Clinical trial results:
A randomized, rater-blinded cross-over multicenter study comparing the clinical efficacy of Ritalin® LA (methylphenidate) treatment (20 or 40 mg orally o.d.) in children with ADHD under different breakfast conditions over two weeks

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2006-006441-14
Trial protocol	DE
Global end of trial date	18 December 2007

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CRIT124DDE04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00428792
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	Yes

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the clinical efficacy of a modified-release oral dosage of methylphenidate under nearly fasted conditions and standard breakfast conditions in children with Attention deficit hyperactivity disorder (ADHD) after treatment for one week assessed by weekly teacher-based ratings Fremdbeobachtungsbogen Aufmerksamkeitsdefizit-Hyperaktivitätssyndrom (FBB-ADHS) scale.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	131
Adolescents (12-17 years)	19
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 13 centres in Germany.

Pre-assignment

Screening details:

A total of 159 subjects were screened, of which 150 were randomized to this cross-over study.Remaining 9 subjects were screen failures.

Period 1

Period 1 title	First Intervention Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

The study was considered rater-blinded i.e. teachers and treating physicians. Primary evaluations were carried out by teachers who were blinded to the treatment arms. Individual sets of code-breaker scratch cards containing the actual treatment assignment were prepared for each container of medication and distributed to each investigator. The scratch cards were not to be opened unless an actual emergency occurred, and were returned to sponsor at end of study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Methylphenidate+VLB then Methylphenidate+SB

Arm description:

All subjects who were randomized to treatment sequence 1, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with very light breakfast (VLB) of 150 -180 calories once daily for a week in treatment period 1. In treatment period 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with standard breakfast (SB) of 450 -600 calories once daily for a week.

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	RIT124
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Methylphenidate (20 mg or 40 mg) was administered with VLB or SB once daily for a week.

Arm title	Methylphenidate+SB then Methylphenidate+VLB

Arm description:

All subjects who were randomized to treatment sequence 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week in treatment period 1. In treatment period 2, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week.

Arm type	Active comparator
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	RIT124
Other name	Ritalin LA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Methylphenidate (20 mg or 40 mg) was administered with SB or VLB once daily for a week.

Number of subjects in period 1	Methylphenidate+VLB then Methylphenidate+SB	Methylphenidate+SB then Methylphenidate+VLB
Started	80	70
Completed	79	68
Not completed	1	2
Lack of efficacy	1	2

Period 2

Period 2 title	Second Intervention Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Blinding implementation details:

The study was rater-blinded i.e. teachers and treating physicians. Primary evaluations were carried out by teachers who were blinded to the treatment arms. Individual sets of code-breaker scratch cards containing the actual treatment assignment were prepared for each container of medication and distributed to each investigator. The scratch cards were not to be opened unless an actual emergency occurred, and were returned to sponsor at end of study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Methylphenidate+VLB then Methylphenidate+SB

Arm description:

All subjects who were randomized to treatment sequence 1, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week in treatment period 1. In treatment period 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week.

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	RIT124
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Methylphenidate (20 mg or 40 mg) was administered with VLB or SB once daily for a week.

Arm title	Methylphenidate+SB then Methylphenidate+VLB

Arm description:

All subjects who were randomized to treatment sequence 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week in treatment period 1. In treatment period 2, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week.

Arm type	Active comparator

Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	RIT124
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Methylphenidate (20 mg or 40 mg) was administered with SB or VLB once daily for a week.

Number of subjects in period 2	Methylphenidate+VLB then Methylphenidate+SB	Methylphenidate+SB then Methylphenidate+VLB
Started	79	68
Completed	79	66
Not completed	0	2
Lost to follow-up	-	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Methylphenidate+VLB then Methylphenidate+SB

Reporting group description:

All subjects who were randomized to treatment sequence 1, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with very light breakfast (VLB) of 150 -180 calories once daily for a week in treatment period 1. In treatment period 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with standard breakfast (SB) of 450 -600 calories once daily for a week.

Reporting group title	Methylphenidate+SB then Methylphenidate+VLB

Reporting group description:

All subjects who were randomized to treatment sequence 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week in treatment period 1. In treatment period 2, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week.

Reporting group values	Methylphenidate+VLB then Methylphenidate+SB	Methylphenidate+SB then Methylphenidate+VLB	Total
Number of subjects	80	70	150
Age categorical Units: Subjects			
Children (6-12 years)	80	70	150
Age continuous Units: years			
arithmetic mean	9.6	9.7	
standard deviation	± 1.6	± 1.5	-
Gender categorical Units: Subjects			
Female	25	13	38
Male	55	57	112

End points

End points reporting groups

Reporting group title	Methylphenidate+VLB then Methylphenidate+SB

Reporting group description:

All subjects who were randomized to treatment sequence 1, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with very light breakfast (VLB) of 150 -180 calories once daily for a week in treatment period 1. In treatment period 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with standard breakfast (SB) of 450 -600 calories once daily for a week.

Reporting group title	Methylphenidate+SB then Methylphenidate+VLB

Reporting group description:

All subjects who were randomized to treatment sequence 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week in treatment period 1. In treatment period 2, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week.

Reporting group title	Methylphenidate+VLB then Methylphenidate+SB

Reporting group description:

All subjects who were randomized to treatment sequence 1, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week in treatment period 1. In treatment period 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week.

Reporting group title	Methylphenidate+SB then Methylphenidate+VLB

Reporting group description:

All subjects who were randomized to treatment sequence 2, subjects received methylphenidate (20 mg or 40 mg depending on their previous treatment) with SB of 450 -600 calories once daily for a week in treatment period 1. In treatment period 2, received methylphenidate (20 mg or 40 mg depending on their previous treatment) along with VLB of 150 -180 calories once daily for a week.

Subject analysis set title	Methylphenidate + SB
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received methylphenidate along with SB of 450-600 calories once daily for two weeks in this cross-over study.

Subject analysis set title	Methylphenidate + VLB
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who received methylphenidate (20 mg or 40 mg) with VLB of 150-180 calories once daily for two weeks in this cross-over study.

Primary: Fremdbeurteilungsbogen for attention deficit/hyperactivity disorder (FBB-ADHS) rating total score in Intent to Treat population

End point title	Fremdbeurteilungsbogen for attention deficit/hyperactivity disorder (FBB-ADHS) rating total score in Intent to Treat population

End point description:

The FBB-ADHS was a 20-item rating scale, where each item described a typical ADHD symptoms. The 20 items were divided into 3 subscales: attention deficit (9 items), hyperactivity (7 items), and impulsiveness (4 items). Each item was rated on a scale of 0 up to 3 (0: not at all, 3: very much). A total score was calculated by averaging out the scores of 20 items and ranged from 0 to 3. A higher score signifies more severe symptoms of ADHD. The analysis was performed in Intention to treat population, defined as all randomized subjects with at least one post-baseline measurement of the primary endpoint in both study periods.

End point type	Primary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144[1]	144[2]		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.97 (± 0.63)	1.01 (± 0.63)		

Notes:

[1] - Intent to treat population

[2] - Intent to treat population

Statistical analyses

Statistical analysis title	Test for non-inferiority
Comparison groups	Methylphenidate + VLB v Methylphenidate + SB
Number of subjects included in analysis	288
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [3]
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.02

Notes:

[3] - [4] - 1-sided p-value of the test for non-inferiority (Δ=0.3 points)

Secondary: FBB-ADHS teacher-rated attention deficit subscale score

End point title	FBB-ADHS teacher-rated attention deficit subscale score

End point description:

The FBB-ADHS was a 20-item rating scale, where each item described a typical ADHD symptom. Teacher rated 9 items of the attention deficit subscale of FBB-ADHS on a scale of 0 up to3 (0: not at all to 3: very much). A total score was calculated by averaging out the scores of 9 items and ranged from 0 to 3. A higher score signifies more severe symptoms of ADHD. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.19 (± 0.68)	1.23 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: FBB-ADHS teacher-rated hyperactivity subscale score

End point title	FBB-ADHS teacher-rated hyperactivity subscale score

End point description:

The FBB-ADHS was a 20-item rating scale, where each item described a typical ADHD symptom. Teacher rated 7 items of the hyperactivity subscale of FBB-ADHS on a scale of 0 up to 3 (0: not at all to 3: very much). A total score was calculated by averaging out the scores of 7 items and ranged from 0 to 3. A higher score signifies more severe symptoms of ADHD. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.72 (± 0.7)	0.75 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: FBB-ADHS teacher-rated impulsiveness subscale score

End point title	FBB-ADHS teacher-rated impulsiveness subscale score

End point description:

The FBB-ADHS was a 20-item rating scale, where each item described a typical ADHD symptom. Teacher rated 4 items of the impulsiveness subscale of FBB-ADHS on a scale of 0 up to 3 (0: not at all to 3: very much). A total score was calculated by averaging out the scores of 4 items and ranged from 0 to 3. A higher score signifies more severe symptoms of ADHD. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	144	144		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.93 (± 0.92)	0.99 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: FBB-ADHS parent-rated total score

End point title	FBB-ADHS parent-rated total score

End point description:

The FBB-ADHS was a 20-item rating scale, where each item described a typical ADHD symptom. The 20 items were divided into 3 subscales: attention deficit (9 items), hyperactivity (7 items), and impulsiveness (4 items). Each item was rated on a scale of 0 up to 3 (0: not at all, 3: very much). A total score was calculated by averaging out the scores of 20 items and ranged from 0 to 3. A higher score signifies more severe symptoms of ADHD. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	144		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.15 (± 0.6)	1.11 (± 0.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Math test objective rating score

End point title	Math test objective rating score

End point description:

A standardized 10-Minute Math Test, consisting of math problems presented in ascending order of difficulty (requiring addition, subtraction, multiplication and division calculations respectively) was provided to the subjects. Test difficulty was altered for subjects at different skill levels and ages. The number of problems attempted and the number of problems correctly answered were generated as objective measures related to academic productivity. The test was carried out under supervision of a trained teacher. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 1, Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	142		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Problems attempted	116.3 (± 56.14)	118.1 (± 57.74)		
Problems solved	106.7 (± 58.34)	108.6 (± 60.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical global impression severity (CGI-S) physician-rated score

End point title	Clinical global impression severity (CGI-S) physician-rated score

End point description:

The CGI scale was utilized to assess the global severity of illness (CGI-S). The physician provided rating based on one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Ratings were on a 7-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill subjects. The rating was based upon the average observed and reported symptoms, behavior, and function in the past 7 days. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	143		
Units: Units on a scale				
arithmetic mean (standard deviation)	2.75 (± 1.45)	2.74 (± 1.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical global impression improvement (CGI-I) physician-rated score

End point title	Clinical global impression improvement (CGI-I) physician-rated score

End point description:

The CGI-I scale was utilized to assess improvement (change in state) of illness. The rating was based on the investigator answering one question: "Compared to the patient's condition prior to medication, this patient's condition is: 1=very much improved since the initiation of treatment; 2=much improved; 3=minimally improved; 4=no change from baseline (the initiation of treatment); 5=minimally worse; 6= much worse; 7=very much worse since the initiation of treatment." The investigator compared the patient's overall clinical condition to week just prior to the initiation of medication. The analysis was performed in ITT population.

End point type	Secondary

End point timeframe:

Day 8, Day 15

End point values	Methylphenidate + VLB	Methylphenidate + SB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	142		
Units: Units on a scale				
arithmetic mean (standard deviation)	3.49 (± 1.08)	3.56 (± 1.18)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Total

Reporting group description:

All subjects who received methylphenidate along with breakfast once daily for two weeks in this cross-over study.

Reporting group title	Methylphenidate + SB

Reporting group description:

All subjects who received methylphenidate along with SB of 450-600 calories once daily for two weeks in this cross-over study.

Reporting group title	Methylphenidate + VLB

Reporting group description:

All subjects who received methylphenidate (20 mg or 40 mg) with VLB of 150-180 calories once daily for two weeks in this cross-over study.

Serious adverse events	Total	Methylphenidate + SB	Methylphenidate + VLB
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	0 / 148 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Total	Methylphenidate + SB	Methylphenidate + VLB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 150 (12.67%)	9 / 149 (6.04%)	11 / 148 (7.43%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	8 / 150 (5.33%)	3 / 149 (2.01%)	6 / 148 (4.05%)
occurrences (all)	9	3	6
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	9 / 150 (6.00%)	4 / 149 (2.68%)	5 / 148 (3.38%)
occurrences (all)	9	4	5
NAUSEA			
subjects affected / exposed	8 / 150 (5.33%)	4 / 149 (2.68%)	4 / 148 (2.70%)
occurrences (all)	8	4	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2007	1. The study completion visits for the different extension phases were harmonized. 2. The definition of the per-protocol population was modified by adding the breakfast compliance for inclusion in the per-protocol analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: