Clinical trial results:
An open-label, behavioral-treatment-controlled evaluation of the effects of extended release methylphenidate (Ritalin® LA) on the frequency of cytogenetic abnormalities in children 6 – 12 years of age with attention deficit hyperactivity disorder (ADHD) followed by an observation phase up to 24-months

Summary

EudraCT number	2015-004444-19
Trial protocol	Outside EU/EEA
Global end of trial date	05 March 2008

Results information

Result version number	v1 (current)
This version publication date	21 December 2016
First version publication date	21 December 2016

Trial information

Trial identification

Sponsor protocol code	CRIT124D2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00409708
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 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the frequency of chromosomal abnormalities (chromosomal aberrations per 100 cells excluding gaps and micronuclei per 1000 binucleated cells) before and after three months of treatment with Ritalin® LA (extended release MPH) and behavioral treatment, compared to behavioral treatment alone.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2006
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	United States: 109
Worldwide total number of subjects	109
EEA total number of subjects	0

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)	104
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 142 participants were screened for the study but only 109 were randomized to treatment

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ritalin LA Plus Behavior Therapy

Arm description:

10-60 mg/day

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

Dosage and administration details:

10 mg/day to 60 mg/day

Arm title	Behavior Therapy

Arm description:

0 mg/day Ritalin LA

Arm type	Behavioral therapy

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Ritalin LA Plus Behavior Therapy	Behavior Therapy
Started	53	56
Completed	38	39
Not completed	15	17
Consent withdrawn by subject	3	8
Administrative problems	5	-
Lost to follow-up	-	6
Abnormal test procedure result(s)	1	-
Protocol deviation	6	2
Lack of efficacy	-	1

Period 2	
Period 2 title	Washout
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Ritalin LA Plus Behavior Therapy
Arm description: 10-60 mg/day	
Arm type	Experimental
Investigational medicinal product name	methylphenidate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 10 mg/day to 60 mg/day	
Arm title	Behavior Therapy
Arm description: 0 mg/day Ritalin LA	
Arm type	Behavioral Therapy
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Ritalin LA Plus Behavior Therapy	Behavior Therapy
Started	38	39
Completed	17	29
Not completed	21	10
Consent withdrawn by subject	11	5
Lost to follow-up	1	3
Lack of efficacy	9	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ritalin LA Plus Behavior Therapy
Reporting group description: 10-60 mg/day	
Reporting group title	Behavior Therapy
Reporting group description: 0 mg/day Ritalin LA	

Reporting group values	Ritalin LA Plus Behavior Therapy	Behavior Therapy	Total
Number of subjects	53	56	109
Age Categorical Units: participants			
<=18 years	53	56	109
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	8.3	8.5	
standard deviation	± 1.75	± 1.91	-
Gender, Male/Female Units: participants			
Female	21	18	39
Male	32	38	70

Subject analysis sets	
Subject analysis set title	Ritalin LA plus behavior therapy
Subject analysis set type	Safety analysis
Subject analysis set description: 10-60 mg/day	
Subject analysis set title	Behavior therapy
Subject analysis set type	Safety analysis
Subject analysis set description: 0 mg/day Ritalin LA	

Reporting group values	Ritalin LA plus behavior therapy	Behavior therapy	
Number of subjects	52	52	
Age Categorical Units: participants			
<=18 years	52	52	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	8.3	8.5	
standard deviation	± 1.75	± 1.91	

Gender, Male/Female Units: participants			
Female	21	17	
Male	31	35	

End points

End points reporting groups

Reporting group title	Ritalin LA Plus Behavior Therapy
Reporting group description: 10-60 mg/day	
Reporting group title	Behavior Therapy
Reporting group description: 0 mg/day Ritalin LA	
Reporting group title	Ritalin LA Plus Behavior Therapy
Reporting group description: 10-60 mg/day	
Reporting group title	Behavior Therapy
Reporting group description: 0 mg/day Ritalin LA	
Subject analysis set title	Ritalin LA plus behavior therapy
Subject analysis set type	Safety analysis
Subject analysis set description: 10-60 mg/day	
Subject analysis set title	Behavior therapy
Subject analysis set type	Safety analysis
Subject analysis set description: 0 mg/day Ritalin LA	

Primary: The number of chromosomal aberrations per 100 cells excluding gaps at baseline and at the end of treatment i.e day 84 (week 12)

End point title	The number of chromosomal aberrations per 100 cells excluding gaps at baseline and at the end of treatment i.e day 84 (week 12)

End point description:

The number of chromosomal aberrations per 100 cells excluding gaps at Baseline (n=33, n=32) and at Week 12 (n=33, n=32) was counted in blood samples cultured for 48 hours using a standard protocol. The types of abnormalities included translocations (reciprocal and non-reciprocal), insertions, dicentrics, fragments, inversions, chromatid exchanges (quadriradials and triradials), breaks, and other unusual observations, eg, aneuploidy, tetraploidy or endoreduplication.

End point type	Primary

End point timeframe:

baseline and at end of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	52		
Units: number of abnormalities				
least squares mean (standard error)				
Baseline	0.6 (± 0.24)	0.44 (± 0.14)		
At the end of treatment i.e. week12: Mean	0.63 (± 0.07)	0.74 (± 0.11)		

Statistical analyses

Statistical analysis title	Ratio of Day 84 (Week 12) to Baseline

Statistical analysis description:

Inferential analysis of change from baseline reported in least square means for cytogenetic endpoints by visit by treatment

Comparison groups	Ritalin LA plus behavior therapy v Behavior therapy
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Poisson model
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	3.4
Variability estimate	Standard error of the mean
Dispersion value	0.64

Notes:

[1] - Ratio less than 1 indicates a decrease from Baseline to Day 84 (Week 12). Least squares means of the ratio of Day 84 (Week 12) to Baseline in either group were estimated by a Poisson model using GEE estimation techniques that included factors for time, treatment by time interaction, sex and age group as covariates.

Primary: The Number of Micronuclei per 1000 Binucleated Cells Endpoints at Baseline and at the End of Treatment i.e Day 84 (Week 12)

End point title	The Number of Micronuclei per 1000 Binucleated Cells Endpoints at Baseline and at the End of Treatment i.e Day 84 (Week 12)[2]

End point description:

The number of micronuclei per 1000 binucleated cells was measured at Baseline (n=34 , n=29) and at the end of treatment, Week 12 (n =34, n= 29), in blood cultured for 48 hours using a standard protocol.

End point type	Primary

End point timeframe:

baseline and at end of treatment (Week 12)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary analysis performed per groups

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	35		
Units: number of micronuclei per 1000 binucleat				
arithmetic mean (standard deviation)				

At Baseline	5.76 (± 2.336)	5.71 (± 4.535)		
At the end of treatment i.e. Week 12	3.63 (± 2.053)	4.19 (± 2.737)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Sister Chromatoid Exchanges Per Cell

End point title	Number of Sister Chromatoid Exchanges Per Cell

End point description:

Blood collected at baseline (n=20, n=14) and at the end of treatment, Week 12, (n= 20, n= 14) was cultured for 48 hours using a standard protocol. Giemsa staining and/or fluorescent in situ hybridization (FISH) chromosome painting was done on the cells in metaphase and the number of chromatoid exchanges per cell was recorded by blinded raters.

End point type	Secondary

End point timeframe:

baseline and at end of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: number of sister chromatoid exchanges				
arithmetic mean (standard deviation)				
Baseline	7.807 (± 0.9228)	7.533 (± 1.216)		
At the end of treatment i.e. Week12	7.213 (± 1.0408)	7.303 (± 0.6165)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic/pharmacodynamic relationship of methylphenidate blood levels and cytogenetic changes

End point title	Pharmacokinetic/pharmacodynamic relationship of methylphenidate blood levels and cytogenetic changes

End point description:

Since no cytogenetic effects were observed, blood samples were not analyzed for pharmacokinetics/pharmacodynamics.

End point type	Secondary

End point timeframe:

End of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: Number				

Notes:

[3] - analysis not completed as per protocol

[4] - analysis not completed as per protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment (Week 12) on the Conners' ADHD/DSM-IV Scale for Parents (CADS-P)

End point title	Change from baseline to end of treatment (Week 12) on the Conners' ADHD/DSM-IV Scale for Parents (CADS-P)

End point description:

Parents completed the Conners' ADHD/DSM-IV Scale for Parents (CADS-P) consisting of the ADHD Index (12 items) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)(18 items). Parents rated their child's behavior of the previous week from a list of common problems. When asked "How much of a problem has this been in the last week?" parents selected 0 = none, not at all, seldom, or very infrequently; 3 = very much true, or it occurs very often or frequently; or 1 or 2 for ratings in between. A score of 50 is considered normal and more than 70 markedly atypical.

End point type	Secondary

End point timeframe:

Baseline to end of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: Units on a rating scale				
arithmetic mean (standard deviation)	-17 (± 11.23)	-7 (± 9.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to the end of treatment (Week 12) on the global improvement rating of the Clinical Global Impression scale (CGI-I)

End point title	Change from baseline to the end of treatment (Week 12) on the global improvement rating of the Clinical Global Impression scale (CGI-I)

End point description:

The Clinical Global Impression scale (CGI-I) is a clinician-rated instrument designed to assess the overall change of illness relative to baseline. The CGI-I consists of 7 ratings as follows: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. CGI-I assessments are relative to the patient's status at the Baseline visit.

End point type	Secondary

End point timeframe:

From baseline to the end of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: Units on a rating scale				
arithmetic mean (standard deviation)	1.9 (± 0.81)	3 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to the end of treatment (Week 12) on the severity of illness rating of the Clinical Global Impression scale (CGI-S)

End point title	Change from baseline to the end of treatment (Week 12) on the severity of illness rating of the Clinical Global Impression scale (CGI-S)

End point description:

The Clinical Global Impression scale (CGI-S) is a clinician-rated instrument designed to assess the severity of illness. The CGI-S rating indicates illness severity at each time-point on a scale as follows: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = extremely ill. CGI-S assessments are relative to the patient's status at the Baseline visit.

End point type	Secondary

End point timeframe:

From baseline to the end of treatment (Week 12)

End point values	Ritalin LA plus behavior therapy	Behavior therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: Units on a rating scale				
arithmetic mean (standard deviation)	-1.9 (± 0.98)	-0.6 (± 1.01)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups	
Reporting group title	Behavior
Reporting group description:	
Behavior	
Reporting group title	Ritalin+Behavior
Reporting group description:	
Ritalin+Behavior	

Serious adverse events	Behavior	Ritalin+Behavior	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Behavior	Ritalin+Behavior	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 52 (25.00%)	28 / 52 (53.85%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 52 (1.92%)	7 / 52 (13.46%)	
occurrences (all)	2	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 52 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	4	

Pyrexia			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 52 (3.85%)	5 / 52 (9.62%)	
occurrences (all)	2	5	
Vomiting			
subjects affected / exposed	1 / 52 (1.92%)	5 / 52 (9.62%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 52 (1.92%)	4 / 52 (7.69%)	
occurrences (all)	1	5	
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	0 / 52 (0.00%)	5 / 52 (9.62%)	
occurrences (all)	0	5	
Tearfulness			
subjects affected / exposed	0 / 52 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 52 (7.69%)	4 / 52 (7.69%)	
occurrences (all)	6	4	
Upper respiratory tract infection			
subjects affected / exposed	5 / 52 (9.62%)	6 / 52 (11.54%)	
occurrences (all)	5	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 52 (0.00%)	10 / 52 (19.23%)	
occurrences (all)	0	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2006	To separate the efficacy assessment of the two treatment arms and specify the parameters to be analyzed • To add an additional efficacy questionnaire (SDQ) to the study as exploratory objective • To add GGT to the exclusion criteria • To define the age for the stratification groups • To clarify the different study phases with the different phase- and study-completion visits • To allow patients with co-morbid Oppositional Defiant Disorder (ODD) and with nonsevere Conduct Disorder (CD) into the study • To align the names of the assessments with the names of the corresponding CRF pages and add missing ones to the assessment table • To add and clarify some assessment time-points • To correct the fact that the study data are recorded on paper CRF and not on electronic CRF • To add explanation of the ECG assessments • To correct the strengths of the investigational drug to be dispensed • To add further clarifications to the analysis • To correct that patients, who show chromosomal changes will be followed until it can be determined whether their health is affected • To expand the behavior therapy
22 February 2007	The main purpose of this amendment was to include an observation-phase to follow up those patients who finished the core study 2201 before the last patient was completed. This amendment was designed to obtain additional data concerning potential cytogenetic changes and concurrent medical, social and environmental factors in these patients. These amendments (both before database lock) were not felt to affect the interpretation of study results, as the changes were minor, and occurred at a time when all centers were still recruiting patients into both treatment groups.
23 January 2008	The main purpose of this amendment was to reflect the manner in which cytogenetic data are typically presented in the peer-reviewed literature (Koppen et al, 2007; Lazutka et al. 1999; El-Zein et al, 2005; Neri et al, 2005; Walitza et al, 2007), the final results would be reported as the "number of chromosomal aberrations per 100 cells excluding gaps", and the "number of micronuclei per 1000 binucleated cells". No change was made to sister chromatid exchanges. This amended approach recognized the relatively infrequent cells that contain more than one abnormal event. The actual difference in the means between the two approaches was expected to be modest and probably not biologically meaningful. However, this amended approach was more scientifically accurate. An interim analysis confirmed that the power of the sample size calculation based on number of abnormal events per number of cells (ie: number of CAs/200 cells, number of MNs/2000 binucleated cells) was similar compared to the original calculation, that was based on the number of cells with aberrations.

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.

Since no cytogenetic effects were observed, blood samples were not analyzed for pharmacokinetics/pharmacodynamics.

Notes: