Clinical trial results:
Efficacy and learning skill after OROS Methylphenidate treatment in adolescents with Attention-Deficit/Hyperactivity Disorder: A 12-week, multi-center, open-label study

Summary

EudraCT number	2015-001084-39
Trial protocol	Outside EU/EEA
Global end of trial date	23 April 2010

Results information

Result version number	v2 (current)
This version publication date	01 July 2016
First version publication date	13 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	CONCERTAATT4082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01060150
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research and Development
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group-JB BV, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Janssen Research and Development, ClinicalTrialsEU@its.jnj.com

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	23 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to identify efficacy of 12-week treatment of open-Labeled Osmotic Release Oral System (OROS) methylphenidate by changes of K-ADHD Rating Scale (K-ARS) and Clinical Global Impression – Severity (CGI) scores in Korean Attention Deficit Hyperactivity Disorder (ADHD) adolescents and to evaluate by changes of Learning Skill Test (LST) scores whether there was a change in learning skill in adolescents affected by drug treatment.

Protection of trial subjects:

Safety evaluations for this study included the monitoring of adverse events, clinical laboratory tests (hematology, serum chemistry and urinalysis), vital sign measurements, physical examination and electrocardiogram (EKG).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2008
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	Korea, Republic of: 113
Worldwide total number of subjects	113
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)	0
Adolescents (12-17 years)	104
Adults (18-64 years)	9
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 115 subjects were enrolled in this study, of which 23 subjects were terminated early and a total of 92 subjects completed the study.

Pre-assignment

Screening details:

Participants received OROS methylphenidate once daily between 6:30 am and 9:00 am regardless of meals for 12 weeks during the study period. In case of participants who were taking a drug for Attention Deficit Hyperactivity Disorder (ADHD) treatment other than OROS methylphenidate, a washout period was given for one week or more.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	OROS methylphenidate

Arm description:

OROS methylphenidate (or methylphenidate hydrochloride) once daily between 6:30 am and 9:00 am regardless of meals for 12 weeks during the study period.

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

Dosage and administration details:

CONCERTA capsule 72 mg orally.

Number of subjects in period 1	OROS methylphenidate
Started	113
Completed	92
Not completed	21
Consent withdrawn by subject	8
Adverse event, non-fatal	6
Lost to follow-up	1
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	OROS methylphenidate
Reporting group description:	
OROS methylphenidate (or methylphenidate hydrochloride) once daily between 6:30 am and 9:00 am regardless of meals for 12 weeks during the study period.	

Reporting group values	OROS methylphenidate	Total	
Number of subjects	113	113	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	104	104	
Adults (18-64 years)	9	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	15.2		
standard deviation	± 1.43	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	86	86	

End points

End points reporting groups

Reporting group title	OROS methylphenidate

Reporting group description:

OROS methylphenidate (or methylphenidate hydrochloride) once daily between 6:30 am and 9:00 am regardless of meals for 12 weeks during the study period.

Primary: Korean Version of the Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale (K-ARS) Score

End point title	Korean Version of the Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale (K-ARS) Score[1]

End point description:

The K-ARS is a rating scale that is used for the ADHD diagnosis and the assessment of treatment efficacy and comprises 18 items in total on the basis of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), each item being rated from 0-3 points. The total score ranges from 0-54 with 0=normal and 54=severe condition. Intent-to-treat (ITT) population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline.

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[1] - 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: Descriptive statistics were done, no inferential statistical analyses were performed

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	27.58 (± 8.92)			
Week 12	11.78 (± 7.64)			

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Global Impression - Severity (CGI-S) Score

End point title	Clinical Global Impression - Severity (CGI-S) Score[2]

End point description:

The CGI-S rating scale is a 7 point global assessment that measures the clinician's impression of the severity of illness exhibited by a participant. A rating of 1 is equivalent to "Normal, not at all ill" and a rating of 7 is equivalent to "Among the most extremely ill participants". Higher scores indicate worsening. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline.

End point type	Primary

End point timeframe:

Baseline and 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: Descriptive statistics were done, no inferential statistical analyses were performed

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	4.88 (± 0.79)			
Week 12	2.81 (± 1.12)			

Statistical analyses

No statistical analyses for this end point

Primary: Clinical Global Impression - Improvement (CGI-I) Score

End point title	Clinical Global Impression - Improvement (CGI-I) Score[3]

End point description:

The CGI-I is a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analysed for this endpoint.

End point type	Primary

End point timeframe:

Week 12

Notes:

[3] - 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: Descriptive statistics were done, no inferential statistical analyses were performed

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	103			
Units: units on a scale				
arithmetic mean (standard deviation)	2.14 (± 0.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Learning Skill Test (LST) Total Score

End point title	Learning Skill Test (LST) Total Score

End point description:

The LST measures learning ability of student. This scale is composed of 7 sections: self-control, participation, task accomplishment, reading, writing, test taking and information processing. It consists of 70 items for middle school student (age 13-15 years) and 80 items for high school student (age 16-18 years). Each item is rated on a 5-point Likert scale ranging from 1 (never) to 5 (always). The total score range is 70-350 for middle school version and 80-400 for high school version where higher score indicates better ability for learning. In result analysis, each sub-score and total score was converted to T-score for normalization. The T-score is from 1 to 100 with a mean of 50. Higher score indicates better ability for learning. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	98[4]			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	40.97 (± 11.07)			
Week 12	49.61 (± 11.57)			

Notes:

[4] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnostic System (ADS) Test Result for Omission Errors and Commission Errors

End point title	Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnostic System (ADS) Test Result for Omission Errors and Commission Errors

End point description:

The ADS is composed of 4 factors: omission/missing frequency to measure attention dispersibility; false alarm/commission frequency to measure impulse; mean response/reaction time to measure the speed of task processing; and the response variability/standard deviation of response time to measure the consistency of attention. The total value for both, omission errors and commission errors, ranges from 0-100 errors where high value indicates worsening attention. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: units on a scale				
arithmetic mean (standard deviation)				
Omission errors: Baseline	58.88 (± 27.35)			
Omission errors: Week 12	57.4 (± 48.79)			
Commission errors: Baseline	62.39 (± 32.32)			
Commission errors: Week 12	51.7 (± 21.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnostic System (ADS) Test Score for Reaction Time and Response Variability

End point title	Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnostic System (ADS) Test Score for Reaction Time and Response Variability

End point description:

The ADS is composed of 4 factors: omission/missing frequency to measure attention dispersibility; false alarm/commission frequency to measure impulse; mean response/reaction time to measure the speed of task processing; and the response variability/standard deviation of response time to measure the consistency of attention. The score range for both, reaction time and response variability, is 0-100. High score indicates worsening attention. If one or over factor's score is over 65 point, the participant is resulted in having attention deficit. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: units on a scale				
arithmetic mean (standard deviation)				
Reaction time average: Baseline	54.32 (± 15.45)			
Reaction time average: Week 12	49.73 (± 26.33)			

Response variability: Baseline	85.77 (± 60.21)			
Response variability: Week 12	59.42 (± 64.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Digit Span Test Score

End point title	Digit Span Test Score

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: units on a scale				
arithmetic mean (standard deviation)				
Forward: Baseline	11.19 (± 2.92)			
Forward: Week 12	11.56 (± 2.9)			
Backward: Baseline	7.09 (± 2.39)			
Backward: Week 12	7.32 (± 2.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Finger Window (FW) Test Score

End point title	Finger Window (FW) Test Score

End point description:

In Finger Window (FW) test, a participant shows memory of a demonstrated visual pattern using an 8x11 inch plastic template containing 9 asymmetrically located holes. The examiner models a given sequence of holes and asks the participant to imitate the sequence by placing his/her finger through the same holes in the correct order. The total number of correct sequences constitutes the total score which ranges from 0-24 (forward FW) and 0-28 (backward FW) with higher score indicating a more favorable health state. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: units on a scale				
arithmetic mean (standard deviation)				
Forward FW: Baseline	18.42 (± 4.6)			
Forward FW: Week 12	19.09 (± 4.49)			
Backward FW: Baseline	15.59 (± 4.97)			
Backward FW: Week 12	17.36 (± 3.84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Controlled Oral Words Association Test (COWAT) Score

End point title	Controlled Oral Words Association Test (COWAT) Score

End point description:

This test measures the executive function of the frontal lobe and is consisted of examinations of category/meaning fluency and letter/phoneme fluency. It consisted of three 60 second word generation trials in which the participant orally generates as many words as possible that begin with target letters F, A and S. Dependent variables included total number of acceptable words generated for each target letter and total number of words generated across all three letter trials. Total score was calculated as sum of acceptable words generated, with higher scores indicating better verbal fluency. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: words				
arithmetic mean (standard deviation)				
Category/semantic: Baseline	29.71 (± 5.86)			
Category/semantic: Week 12	30.62 (± 6.16)			
Letter/phenomic: Baseline	28.71 (± 10.82)			
Letter/phenomic: Week 12	33.78 (± 11.18)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stroop Test Result for Reaction Time

End point title	Stroop Test Result for Reaction Time

End point description:

This test consists of 3 trials: color trial (simple execution), word trial (middle execution) and word-color interference trial (interfering execution). In simple execution, participants have to read the written color names of the words independent of the color of the ink. In middle execution, participants have to read words written in black letters. In interfering experiment, participants have to say the color of the letters independent of the written word. This test estimates spending time for execution. High spending time indicates low ability of suppression of automation. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: seconds				
arithmetic mean (standard deviation)				
Simple execution false reaction: Baseline	14.78 (± 3.8)			
Simple execution false reaction: Week 12	13.64 (± 3.27)			
Middle execution false reaction: Baseline	15.88 (± 3.56)			
Middle execution false reaction: Week 12	15.04 (± 4.57)			
Interfering execution false reaction: Baseline	22.12 (± 6.18)			
Interfering execution time: Week 12	19.72 (± 5.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stroop Test Result for False Reaction

End point title	Stroop Test Result for False Reaction

End point description:

This test consists of 3 trials: color trial (simple execution), word trial (middle execution) and word-color interference trial (interfering execution). In simple execution, participants have to read the written color names of the words independent of the color of the ink. In middle execution, participants have to read words written in black letters. In interfering experiment, participants have to say the color of the letters independent of the written word. The total value ranges from 0-24 errors for each execution where high value indicates worsening attention. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: errors				
arithmetic mean (standard deviation)				
Simple execution false reaction: Baseline	0.4 (± 0.77)			
Simple execution false reaction: Week 12	0.16 (± 0.39)			
Middle execution false reaction: Baseline	0.3 (± 0.67)			
Middle execution false reaction: Week 12	0.2 (± 0.47)			
Interfering execution false reaction: Baseline	1.04 (± 1.29)			
Interfering execution false reaction: Week 12	0.84 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stroop Test Score for Ratio Interference

End point title	Stroop Test Score for Ratio Interference

End point description:

Ratio interference is calculated by dividing simple execution time by interfering execution time. The score range is 0-1. Higher value indicates better ability of suppression of automation. ITT population included all participants who received the study drug at least once, satisfied the inclusion/exclusion criteria and had efficacy assessment data at the Baseline. Here 'N' signifies number of participants analyzed for this end point.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	OROS methylphenidate			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	0.7 (± 0.19)			
Week 12	0.72 (± 0.19)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	OROS methylphenidate
Reporting group description:	
OROS methylphenidate (or methylphenidate hydrochloride) once daily between 6:30 am and 9:00 am regardless of meals for 12 weeks during the study period.	

Serious adverse events	OROS methylphenidate		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 113 (1.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 113 (0.88%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 113 (0.88%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	OROS methylphenidate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 113 (86.73%)		
Cardiac disorders			

Palpitations			
subjects affected / exposed	8 / 113 (7.08%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 113 (9.73%)		
occurrences (all)	12		
Headache			
subjects affected / exposed	31 / 113 (27.43%)		
occurrences (all)	34		
Somnolence			
subjects affected / exposed	8 / 113 (7.08%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 113 (11.50%)		
occurrences (all)	14		
Irritability			
subjects affected / exposed	16 / 113 (14.16%)		
occurrences (all)	18		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	19 / 113 (16.81%)		
occurrences (all)	19		
Diarrhoea			
subjects affected / exposed	6 / 113 (5.31%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	32 / 113 (28.32%)		
occurrences (all)	38		
Stomach discomfort			
subjects affected / exposed	15 / 113 (13.27%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	7 / 113 (6.19%)		
occurrences (all)	8		

Psychiatric disorders Anger subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Nervousness subjects affected / exposed occurrences (all)	 6 / 113 (5.31%) 6 9 / 113 (7.96%) 9 9 / 113 (7.96%) 9 37 / 113 (32.74%) 40 7 / 113 (6.19%) 7		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	 6 / 113 (5.31%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 19 / 113 (16.81%) 22		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 66 / 113 (58.41%) 75		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Subject or investigator bias due to placebo effect could not be excluded because this study was conducted in an open-label, single-arm design and learning skill of subjects could not be evaluated by parents and teachers but only depended on subjects.

Notes: