(12.7)	44	(12.2)	6	(5.0)
Headache	12	(10.6)	14	(10.8)	11	(9.3)	37	(10.2)	9	(7.4)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with AEs during the entire study by primary system organ class and treatment (Safety Analysis Set for Period 1)

	All Ritalin LA N=695 n(%)		Placebo N=275 n(%)	
Primary system organ class				
Any primary system organ class	566	(81.4)	143	(52.0)
Blood and Lymphatic System Disorders	5	(0.7)	0	(0.0)
Cardiac Disorders	115	(16.5)	3	(1.1)
Congenital, Familial and Genetic Disorders	1	(0.1)	0	(0.0)
Ear and Labyrinth Disorders	35	(5.0)	5	(1.8)
Endocrine Disorders	3	(0.4)	0	(0.0)
Eye Disorders	30	(4.3)	4	(1.5)
Gastrointestinal Disorders	280	(40.3)	34	(12.4)
General Disorders and Administration Site Conditions	164	(23.6)	34	(12.4)
Hepatobiliary Disorders	1	(0.1)	0	(0.0)
Immune System Disorders	9	(1.3)	0	(0.0)
Infections and Infestations	223	(32.1)	56	(20.4)
Injury, Poisoning and Procedural Complications	49	(7.1)	5	(1.8)
Investigations	75	(10.8)	10	(3.6)
Metabolism and Nutrition Disorders	186	(26.8)	15	(5.5)
Musculoskeletal and Connective Tissue Disorders	77	(11.1)	19	(6.9)
Nervous System Disorders	267	(38.4)	57	(20.7)
Psychiatric Disorders	301	(43.3)	36	(13.1)
Renal and Urinary Disorders	12	(1.7)	0	(0.0)
Reproductive System and Breast Disorders	21	(3.0)	3	(1.1)
Respiratory, Thoracic and Mediastinal Disorders	63	(9.1)	7	(2.5)
Skin and Subcutaneous Tissue Disorders	86	(12.4)	13	(4.7)
Vascular Disorders	29	(4.2)	2	(0.7)

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

NOVARTIS

Number (%) of patients with most frequent AEs during the entire study by preferred term and treatment (>= 5% for any group) (Safety Analysis Set for Period 1)

	All Ritalin LA N=695 n(%)		Placebo N=275 n(%)	
Total no. of patients with AEs	**566**	**(81.4)**	**143**	**(52.0)**
Decreased appetite	182	(26.2)	8	(2.9)
Headache	178	(25.6)	39	(14.2)
Dry mouth	142	(20.4)	4	(1.5)
Nasopharyngitis	122	(17.6)	22	(8.0)
Nausea	93	(13.4)	9	(3.3)
Insomnia	77	(11.1)	9	(3.3)
Fatigue	64	(9.2)	14	(5.1)
Palpitations	63	(9.1)	2	(0.7)
Hyperhidrosis	62	(8.9)	5	(1.8)
Tachycardia	56	(8.1)	0	(0.0)
Dizziness	55	(7.9)	5	(1.8)
Anxiety	50	(7.2)	3	(1.1)
Irritability	50	(7.2)	9	(3.3)
Restlessness	48	(6.9)	7	(2.5)
Diarrhoea	31	(4.5)	14	(5.1)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with AEs adjusted for exposure time starting in Period 1 based on All Ritalin LA AEs with IDR difference of >=1 per 1000 patient weeks compared to Placebo (Safety analysis set for Period 1)

Primary SOC	Ritalin LA 40 mg N=180 FT=1493.0		Ritalin LA 60 mg N=181 FT=1447.3		Ritalin LA 80 mg N=181 FT=1419.4		All Ritalin LA N=542 FT=4359.7		Placebo N=180 FT=1492.3		Frequency range for Ritalin LA 40 mg
PT	n (%)	IDR	n (%)	IDR	n (%)	IDR	n (%)	IDR	N (%)	IDR	
Cardiac Disorders											
Palpitations	8 (4.4),	5.4	15 (8.3)	10.4	16 (8.8)	11.3	39 (7.2)	8.9	1 (0.6)	0.7	common
Tachycardia	6 (3.3)	4.0	10 (5.5)	6.9	10 (5.5)	7.0	26 (4.8)	6.0	0 (0.0)	0.0	common
Gastrointestinal Disorders											
Dry mouth	34 (18.9)	22.8	39 (21.5)	26.5	37 (20.4)	26.1	110 (20.3)	25.2	4 (2.2)	2.7	very common
Nausea	15 (8.3)	10.0	20 (11.0)	13.8	23 (12.7)	16.2	58 (10.7)	13.3	9 (5.0)	6.0	common
Dyspepsia	2 (1.1)	1.3	3 (1.7)	2.1	2 (1.1)	1.4	7 (1.3)	1.6	0 (0.0)	0.0	common
Toothache	3 (1.7)	2.0	2 (1.1)	1.4	2 (1.1)	1.4	7 (1.3)	1.6	0 (0.0)	0.0	common
Abdominal pain	1 (0.6)	0.7	1 (0.6)	0.7	3 (1.7)	2.1	5 (0.9)	1.1	0 (0.0)	0.0	uncommon
General disorders and administration site conditions											
Irritability	11 (6.1)	7.4	12 (6.6)	8.3	9 (5.0)	6.3	32 (5.9)	7.3	8 (4.4)	5.4	common
Thirst	3 (1.7)	2.0	2 (1.1)	1.4	6 (3.3)	4.2	11 (2.0)	2.5	1 (0.6)	0.7	common
Feeling jittery	2 (1.1)	1.3	1 (0.6)	0.7	2 (1.1)	1.4	5 (0.9)	1.1	0 (0.0)	0.0	common
Infections and infestations											
Naso-pharyngitis	22 (12.2)	14.7	15 (8.3)	10.4	17 (9.4)	12.0	54 (10.0)	12.4	17 (9.4)	11.4	very common
Gastro-enteritis	1 (0.6)	0.7	3 (1.7)	2.1	1 (0.6)	0.7	5 (0.9)	1.1	0 (0.0)	0.0	uncommon
Investigations											
Weight decreased	5 (2.8)	3.3	5 (2.8)	3.5	6 (3.3)	4.2	16 (3.0)	3.7	2 (1.1)	1.3	common
Blood pressure increased	4 (2.2)	2.7	0 (0.0)	0.0	8 (4.4)	5.6	12 (2.2)	2.8	1 (0.6)	0.7	common
Heart rate increased	1 (0.6)	0.7	0 (0.0)	0.0	6 (3.3)	4.2	7 (1.3)	1.6	0 (0.0)	0.0	uncommon
Metabolism and nutrition disorders											
Decreased appetite	39 (21.7)	26.1	49 (27.1)	33.9	48 (26.5)	33.8	136 (25.1)	31.2	8 (4.4)	5.4	very common

Primary SOC PT	Ritalin LA 40 mg N=180 FT=1493.0 n (%)	IDR	Ritalin LA 60 mg N=181 FT=1447.3 n (%)	IDR	Ritalin LA 80 mg N=181 FT=1419.4 n (%)	IDR	All Ritalin LA N=542 FT=4359.7 n (%)	IDR	Placebo N=180 FT=1492.3 N (%)	IDR	Frequency range for Ritalin LA 40 mg
Musculoskeletal and connective tissue disorders											
Muscle tightness	0 (0.0)	0.0	4 (2.2)	2.8	1 (0.6)	0.7	5 (0.9)	1.1	0 (0.0)	0.0	--
Nervous system disorders											
Headache	39 (21.7)	26.1	42 (23.2)	29.0	30 (16.6)	21.1	111 (20.5)	25.5	30 (16.7)	20.1	very common
Dizziness	12 (6.7)	8.0	9 (5.0)	6.2	11 (6.1)	7.7	32 (5.9)	7.3	5 (2.8)	3.4	common
Tremor	7 (3.9)	4.7	6 (3.3)	4.1	5 (2.8)	3.5	18 (3.3)	4.1	1 (0.6)	0.7	common
Akathisia	1 (0.6)	0.7	2 (1.1)	1.4	2 (1.1)	1.4	5 (0.9)	1.1	0 (0.0)	0.0	uncommon
Psychiatric disorders											
Insomnia	13 (7.2)	8.7	18 (9.9)	12.4	13 (7.2)	9.2	44 (8.1)	10.1	7 (3.9)	4.7	common
Anxiety	8 (4.4)	5.4	11 (6.1)	7.6	10 (5.5)	7.0	29 (5.4)	6.7	1 (0.6)	0.7	common
Initial insomnia	9 (5.0)	6.0	4 (2.2)	2.8	15 (8.3)	10.6	28 (5.2)	6.4	2 (1.1)	1.3	common
Restlessness	9 (5.0)	6.0	10 (5.5)	6.9	7 (3.9)	4.9	26 (4.8)	6.0	5 (2.8)	3.4	common
Agitation	5 (2.8)	3.3	3 (1.7)	2.1	7 (3.9)	4.9	15 (2.8)	3.4	1 (0.6)	0.7	common
Sleep disorder	5 (2.8)	3.3	5 (2.8)	3.5	4 (2.2)	2.8	14 (2.6)	3.2	3 (1.7)	2.0	common
Depression	5 (2.8)	3.3	5 (2.8)	3.5	3 (1.7)	2.1	13 (2.4)	3.0	1 (0.6)	0.7	common
Libido decreased	1 (0.6)	0.7	4 (2.2)	2.8	3 (1.7)	2.1	8 (1.5)	1.8	0 (0.0)	0.0	uncommon
Panic attack	2 (1.1)	1.3	1 (0.6)	0.7	5 (2.8)	3.5	8 (1.5)	1.8	1 (0.6)	0.7	common
Nervousness	3 (1.7)	2.0	3 (1.7)	2.1	1 (0.6)	0.7	7 (1.3)	1.6	0 (0.0)	0.0	common
Stress	0 (0.0)	0.0	1 (0.6)	0.7	5 (2.8)	3.5	6 (1.1)	1.4	0 (0.0)	0.0	--
Tension	1 (0.6)	0.7	3 (1.7)	2.1	1 (0.6)	0.7	5 (0.9)	1.1	0 (0.0)	0.0	uncommon
Respiratory, thoracic and mediastinal disorders											
Dyspnoea	2 (1.1)	1.3	4 (2.2)	2.8	4 (2.2)	2.8	10 (1.8)	2.3	0 (0.0)	0.0	common
Cough	2 (1.1)	1.3	1 (0.6)	0.7	4 (2.2)	2.8	7 (1.3)	1.6	0 (0.0)	0.0	common
Skin and subcutaneous tissue disorders											
Hyperhidrosis	12 (6.7)	8.0	14 (7.7)	9.7	17 (9.4)	12.0	43 (7.9)	9.9	5 (2.8)	3.4	common

Primary SOC	Ritalin LA 40 mg N=180 FT=1493.0		Ritalin LA 60 mg N=181 FT=1447.3		Ritalin LA 80 mg N=181 FT=1419.4		All Ritalin LA N=542 FT=4359.7		Placebo N=180 FT=1492.3		Frequency range for Ritalin LA 40 mg
PT	n (%)	IDR	n (%)	IDR	n (%)	IDR	n (%)	IDR	N (%)	IDR	
Vascular Disorders											
Peripheral coldness	2 (1.1)	1.3	3 (1.7)	2.1	3 (1.7)	2.1	8 (1.5)	1.8	0 (0.0)	0.0	common

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the All Ritalin LA column.
A patient with multiple occurrences of an AE under on treatment is counted only once in the AE category for that treatment.
Frequences are defined as follows: very common (≥1/10); common(≥1/100 to <1/10); uncommon (≥1/1000 to <1/100).
AEs occurred after patient's treatment end date are not included.
Abbreviations: IDR= Incidence density rate per 1000 person weeks, calculated as 1000*n/FT; FT= follow-up time in weeks; PT=preferred term; and SOC=system organ class

Number (%) of patients with AEs adjusted for exposure time starting in Period 3 based on All Ritalin LA AEs with IDR difference of >=1 per 1000 patient weeks compared to Placebo (Safety analysis set for Period 3)

Primary SOC	Ritalin LA 40 mg N=113 FT=2032.6		Ritalin LA 60 mg N=130 FT=2138.7		Ritalin LA 80 mg N=118 FT=2257.1		All Ritalin LA N=361 FT=6428.4		Placebo N=121 FT=1505.9		Frequency range for Ritalin LA 40 mg
PT	n (%)	IDR	n (%)	IDR	n (%)	IDR	n (%)	IDR	N (%)	IDR	
Cardiac disorders											
Tachycardia	4 (3.5)	2.0	1 (0.8)	0.5	5 (4.2)	2.2	10 (2.8)	1.6	0 (0.0)	0.0	common
Gastrointestinal disorders											
Dry mouth	2 (1.8)	1.0	2 (1.5)	0.9	3 (2.5)	1.3	7 (1.9)	1.1	0 (0.0)	0.0	common
Infections and Infestations											
Nasopharyngitis	11 (9.7)	5.4	18 (13.8)	8.4	15 (12.7)	6.6	44 (12.2)	6.8	6 (5.0)	4.0	common
Metabolism and nutrition disorders											
Decreased appetite	4 (3.5)	2.0	6 (4.6)	2.8	3 (2.5)	1.3	13 (3.6)	2.0	0 (0.0)	0.0	common
Nervous system disorders											
Dizziness	0 (0.0)	0.0	5 (3.8)	2.3	2 (1.7)	0.9	7 (1.9)	1.1	0 (0.0)	0.0	–

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the All Ritalin LA column.
A patient with multiple occurrences of an AE under on treatment is counted only once in the 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).
AEs occurred after patient's treatment end date are not included.
Abbreviations: FT= follow-up time in weeks; IDR = Incidence density rate per 1000 person weeks, calculated as 1000*n/FT; PT=preferred terms; and SOC=system organ class.

NOVARTIS

Number (%) of patients with AEs adjusted for exposure time starting during the entire study based on All Ritalin LA AEs with IDR difference of >=1 per 1000 patient weeks compared to Placebo (Safety analysis set for Period 1)

Primary SOC PT	All Ritalin LA N=695 FT=13635.6		Placebo N=275 FT=2998.9		Frequency range for All Ritalin LA
	n (%)	IDR	n (%)	IDR	
Cardiac disorders					
Palpitations	63 (9.1)	4.6	2 (0.7)	0.7	common
Tachycardia	56 (8.1)	4.1	0 (0.0)	0.0	common
Gastrointestinal disorders					
Dry mouth	142 (20.4)	10.4	4 (1.5)	1.3	very common
Nausea	93 (13.4)	6.8	9 (3.3)	3.0	very common
Dyspepsia	13 (1.9)	1.0	0 (0.0)	0.0	common
Toothache	13 (1.9)	1.0	0 (0.0)	0.0	common
General disorders administrative site conditions					
Feeling jittery	15 (2.2)	1.1	0 (0.0)	0.0	common
Infections and infestations					
Nasopharyngitis	122 (17.6)	8.9	22 (8.0)	7.3	very common
Investigations					
Weight decreased	27 (3.9)	2.0	2 (0.7)	0.7	common
Metabolism and nutrition disorders					
Decreased appetite	182 (26.2)	13.3	8 (2.9)	2.7	very common
Nervous system disorders					
Dizziness	55 (7.9)	4.0	5 (1.8)	1.7	common
Tremor	31 (4.5)	2.3	1 (0.4)	0.3	common
Psychiatric disorders					
Insomnia	77 (11.1)	5.6	9 (3.3)	3.0	very common
Anxiety	50 (7.2)	3.7	3 (1.1)	1.0	common
Restlessness	48 (6.9)	3.5	7 (2.5)	2.3	common
Initial insomnia	34 (4.9)	2.5	2 (0.7)	0.7	common
Nervousness	30 (4.3)	2.2	0 (0.0)	0.0	common
Sleep disorder	28 (4.0)	2.1	3 (1.1)	1.0	common
Agitation	23 (3.3)	1.7	1 (0.4)	0.3	common
Respiratory thoracic and mediastinal disorders					
Cough	22 (3.2)	1.6	1 (0.4)	0.3	common
Skin subcutaneous tissue disorders					
Hyperhidrosis	62 (8.9)	4.5	5 (1.8)	1.7	common

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in the All Ritalin LA column.
A patient with multiple occurrences of an AE under on treatment is counted only once in the 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).
AEs occurred after patient's treatment end date are not included.
Abbreviations: FT= follow-up time in weeks; IDR = Incidence density rate per 1000 person weeks, calculated as 1000*n/FT, PT=preferred term; and SOC=system organ class.

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Number (%) of patients who had adverse events starting in Period 2 by time interval of onset and preferred term, displayed by Period 1 treatment (Safety analysis set for Period 2)

	All Ritalin LA in Period 1 N=428		Placebo in Period 1 N=152	
Week 0-1	**n**	**%**	**n**	**%**
Total no. pts with AEs	**56**	**(13.1)**	**32**	**(21.1)**
Fatigue	4	(0.9)	2	(1.3)
Irritability	2	(0.5)	1	(0.7)
Increased appetite	2	(0.5)	0	(0.0)
Somnolence	2	(0.5)	0	(0.0)
Tension	2	(0.5)	0	(0.0)
Panic attack	1	(0.2)	0	(0.0)
Anxiety	0	(0.0)	1	(0.7)
Nervousness	0	(0.0)	5	(3.3)
Restlessness	0	(0.0)	1	(0.7)
Week 1-2				
Total no. pts with AEs	**74**	**(17.3)**	**37**	**(24.3)**
Irritability	8	(1.9)	0	(0.0)
Fatigue	3	(0.7)	1	(0.7)
Feeling jittery	1	(0.2)	1	(0.7)
Depressed level of consciousness	1	(0.2)	0	(0.0)
Sedation	1	(0.2)	0	(0.0)
Anxiety	2	(0.5)	3	(2.0)
Nervousness	3	(0.7)	0	(0.0)
Restlessness	2	(0.5)	2	(1.3)
Depressed mood	1	(0.2)	1	(0.7)
Depression	1	(0.2)	1	(0.7)
Agitation	0	(0.0)	1	(0.7)

A patient with multiple occurrences of an AE under on treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
AEs occurred after patient's treatment end date are not included.

Number (%) of patients who had adverse events starting in Period 3 by time interval of onset and preferred term (Safety analysis set for Period 3)

	All Ritalin LA N=361		Placebo N=121	
Week 0-2	**n**	**%**	**n**	**%**
Total no. pts with AEs	**62**	**(17.2)**	**16**	**(13.2)**
Fatigue	2	(0.6)	2	(1.7)
Irritability	2	(0.6)	0	(0.0)
Increased appetite	1	(0.3)	0	(0.0)
Restlessness	4	(1.1)	1	(0.8)
Depressed mood	1	(0.3)	0	(0.0)
Panic attack	1	(0.3)	0	(0.0)
Week 2-6				
Total no. pts with AEs	49	(13.6)	9	(7.4)
Irritability	2	(0.6)	0	(0.0)
Depression	1	(0.3)	0	(0.0)
Major depression	1	(0.3)	0	(0.0)
Panic attack	1	(0.3)	1	(0.8)

A patient with multiple occurrences of an AE under on treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
AEs occurred after patient's treatment end date are not included.

Number (%) of patients who died, had SAEs, or discontinued because of AEs/SAEs starting in Period 1 by treatment (Safety Analysis Set for Period 1)

	Ritalin LA 40 mg N=180 n (%)		Ritalin LA 60 mg N=181 n (%)		Ritalin LA 80 mg N=181 n (%)		All Ritalin LA N=542 n (%)		Placebo N=180 n (%)	
Total no. of patients with AEs	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Serious AEs or significant AEs										
Death	0		0		0		0		0	
SAE(s)	1	(0.6)	2	(1.1)	1	(0.6)	4	(0.7)	2	(1.1)
Discontinued due to AE(s)	12	(6.7)	21	(11.6)	28	(15.5)	61	(11.3)	4	(2.2)
Discontinued due to SAE(s)	0		0		0		0		1	(0.6)

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

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Number (%) of patients who died, had SAEs, or discontinued because of AEs/SAEs starting in Period 2 by treatment (Safety Analysis Set for Period 2)

	All Ritalin LA N=580 n (%)	
Total no. of patients with AEs	**378**	**(65.2)**
Serious AEs or significant AEs		
Death	0	
SAE(s)	2	(0.3)
Discontinued due to AE(s)	22	(3.8)
Discontinued due to SAE(s)	1	(0.2)

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

Number (%) of patients who died, had SAEs, or discontinued because of AEs/SAEs starting in Period 3 by treatment (Safety Analysis Set for Period 3)

	Ritalin LA 40 mg N=113 n (%)		Ritalin LA 60 mg N=130 n (%)		Ritalin LA 80 mg N=118 n (%)		All Ritalin LA N=361 n (%)		Placebo N=121 n (%)	
Total no. of patients with AEs	**64**	**(56.6)**	**75**	**(57.7)**	**58**	**(49.2)**	**197**	**(54.6)**	**44**	**(36.4)**
Serious AEs or significant AEs										
Death	0		0		0		0		0	
SAE(s)	0		0		3	(2.5)	3	(0.8)	2	(1.7)
Discontinued due to AE(s)	3	(2.7)	9	(6.9)	6	(5.1)	18	(5.0)	4	(3.3)
Discontinued due to SAE(s)	0		0		1	(0.8)	1	(0.3)	0	

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

Number (%) of patients who died, had SAEs, or discontinued because of AEs/SAEs during entire study by treatment (Safety Analysis Set for Period 1)

	All Ritalin LA N=695 n (%)		Placebo N=275 n (%)	
Total no. of patients with AEs	**566**	**(81.4)**	**143**	**(52.0)**
Serious AEs or significant AEs				
Death	0		0	
SAE(s)	9	(1.3)	4	(1.5)
Discontinued due to AE(s)	99	(14.2)	8	(2.9)
Discontinued due to SAE(s)	2	(0.3)	1	(0.4)

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

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Number (%) of patients with SAEs by primary system organ class and preferred term starting in Period 1 by treatment (Safety Analysis Set for Period 1)

Primary system organ class/ and preferred term	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Total	**1**	**(0.6)**	**2**	**(1.1)**	**1**	**(0.6)**	**4**	**(0.7)**	**2**	**(1.1)**
Ear and Labyrinth Disorders										
-Total	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Sudden hearing loss	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Vertigo	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Endocrine Disorders										
-Total	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Goitre	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Infections and Infestations										
-Total	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	1	(0.6)
Infected bites	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	0	(0.0)
Eye infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Nervous System Disorders										
-Total	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)	1	(0.6)
Loss of consciousness	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)	0	(0.0)
Syncope	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Psychiatric Disorders										
-Total	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Agitation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Depression	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Reproductive System and Breast Disorders										
-Total	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)	0	(0.0)
Ovarian cyst ruptured	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)	0	(0.0)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in All Ritalin LA column.
AEs occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with SAEs by primary system organ class and preferred term starting in Period 2 by treatment (Safety Analysis Set for Period 2)

Primary system organ class/ and preferred term	All Ritalin LA N=580 n(%)	
Total	**2**	**(0.3)**
Injury, Poisoning and Procedural Complications		
-Total	1	(0.2)
Concussion	1	(0.2)
Rib fracture	1	(0.2)
Psychiatric Disorders		
-Total	1	(0.2)
Panic attack	1	(0.2)

Primary system organ classes are presented alphabetically. preferred terms are sorted within primary system organ class in descending order of frequency in All Ritalin LA column.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with SAEs by primary system organ class and preferred term starting in Period 3 by treatment (Safety Analysis Set for Period 3)

Primary system organ class/ and preferred term	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Total	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(2.5)**	**3**	**(0.8)**	**2**	**(1.7)**
Hepatobiliary Disorders										
-Total	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Cholecystitis	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Cholelithiasis	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Infections and Infestations										
-Total	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Localised infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Psychiatric Disorders										
-Total	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Adjustment disorder	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Suicide attempt	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Renal and Urinary Disorders										
-Total	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Nephrolithiasis	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Respiratory, Thoracic and Mediastinal Disorders										
-Total	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
Tonsillar hypertrophy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in All Ritalin LA column.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients with SAEs by primary system organ class and preferred term during the entire study by treatment (Safety Analysis Set for Period 1)

Primary system organ class/ and preferred term	All Ritalin LA N=695 n(%)		Placebo N=275 n(%)	
Total	**9**	**(1.3)**	**4**	**(1.5)**
Ear and Labyrinth Disorders				
-Total	0	(0.0)	1	(0.4)
Sudden hearing loss	0	(0.0)	1	(0.4)
Vertigo	0	(0.0)	1	(0.4)
Endocrine Disorders				
-Total	1	(0.1)	0	(0.0)
Goitre	1	(0.1)	0	(0.0)
Hepatobiliary Disorders				
-Total	1	(0.1)	0	(0.0)
Cholecystitis	1	(0.1)	0	(0.0)
Cholelithiasis	1	(0.1)	0	(0.0)
Infections and Infestations				
-Total	1	(0.1)	2	(0.7)
Infected bites	1	(0.1)	0	(0.0)
Eye infection	0	(0.0)	1	(0.4)
Localised infection	0	(0.0)	1	(0.4)
Injury, Poisoning and Procedural Complications				
-Total	1	(0.1)	0	(0.0)
Concussion	1	(0.1)	0	(0.0)
Rib fracture	1	(0.1)	0	(0.0)

Primary system organ class/ and preferred term	All Ritalin LA N=695 n(%)		Placebo N=275 n(%)	
Nervous System Disorders				
-Total	1	(0.1)	1	(0.4)
Loss of consciousness	1	(0.1)	0	(0.0)
Syncope	0	(0.0)	1	(0.4)
Psychiatric Disorders				
-Total	2	(0.3)	1	(0.4)
Adjustment disorder	1	(0.1)	0	(0.0)
Panic attack	1	(0.1)	0	(0.0)
Suicide attempt	1	(0.1)	0	(0.0)
Agitation	0	(0.0)	1	(0.4)
Depression	0	(0.0)	1	(0.4)
Renal and Urinary Disorders				
-Total	1	(0.1)	0	(0.0)
Nephrolithiasis	1	(0.1)	0	(0.0)
Reproductive System and Breast Disorders				
-Total	1	(0.1)	0	(0.0)
Ovarian cyst ruptured	1	(0.1)	0	(0.0)
Respiratory, Thoracic and Mediastinal Disorders				
-Total	0	(0.0)	1	(0.4)
Tonsillar hypertrophy	0	(0.0)	1	(0.4)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in All Ritalin LA column.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients who discontinued due to adverse events starting in Period 1 by preferred term and treatment (>= 0.4% patients in All Ritalin LA group) (Safety Analysis Set for Period 1)

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Total no. of patients with AEs	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
No. discontinued due to AE	**12**	**(6.7)**	**21**	**(11.6)**	**28**	**(15.5)**	**61**	**(11.3)**	**4**	**(2.2)**
Anxiety	3	(1.7)	4	(2.2)	2	(1.1)	9	(1.7)	1	(0.6)
Decreased appetite	0	(0.0)	2	(1.1)	4	(2.2)	6	(1.1)	0	(0.0)
Headache	1	(0.6)	3	(1.7)	2	(1.1)	6	(1.1)	0	(0.0)
Agitation	1	(0.6)	1	(0.6)	3	(1.7)	5	(0.9)	1	(0.6)
Depressed mood	2	(1.1)	1	(0.6)	2	(1.1)	5	(0.9)	0	(0.0)
Depression	1	(0.6)	3	(1.7)	1	(0.6)	5	(0.9)	1	(0.6)
Insomnia	1	(0.6)	1	(0.6)	3	(1.7)	5	(0.9)	0	(0.0)
Dizziness	2	(1.1)	1	(0.6)	1	(0.6)	4	(0.7)	0	(0.0)
Fatigue	0	(0.0)	4	(2.2)	0	(0.0)	4	(0.7)	0	(0.0)
Irritability	1	(0.6)	1	(0.6)	2	(1.1)	4	(0.7)	0	(0.0)
Nausea	1	(0.6)	1	(0.6)	2	(1.1)	4	(0.7)	0	(0.0)
Palpitations	1	(0.6)	2	(1.1)	1	(0.6)	4	(0.7)	0	(0.0)
Restlessness	1	(0.6)	1	(0.6)	2	(1.1)	4	(0.7)	0	(0.0)
Tachycardia	2	(1.1)	1	(0.6)	1	(0.6)	4	(0.7)	0	(0.0)
Dry mouth	2	(1.1)	0	(0.0)	1	(0.6)	3	(0.6)	0	(0.0)
Dyspnoea	0	(0.0)	2	(1.1)	1	(0.6)	3	(0.6)	0	(0.0)
Hyperhidrosis	0	(0.0)	1	(0.6)	2	(1.1)	3	(0.6)	0	(0.0)
Aggression	1	(0.6)	0	(0.0)	1	(0.6)	2	(0.4)	0	(0.0)
Apathy	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.4)	0	(0.0)
Blood pressure increased	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.4)	0	(0.0)
Disturbance in attention	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
Impulse-control disorder	1	(0.6)	0	(0.0)	1	(0.6)	2	(0.4)	0	(0.0)
Panic attack	0	(0.0)	0	(0.0)	2	(1.1)	2	(0.4)	1	(0.6)
Tremor	0	(0.0)	1	(0.6)	1	(0.6)	2	(0.4)	0	(0.0)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients who discontinued due to adverse events starting in Period 2 by preferred term and treatment (Safety Analysis Set for Period 2)

	All Ritalin LA N=580 n(%)	
Total no. of patients with AEs	**378**	**(65.2)**
No. discontinued due to AE	**22**	**(3.8)**
Anxiety	4	(0.7)
Nervousness	4	(0.7)
Blood creatine phosphokinase increased	2	(0.3)
Depression	2	(0.3)
Aggression	1	(0.2)
Agitation	1	(0.2)
Blood pressure increased	1	(0.2)
Change in sustained attention	1	(0.2)
Cognitive disorder	1	(0.2)
Decreased appetite	1	(0.2)
Depressed mood	1	(0.2)
Heart rate abnormal	1	(0.2)
Heart rate increased	1	(0.2)
Hepatic enzyme increased	1	(0.2)
Hyperhidrosis	1	(0.2)
Irritability	1	(0.2)
Lethargy	1	(0.2)
Loss of libido	1	(0.2)
Muscle twitching	1	(0.2)
Nausea	1	(0.2)
Palpitations	1	(0.2)
Panic attack	1	(0.2)
Psychotic disorder	1	(0.2)
Rash	1	(0.2)
Sleep disorder	1	(0.2)
Somnolence	1	(0.2)
Weight decreased	1	(0.2)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients who discontinued due to adverse events starting in Period 3 by preferred term and treatment (>=0.5% in All Ritalin LA group) (Safety Analysis Set for Period 3)

	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Total no. of patients with AEs	**64**	**(56.6)**	**75**	**(57.7)**	**58**	**(49.2)**	**197**	**(54.6)**	**44**	**(36.4)**
No. discontinued due to AE	3	(2.7)	9	(6.9)	6	(5.1)	18	(5.0)	4	(3.3)
Decreased appetite	1	(0.9)	0	(0.0)	1	(0.8)	2	(0.6)	0	(0.0)
Depression	0	(0.0)	1	(0.8)	1	(0.8)	2	(0.6)	1	(0.8)
Headache	0	(0.0)	1	(0.8)	1	(0.8)	2	(0.6)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	2	(1.7)	2	(0.6)	0	(0.0)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs occurred after patient's treatment end date are not included.

NOVARTIS

Number (%) of patients (>= 0.3% patients in All Ritalin LA) who discontinued due to adverse events during the entire study by preferred term and treatment (Safety Analysis Set for Period 1)

	All Ritalin LA N=695 n(%)		Placebo N=275 n(%)	
Total no. of patients with AEs	**566**	**(81.4)**	**143**	**(52.0)**
No. discontinued due to AE	99	(14.2)	8	(2.9)
Anxiety	14	(2.0)	1	(0.4)
Decreased appetite	9	(1.3)	0	(0.0)
Depression	9	(1.3)	2	(0.7)
Headache	8	(1.2)	0	(0.0)
Nausea	7	(1.0)	0	(0.0)
Agitation	6	(0.9)	1	(0.4)
Depressed mood	6	(0.9)	0	(0.0)
Irritability	6	(0.9)	0	(0.0)
Palpitations	6	(0.9)	0	(0.0)
Insomnia	5	(0.7)	0	(0.0)
Dizziness	4	(0.6)	0	(0.0)
Fatigue	4	(0.6)	0	(0.0)
Hyperhidrosis	4	(0.6)	0	(0.0)
Nervousness	4	(0.6)	0	(0.0)
Panic attack	4	(0.6)	1	(0.4)
Restlessness	4	(0.6)	0	(0.0)
Tachycardia	4	(0.6)	0	(0.0)
Aggression	3	(0.4)	0	(0.0)
Apathy	3	(0.4)	0	(0.0)
Blood pressure increased	3	(0.4)	0	(0.0)
Dry mouth	3	(0.4)	0	(0.0)
Dyspnoea	3	(0.4)	0	(0.0)
Sleep disorder	3	(0.4)	0	(0.0)
Anger	2	(0.3)	0	(0.0)
Blood creatine phosphokinase increased	2	(0.3)	0	(0.0)
Constipation	2	(0.3)	0	(0.0)
Disturbance in attention	2	(0.3)	0	(0.0)
Flat affect	2	(0.3)	0	(0.0)
Heart rate increased	2	(0.3)	0	(0.0)
Impulse-control disorder	2	(0.3)	0	(0.0)
Loss of libido	2	(0.3)	0	(0.0)
Major depression	2	(0.3)	0	(0.0)
Tremor	2	(0.3)	0	(0.0)
Weight decreased	2	(0.3)	0	(0.0)

AEs are sorted by descending frequency within "All Ritalin LA" group.
AEs that occurred after patient's treatment end date are not included.

Other Relevant Findings

Number (%) of patients with newly occurring clinically notable abnormalities in Hematology/Chemistry values during Period 1 by treatment (Safety analysis set for Period 1)

		Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Parameter	**Criterion**	**Total n(%)**	**Total n(%)**	**Total n(%)**	**Total n(%)**	**Total n(%)**
Glucose	< 2.78 mmol/L	17 0 (0.0)	26 0 (0.0)	28 1 (3.6)	71 1 (1.4)	15 0 (0.0)
	> 11.1 mmol/L	17 0 (0.0)	26 0 (0.0)	28 2 (7.1)	71 2 (2.8)	15 0 (0.0)
SGPT (ALT)	> 110 U/L	17 0 (0.0)	25 0 (0.0)	28 1 (3.6)	70 1 (1.4)	15 0 (0.0)
WBC (total)	> 15 10^9/L	17 0 (0.0)	26 0 (0.0)	28 1 (3.6)	71 1 (1.4)	15 0 (0.0)

Consider patients who discontinued in Period 1.
Total = Number of patients with evaluable criterion (i.e. 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 i.e. whose post-baseline laboratory values are clinically notably abnormal.
Patients are assigned to the treatment they were receiving during Period 1.
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 during Period 2 by treatment (Safety analysis set for Period 2)

Parameter	Criterion	Total	n(%)
Creatinine	> 176.8 µmol/L	544	2 (0.4)
Platelet count (direct)	< 100 10^9/L	538	1 (0.2)
Gamma Glutamyltransferase	> 120 U/L	542	1 (0.2)
Glucose	< 2.78 mmol/L	542	2 (0.4)
	> 11.1 mmol/L	542	1 (0.2)
Haematocrit	< 0.3 v/v	537	1 (0.2)
LDH	> 500 U/L	529	2 (0.4)
Lymphocytes	< 10 %	537	3 (0.6)
	> 60 %	537	2 (0.4)
Potassium	> 6 U/L	544	1 (0.2)
SGOT (AST)	> 100 U/L	545	4 (0.7)
SGPT (ALT)	> 110 U/L	545	2 (0.4)
Sodium	> 154 U/L	546	1 (0.2)
Uric Acid	> 594.8 mmol/L	544	1(0.2)

Total = Number of patients with evaluable criterion (i.e. 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 i.e. whose post-baseline laboratory values are clinically notably abnormal.
Denominators for the percentage calculations are the number of patients with evaluable criterion.

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Number (%) of patients with newly occurring clinically notable abnormalities in Hematology/Chemistry values during Period 3 by treatment (Safety analysis set for Period 3)

Parameter	Criterion	Ritalin LA 40 mg Total n(%)	Ritalin LA 60 mg Total n(%)	Ritalin LA 80 mg Total n(%)	All Ritalin LA Total n(%)	Placebo Total n(%)
Creatinine	> 176.8 umol/L	100 0 (0.0)	118 0 (0.0)	108 0 (0.0)	326 0 (0.0)	106 1 (0.9)
Eosinophils	> 10 %	99 1(1.0)	118 1 (0.8)	107 0 (0.0)	324 2 (0.6)	104 1 (1.0)
Gamma Glutamyltransferase	> 120 U/L	100 0 (0.0)	118 0 (0.0)	105 1 (1.0)	323 1 (0.3)	104 0 (0.0)
Glucose	< 2.78 mmol/L	98 0 (0.0)	117 0 (0.0)	108 0 (0.0)	323 0 (0.0)	103 1 (1.0)
Haematocrit	< 0.3 v/v	99 0 (0.0)	117 0 (0.0)	108 1 (0.9)	324 1 (0.3)	106 0 (0.0)
Lymphocytes	< 10 %	99 1 (1.0)	118 0 (0.0)	108 0 (0.0)	325 1 (0.3)	106 0(0.0)
Potassium	> 6 U/L	100 0 (0.0)	117 0 (0.0)	108 0 (0.0)	325 0 (0.0)	105 1 (1.0)
SGOT (AST)	> 100 U/L	100 0 (0.0)	117 0 (0.0)	108 1 (0.9)	325 1 (0.3)	104 0 (0.0)
SGPT (ALT)	> 110 U/L	100 0 (0.0)	117 0 (0.0)	108 1 (0.9)	325 1 (0.3)	104 0 (0.0)
Bilirubin (total)	> 34.2 umol/L	100 0 (0.0)	119 0 (0.0)	108 1 (0.9)	327 1 (0.3)	106 0 (0.0)
Uric Acid	> 594.8 mmol/L	100 0 (0.0)	119 0 (0.0)	107 1 (0.9)	326 1 (0.3)	105 0 (0.0)

Total = Number of patients with evaluable criterion (i.e. 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 i.e. whose post-baseline laboratory values are clinically notably abnormal.
Patients are assigned to the treatment they were receiving during Period 3.
Denominators for the percentage calculations are the number of patients with evaluable criterion.

NOVARTIS

Number (%) of patients with clinically notable changes in vital signs at any time during Period 1 by treatment (Safety analysis set for Period 1)

		Ritalin LA 40 mg n % N=180 n(%)		Ritalin LA 60 mg n % N=181 n(%)		Ritalin LA 80 mg n % N=181 n(%)		All Ritalin LA n % N=542 n(%)		Placebo N=180 n(%)	
Systolic BP (mmHg)	High	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Low	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
	High and Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	2	(1.1)	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)
Diastolic BP (mmHg)	High	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)	0	(0.0)
	Low	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	0	(0.0)
	High and Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	0	(0.0)	1	(0.6)	1	(0.6)	2	(0.4)	0	(0.0)
Heart Rate (bpm)	High	0	(0.0)	3	(1.7)	2	(1.1)	5	(0.9)	0	(0.0)
	Low	1	(0.6)	1	(0.6)	0	(0.0)	2	(0.4)	1	(0.6)
	High and Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	1	(0.6)	4	(2.2)	2	(1.1)	7	(1.3)	1	(0.6)
Weight (kg)	Decrease	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Consider patients who discontinued in Period 1.
N: the number of patients with both baseline 1 and non-missing post-baseline measurements.
n: the number of patients with one or more notable change during the period.
Patients who discontinued in Period 1 are considered. Only values within the time window of the scheduled visit are used in the analyses.
Notable ranges:
Heart Rate >120 bpm and increase by 15; < 50 bpm and decrease by 15
Systolic Blood Pressure >180 mmHg and increase by 20; < 90 mmHg and decrease by 20
Diastolic Blood Pressure >105 mmHg and increase by 15; < 50 mmHg and decrease by 15
Weight ≥7% decrease from Baseline weight

NOVARTIS

Number (%) of patients with clinically notable changes in vital signs at any time during Period 2 by treatment (Safety analysis set for Period 2)

		All Ritalin LA n % N=580 n(%)	
Systolic BP (mmHg)	High	0	(0.0)
	Low	0	(0.0)
	High and Low	0	(0.0)
	Total	0	(0.0)
Diastolic BP (mmHg)	High	2	(0.4)
	Low	1	(0.2)
	High and Low	0	(0.0)
	Total	3	(0.5)
Heart Rate (bpm)	High	1	(0.2)
	Low	2	(0.4)
	High and Low	0	(0.0)
	Total	3	(0.5)
Weight (kg)	Decrease	36	(7.3)

N: the number of patients with both baseline 1 and non-missing post-baseline measurements during Period 2.
n: the number of patients with one or more notable change during the period.
Patients who discontinued in Period 2 are considered.
Only values within the time window of the scheduled visit are used in the analyses.
Notable ranges:
Heart Rate >120 bpm and increase by 15; < 50 bpm and decrease by 15
Systolic Blood Pressure >180 mmHg and increase by 20; < 90 mmHg and decrease by 20
Diastolic Blood Pressure >105 mmHg and increase by 15; < 50 mmHg and decrease by 15
Weight ≥7% decrease from Baseline weight

NOVARTIS

Number (%) of patients with clinically notable changes in vital signs at any time during Period 3 by treatment (Safety analysis set for Period 3)

		Ritalin LA 40 mg n % N=113 n(%)		Ritalin LA 60 mg n % N=130 n(%)		Ritalin LA 80 mg n % N=118 n(%)		All Ritalin LA n % N=361 n(%)		Placebo N=121 n(%)	
Systolic BP (mmHg)	High	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Low	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
	High&Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Diastolic BP (mmHg)	High	1	(0.9)	0	(0.0)	3	(2.5)	4	(1.1)	0	(0.0)
	Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	High&Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	1	(0.9)	0	(0.0)	3	(2.5)	4	(1.1)	0	(0.0)
Heart Rate (bpm)	High	1	(0.9)	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)
	Low	0	(0.0)	0	(0.0)	3	(2.5)	3	(0.8)	0	(0.0)
	High&Low	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	1	(0.9)	0	(0.0)	3	(2.5)	4	(1.1)	0	(0.0)
Weight (kg)	Decrease	4	(3.8)	4	(3.3)	7	(6.5)	15	(4.5)	0	(0.0)

N: the number of patients with both baseline 2 and non-missing post-baseline measurements during Period 3.
n: the number of patients with one or more notable change during the period.
Patients who discontinued in Period 3 are considered..
Only values within the time window of the scheduled visit are used in the analyses.
Notable ranges:
Heart Rate >120 bpm and increase by 15; < 50 bpm and decrease by 15
Systolic Blood Pressure >180 mmHg and increase by 20; < 90 mmHg and decrease by 20
Diastolic Blood Pressure >105 mmHg and increase by 15; < 50 mmHg and decrease by 15
Weight ≥7% decrease from Baseline weight

NOVARTIS

Number (%) of patients with ECG abnormalities during Period 1 by treatment (Safety analysis set for Period 1)

Abnormality type/Finding	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Any ECG abnormality	**2**	**(8.3)**	**7**	**(20.0)**	**4**	**(11.8)**	**13**	**(14.0)**	**8**	**(30.8)**
Rhythm										
Sinus bradycardia	0	(0.0)	2	(5.7)	0	(0.0)	2	(2.2)	0	(0.0)
Sinus tachycardia	0	(0.0)	1	(2.9)	1	(2.9)	2	(2.2)	0	(0.0)
Ectopic Supraventricular Rhythm	0	(0.0)	1	(2.9)	0	(0.0)	1	(1.1)	0	(0.0)
Conduction										
First degree AV block	1	(4.2)	2	(5.7)	0	(0.0)	3	(3.2)	1	(3.8)
RBBB	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)
IVCD	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)
LAH	0	(0.0)	1	(2.9)	0	(0.0)	1	(1.1)	1	(3.8)
IRBBB	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(7.7)
ST segment										
Depressed ST segment	1	(4.2)	0	(0.0)	0	(0.0)	1	(1.1)	0	(0.0)
T waves										
Flat T waves	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.8)
Inverted T waves	1	(4.2)	0	(0.0)	1	(2.9)	2	(2.2)	1	(3.8)
ECTOPY										
VPC	0	(0.0)	1	(2.9)	0	(0.0)	1	(1.1)	1	(3.8)
APC	0	(0.0)	0	(0.0)	2	(5.9)	2	(2.2)	1	(3.8)

Consider patients who discontinued in Period 1.
Patients are assigned to the treatment they were receiving in Period 1.
Percentages are based on the number of patients with available data during the period.
APC=atrial premature contraction; AV=atrioventricular; IRBBB=incomplete right bundle branch block; IVCD=intraventricular conduction delay; LAH=left anterior hemiblock; RBBB=right bundle branch block; VPC=ventricular premature contraction.

NOVARTIS

Number (%) of patients with ECG abnormalities during Period 2 by treatment (Safety Analysis Set for Period 2)

Abnormality type/Finding	All Ritalin LA N=580 n	(%)
Any ECG abnormality	**65**	**(11.8)**
Rhythm		
Sinus bradycardia	2	(0.4)
Sinus tachycardia	17	(3.1)
Ectopic Supraventricular Rhythm	4	(0.7)
Conduction		
First degree AV block	12	(2.2)
RBBB	2	(0.4)
IVCD	3	(0.5)
LAH	4	(0.7)
IRBBB	4	(0.7)
ST segment		
Depressed ST segment	2	(0.4)
T waves		
Flat T waves	7	(1.3)
Inverted T waves	6	(1.1)
ECTOPY		
VPC	4	(0.7)
APC	8	(1.4)

APC=atrial premature contraction; AV=atrioventricular; IRBBB=incomplete right bundle branch block; IVCD=intraventricular conduction delay; LAH=left anterior hemiblock; RBBB=right bundle branch block; VPC=ventricular premature contraction.
Patients are assigned to the treatment they were receiving in Period 2.
Patients who discontinued in Period 2 are considered.
Percentages are based on the number of patients with available data during the period.

NOVARTIS

Number (%) of patients with ECG abnormalities during Period 3 by treatment (Safety analysis set for Period 3)

Abnormality type/Finding	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Any ECG abnormality	**12**	**(12.0)**	**6**	**(5.0)**	**16**	**(14.5)**	**34**	**(10.3)**	**11**	**(9.9)**
Rhythm										
Sinus bradycardia	1	(1.0)	1	(0.8)	2	(1.8)	4	(1.2)	3	(2.7)
Sinus tachycardia	5	(5.0)	2	(1.7)	1	(0.9)	8	(2.4)	1	(0.9)
Ectopic Supraventricular Rhythm	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)	0	(0.0)
Conduction										
First degree AV block	1	(1.0)	0	(0.0)	3	(2.7)	4	(1.2)	2	(1.8)
RBBB	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
IVCD	0	(0.0)	1	(0.8)	1	(0.9)	2	(0.6)	2	(1.8)
LAH	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.9)
ST segment										
Depressed ST segment	1	(1.0)	0	(0.0)	1	(0.9)	2	(0.6)	0	(0.0)
T waves										
Flat T waves	1	(1.0)	0	(0.0)	1	(0.9)	2	(0.6)	2	(1.8)
Inverted T waves	0	(0.0)	1	(0.8)	2	(1.8)	3	(0.9)	0	(0.0)
ECTOPY										
VPC	1	(1.0)	1	(0.8)	4	(3.6)	6	(1.8)	0	(0.0)
APC	1	(1.0)	0	(0.0)	2	(1.8)	3	(0.9)	1	(0.9)
Other Arrhythmia	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)	0	(0.0)

APC=atrial premature contraction; AV=atrioventricular; IVCD=intraventricular conduction delay; LAH=left anterior hemiblock; RBBB=right bundle branch block; VPC=ventricular premature contraction.
Patients are assigned to the treatment they were receiving in Period 3.
Percentages are based on the number of patients with available data during the period.
Patients who discontinued in Period 3 are considered.

NOVARTIS

Number (%) of patients with clinically notable changes in ECG during Period 1 by treatment (Safety analysis set for Period 1)

	Ritalin LA 40 mg N=180 n(%)	Ritalin LA 60 mg N=181 n(%)	Ritalin LA 80 mg N=181 n(%)	All Ritalin LA N=542 n(%)	Placebo N=180 n(%)
QT > 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcB > 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTcF > 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QT inc from baseline ≥30 ms	1 (5.6)	7 (23.3)	0 (0.0)	8 (10.3)	1 (5.6)
QTcB inc from baseline ≥30 ms	0 (0.0)	3 (10.0)	3 (10.0)	6 (7.7)	1 (5.6)
QTcF inc from baseline ≥30 ms	0 (0.0)	3 (10.0)	0 (0.0)	3 (3.8)	0 (0.0)
PR inc from baseline > 25% to a value >200 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QRS inc from baseline > 25% to a value >100 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Consider patients who discontinued in Period 1.
Percentages are based on patients with both baseline and post baseline values.

Number (%) of patients with clinically notable changes in ECG during Period 2 by treatment (Safety analysis set for Period 2)

	All Ritalin LA N=580 n(%)
QT > 500 ms	0 (0.0)
QTcB > 500 ms	0 (0.0)
QTcF > 500 ms	0 (0.0)
QT inc from baseline ≥30 ms	25 (5.2)
QTcB inc from baseline ≥30 ms	64 (13.2)
QTcF inc from baseline ≥30 ms	16 (3.3)
PR inc from baseline > 25% to a value >200 ms	0 (0.0)
QRS inc from baseline > 25% to a value >100 ms	0 (0.0)

n: the number of patients meeting the criterion.
Only patients with both baseline and post-baseline measurements are included in the table.
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).
Percentages are based on patients with both baseline and post baseline values.

Number (%) of patients with clinically notable changes in ECG during Period 3 by treatment (Safety analysis set for Period 3)

	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
QT > 500 ms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
QTcB > 500 ms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
QTcF > 500 ms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
QT inc from baseline ≥30 ms	8	(8.1)	12	(10.2)	14	(12.8)	34	(10.4)	26	(24.1)
QTcB inc from baseline ≥30 ms	9	(9.1)	8	(6.8)	7	(6.4)	24	(7.4)	2	(1.9)
QTcF inc from baseline ≥30 ms	3	(3.0)	3	(2.5)	4	(3.7)	10	(3.1)	4	(3.7)
PR inc from baseline > 25% to a value >200 ms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
QRS inc from baseline > 25% to a value >100 ms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Patients are assigned to the treatment they were receiving in Period 3.
Patients who discontinued in Period 3 are considered.
Percentages are based on patients with both baseline and post baseline values.

Date of Clinical Trial Report

7 November 2012

Date Inclusion on Novartis Clinical Trial Results Database

06 August 2013