Clinical trial results:
A prospective, open-labeled, multicenter study of optimal dosages of Osmotic Release Oral System (OROS)-methylphenidate in treating children and adolescents with Attention-Deficit Hyperactivity Disorder

Summary

EudraCT number	2015-001218-92
Trial protocol	Outside EU/EEA
Global end of trial date	17 September 2007

Results information

Result version number	v2 (current)
This version publication date	01 July 2016
First version publication date	31 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	CON-KOR-012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Janssen Korea Ltd
Sponsor organisation address	25th Floor LS Yongsan Tower, 191, Hangangno 2-GA Yongsan-Gu Seoul, Korea, Republic of, 140702
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	17 September 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the optimal dosages of Osmotic Release Oral System (OROS) methylphenidate in Subjects with Attention Deficit Hyperactivity Disorder (ADHD).

Protection of trial subjects:

Safety were evaluated throughout the study by monitoring of adverse events (AEs), by rating symptom scale, performing laboratory tests, measurement of vital signs, and performing physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 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	Korea, Republic of: 144
Worldwide total number of subjects	144
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)	121
Adolescents (12-17 years)	23
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 7 hospitals from August 21, 2006 to September 17, 2007.

Pre-assignment

Screening details:

A total of 145 subjects were enrolled in the study and 144 subjects started the study out of these 116 subjects completed the study and 29 subject's withdrawal the study.

Period 1

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

Arms

Arm title	Concerta

Arm description:

Methylphenidate HCl initially either 18 milligram (mg) or 27 mg for weight less than 25 kilogram (kg) and more than 30 kg, respectively, once daily orally. Initial dose was adjusted by the investigator based on the maintenance dose of a previous drug or clinical symptoms.

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

Dosage and administration details:

Subject was administered the once daily dose of oral capsule of Methylphenidate hydrochloride in morning.

Number of subjects in period 1	Concerta
Started	144
Completed	116
Not completed	28
Adverse event, non-fatal	8
Other	14
Lost to follow-up	6

Baseline characteristics

Reporting groups	
Reporting group title	Concerta

Reporting group description:

Methylphenidate HCl initially either 18 milligram (mg) or 27 mg for weight less than 25 kilogram (kg) and more than 30 kg, respectively, once daily orally. Initial dose was adjusted by the investigator based on the maintenance dose of a previous drug or clinical symptoms.

Reporting group values	Concerta	Total	
Number of subjects	144	144	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	121	121	
Adolescents (12-17 years)	23	23	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	
85 years and over	0	0	
Title for AgeContinuous Units: years			
arithmetic mean	8.9		
standard deviation	± 2.44	-	
Title for Gender Units: subjects			
Female	22	22	
Male	122	122	

End points

End points reporting groups

Reporting group title	Concerta

Reporting group description:

Methylphenidate HCl initially either 18 milligram (mg) or 27 mg for weight less than 25 kilogram (kg) and more than 30 kg, respectively, once daily orally. Initial dose was adjusted by the investigator based on the maintenance dose of a previous drug or clinical symptoms.

Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

ITT population included subjects who were administered with the study drug more than once and provided data for primary efficacy variables.

Primary: Percentage of Subjects with Remission at Week 12

End point title	Percentage of Subjects with Remission at Week 12[1]

End point description:

Remission is defined as the total score of [Korean Version of Adult Attention Deficit Hyperactivity Disorders (ADHD) Rating Scale] (K-ARS) below 18 points and a CGI below 2 (very much improved, much improved). Last observation carried forward (LOCF) was used to impute missing data.

End point type	Primary

End point timeframe:

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	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	136[2]			
Units: Units on a scale				
number (not applicable)	67.86			

Notes:

[2] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ADHD Diagnostic System (ADS) Score

End point title	Change in ADHD Diagnostic System (ADS) Score

End point description:

ADS is an objective and standardized Continuous Performance Test (CPT) to evaluate attention. Date for simple selective visual (ssv) and simple selective aural (SSA) were reported. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	136[3]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): SSV: Missing	69.06 (± 36.86)			
Change at Week (Wk) 12: SSV: Missing	-12.71 (± 43.4)			
BL: SSV: False alarm	72.41 (± 33.59)			
Change at Wk 12: SSV: False alarm	-13.68 (± 25.51)			
BL: SSV: Mean reaction time	53.35 (± 14.72)			
Change at Wk 12: SSV: Mean reaction time	-3.06 (± 11.98)			
BL: SSV: SD reaction time	76.22 (± 34.43)			
Change at Wk 12: SSV: SD reaction time	-10.22 (± 31.45)			
Baseline (BL): SSA: Missing	59.76 (± 21.24)			
Change at Wk 12: SSA: Missing	-9.4 (± 20.24)			
BL: SSA: False alarm	58.23 (± 22.3)			
Change at Wk 12: SSA: False alarm	-8.46 (± 13.91)			
BL: SSA: Mean reaction time	57.03 (± 16.95)			
Change at Wk 12: SSA: Mean reaction time	-1.83 (± 13.56)			
BL: SSA: SD reaction time	62.34 (± 13.99)			
Change at Wk 12: SSA: SD reaction time	-7.76 (± 12.28)			

Notes:

[3] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Inattention/Over Activity With Aggression (IOWA) Conners Behavior Rating Scale - I/O Score at Week 12

End point title	Change From Baseline in Inattention/Over Activity With Aggression (IOWA) Conners Behavior Rating Scale - I/O Score at Week 12

End point description:

IOWA Conners Behavior Rating Scale evaluated by parents provides accurate measurement standards for behavioral change and therapeutic response. It includes 2 sub-scales: Inattention/Over activity (I/O) subscale and Attacks (A), also known as Opposition/Defiant (O/D) sub-scale. IO (primary measurement) will be assessed using 5-items and all Items will be scored on a 4-point scale (from 0=not at all to 3=very much). Total score range is from 0 to 15. Higher scores indicate worsening. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	134[4]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Total score	12.66 (± 5.62)			
Change at Wk12: Total score	-6.08 (± 5.88)			
BL: Carelessness/ Hyperactivity	7.12 (± 2.94)			
Change at Wk 12: Carelessness/ Hyperactivity	-3.58 (± 3.15)			
BL: Hostile /Rebellious	5.5 (± 3.47)			
Change at Wk 12: Hostile /Rebellious	-2.43 (± 3.43)			

Notes:

[4] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Children's Depression Inventory (CDI) Score at week 12

End point title	Change From Baseline in Children's Depression Inventory (CDI) Score at week 12

End point description:

The CDI contains 27 items, and measures symptoms of depression in children and adolescents. The CDI ranges in score from 0-54, where higher scores are indicative of a greater number of symptoms. Changes in scores from Baseline to Week 12 were examined. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	109[5]			
Units: Units on a scale				
median (standard deviation)				
Baseline	14.11 (± 7.06)			
Change at Wk 12	-3.51 (± 5.86)			

Notes:

[5] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in State-Trait Anxiety Inventory for Children (STAI-C) score at Week 12

End point title	Change From Baseline in State-Trait Anxiety Inventory for Children (STAI-C) score at Week 12

End point description:

State anxiety is the temporary emotional state that can be induced by tension, worry and fear under special circumstances and tends to be changeable in the degree, and Trait anxiety reflects a stable tendency throughout life, and is a measurement used to determine personal differences in response to external threats. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Intent-to-treat (ITT) population			
Subject group type	Subject analysis set			
Number of subjects analysed	117			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): State anxiety	34.04 (± 7.67)			
Change at Wk 12: State anxiety	-3.26 (± 8.37)			
Baseline (BL): Trait anxiety	33.25 (± 7.4)			
Change at Wk 12: Trait anxiety	-3.78 (± 5.82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Yale Global Tic Severity Scale (YGTSS) Score at Week 12

End point title	Change from Baseline in Total Yale Global Tic Severity Scale (YGTSS) Score at Week 12

End point description:

The Yale Global Tic Severity Scale (YGTSS) is a semi structured clinician-rated instrument that assesses the severity and frequency of motor and phonic tics over the previous week. Five index scores are obtained during the assessment, where higher scores indicate greater frequency or severity. LOCF was used to impute missing data. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	117[6]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Muscle tic	0.62 (± 2.44)			
Change at Wk 12: Muscle tic	0.36 (± 3.05)			
Baseline : Vocal tic	0.44 (± 2.21)			
Change at Wk 12: Vocal tic	-0.24 (± 1.95)			

Notes:

[6] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Life Participation Scale-Child (LPS-C) Score at Week 12

End point title	Change from Baseline in Life Participation Scale-Child (LPS-C) Score at Week 12

End point description:

LPS-C is a short parent-rated scale that is designed to assess changes in adaptive functioning related to treatment for ADHD. This scale measures improvements in social, emotional, cognitive, educational, and affinitive (family, friends) functioning, which indirectly reflect improvements in executive functioning. Happy/social sub scores range from 0-18, and self-control sub scores range from 0-54. Total scores range from 0-72. Higher scores are better for LPS. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	105[7]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	33.84 (± 9.91)			
Change at Wk 12	7.91 (± 9.63)			

Notes:

[7] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Academic Performance Rating Scale (APRS) Score at Week 12

End point title	Change From Baseline in Academic Performance Rating Scale (APRS) Score at Week 12

End point description:

APRS scale measures four factors in elementary school children such as learning ability, academic performance, impulse control, and social withdrawal. In particular, it is excellent in assessing drug effect on the academic performance not measured by other scales. Score ranges from 19 to 95, higher score means better academic performance. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	111[8]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	54.38 (± 11.32)			
Change at Wk 12	9.04 (± 8.11)			

Notes:

[8] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parenting Questionnaire Form at Week 12

End point title	Change From Baseline in Parenting Questionnaire Form at Week 12

End point description:

It consists of 13 questions to evaluate the parental sense of competency (cognitive dimensions) and parental frustration and anxiety (emotional dimensions). It is rated from 1 to 5 points, and it is reversely rated for 5,6th questions. The questionnaire consists of two subcategories of 'Sense of competency (Questions 1~9)' and 'Sense of anxiety (Questions 10~13)', and the total score of each subcategory is 0 to 45 points and 20 points. A higher score in the 'Sense of competency" subcategories indicates a high parental sense of competency, and a higher score in the 'Sense of anxiety' subcategories indicates high parental frustration and anxiety. LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	117[9]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Parental sense of competency	27.45 (± 5.67)			
Change at Wk 12: Parental sense of competency	0.58 (± 3.6)			

BL: Parental frustration stress and anxiety	13.81 (± 3.39)			
Change at Wk 12:frustration stress, anxiety	-1.25 (± 3.03)			

Notes:

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression Severity (CGI-S) Scale Score at Week 12

End point title	Change From Baseline in Clinical Global Impression Severity (CGI-S) Scale Score at Week 12

End point description:

The Clinical Global Impression Severity (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 . LOCF was used to impute missing data.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Concerta			
Subject group type	Reporting group			
Number of subjects analysed	135[10]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	4.9 (± 0.93)			
Change at Wk12	-2.31 (± 1.18)			

Notes:

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 7 up to Day 84	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0
Reporting groups	
Reporting group title	Concerta
Reporting group description: Methylphenidate HCl initially either 18 milligram (mg) or 27 mg for weight less than 25 kilogram (kg) and more than 30 kg, respectively, once daily orally. Initial dose was adjusted by the investigator based on the maintenance dose of a previous drug or clinical symptoms.	

Serious adverse events	Concerta		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 144 (0.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 144 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Concerta		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 144 (78.47%)		
Investigations			
Weight Decreased			
subjects affected / exposed	4 / 144 (2.78%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			

subjects affected / exposed	16 / 144 (11.11%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	27 / 144 (18.75%)		
occurrences (all)	0		
General disorders and administration site conditions			
Crying			
subjects affected / exposed	7 / 144 (4.86%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	18 / 144 (12.50%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	13 / 144 (9.03%)		
occurrences (all)	0		
Abdominal Pain Upper			
subjects affected / exposed	8 / 144 (5.56%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences (all)	0		
Psychiatric disorders			
Anger			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	0		
Decreased Interest			
subjects affected / exposed	5 / 144 (3.47%)		
occurrences (all)	0		
Daydreaming			

subjects affected / exposed	2 / 144 (1.39%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	11 / 144 (7.64%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	4 / 144 (2.78%)		
occurrences (all)	0		
Depressed Mood			
subjects affected / exposed	2 / 144 (1.39%)		
occurrences (all)	0		
Hostility			
subjects affected / exposed	3 / 144 (2.08%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	42 / 144 (29.17%)		
occurrences (all)	0		
Euphoric Mood			
subjects affected / exposed	5 / 144 (3.47%)		
occurrences (all)	0		
Nervousness			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	0		
Social Avoidant Behaviour			
subjects affected / exposed	6 / 144 (4.17%)		
occurrences (all)	0		
Nightmare			
subjects affected / exposed	9 / 144 (6.25%)		
occurrences (all)	0		
Tic			
subjects affected / exposed	7 / 144 (4.86%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 144 (4.86%)		
occurrences (all)	0		

Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	 93 / 144 (64.58%) 0		

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

None reported