Clinical trial results:
The Effective and Tolerable Titration Scheme and Dosage in Children with Attention-deficit hyperactivity disorder Treated with Osmotic controlled-release oral delivery system (OROS)-Methylphenidate

Summary

EudraCT number	2015-001070-18
Trial protocol	Outside EU/EEA
Global end of trial date	28 June 2007

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	42603ATT4040

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00518232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag Taiwan
Sponsor organisation address	8th Floor, #319, Section 2, Tunhwa South Road, Taipei 106, Taiwan,
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	28 June 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to investigate the clinical benefit of switching children with ADHD (attention deficit/hyperactive disorder) from immediate-release methylphenidate (IR-MPH) to Osmotic controlled-release oral delivery system (OROS)-methylphenidate under the correct dosage conversion scheme.

Protection of trial subjects:

Safety was evaluated based on the following variables: adverse events and serious adverse events, measurement of vital signs and the performance of physical examinations. Barkley's Side Effect Rating Scale (Barkley's SERS) was used to measure side effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 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	Taiwan: 507
Worldwide total number of subjects	507
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)	364
Adolescents (12-17 years)	143
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 from 18 September 2006 to 28 June 2007 and recruited subjects from 6 clinical centers.

Pre-assignment

Screening details:

Total 521 subjects were enrolled in the study and 439 subjects completed 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	OROS Methylphenidate

Arm description:

Subjects receiving IR-MPH therapy at daily dosage of less than or equal to (<=) 15 milligram (mg) per day, were switched to receive OROS methylphenidate 18mg once daily orally up to 6 weeks. Subjects receiving IR-MPH therapy at a daily dosage of greater than >15 mg per day and <=30 mg per day, received OROS methylphenidate 36 mg once daily orally up to 6 weeks. Subjects receiving IR-MPH >30 mg per day, received OROS methylphenidate 54 mg once daily orally up to 6 weeks. Dose of OROS methylphenidate was up titrated or down titrated based on the optimal response and adverse event. The maximum daily dose of OROS methylphenidate was 54 mg per day. The final titration dose of OROS methylphenidate was continued for next 4 weeks.

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

Dosage and administration details:

OROS Methylphenidate in a dose of 18 mg or 36 mg or 54 mg once daily orally.

Number of subjects in period 1	OROS Methylphenidate
Started	507
Completed	439
Not completed	68
Consent withdrawn by subject	21
Adverse event, non-fatal	24
Other	1
Lost to follow-up	12
Lack of efficacy	9
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	OROS Methylphenidate

Reporting group description:

Subjects receiving IR-MPH therapy at daily dosage of less than or equal to (<=) 15 milligram (mg) per day, were switched to receive OROS methylphenidate 18mg once daily orally up to 6 weeks. Subjects receiving IR-MPH therapy at a daily dosage of greater than >15 mg per day and <=30 mg per day, received OROS methylphenidate 36 mg once daily orally up to 6 weeks. Subjects receiving IR-MPH >30 mg per day, received OROS methylphenidate 54 mg once daily orally up to 6 weeks. Dose of OROS methylphenidate was up titrated or down titrated based on the optimal response and adverse event. The maximum daily dose of OROS methylphenidate was 54 mg per day. The final titration dose of OROS methylphenidate was continued for next 4 weeks.

Reporting group values	OROS Methylphenidate	Total	
Number of subjects	507	507	
Title for AgeCategorical Units: subjects			
Children (2-11 years)	364	364	
Adolescents (12-17 years)	143	143	
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	10.4		
standard deviation	± 2.24	-	
Title for Gender Units: subjects			
Female	59	59	
Male	448	448	

End points

End points reporting groups

Reporting group title	OROS Methylphenidate
Reporting group description:	
Subjects receiving IR-MPH therapy at daily dosage of less than or equal to (<=) 15 milligram (mg) per day, were switched to receive OROS methylphenidate 18mg once daily orally up to 6 weeks. Subjects receiving IR-MPH therapy at a daily dosage of greater than >15 mg per day and <=30 mg per day, received OROS methylphenidate 36 mg once daily orally up to 6 weeks. Subjects receiving IR-MPH >30 mg per day, received OROS methylphenidate 54 mg once daily orally up to 6 weeks. Dose of OROS methylphenidate was up titrated or down titrated based on the optimal response and adverse event. The maximum daily dose of OROS methylphenidate was 54 mg per day. The final titration dose of OROS methylphenidate was continued for next 4 weeks.	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subject analysis set description: Intent to treat (ITT) population included all enrolled subjects who received study drug and participated in at least one post-baseline evaluation.	
Subject analysis set title	Efficacy Population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Efficacy population included all enrolled subjects who received study drug and completed the 10 week study duration.	
Subject analysis set title	Safety analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set included all enrolled subjects who received study drug and participated on at least one post-baseline evaluation.	

Primary: Percentage of Subjects With Optimal Response at Week 10

End point title	Percentage of Subjects With Optimal Response at Week 10[1]
End point description:	
Optimal response is defined as a score of 0 or 1 on each of the first 18 Attention-deficit/hyperactivity disorder (ADHD) items in Swanson, Nolan and Pelham-Fourth Edition (SNAP-IV) rating scale. SNAP-IV rating scale consists of 18 ADHD items and 8 Oppositional Defiant Disorder (ODD) items. Each item was scored for severity on a 4-point scale ranging from 0-3, where 0=not at all and 3=very much.	
End point type	Primary
End point timeframe:	
Week 10	

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: Statistical analysis was not reported for this endpoint as inferential analysis was not planned.

End point values	Intent-to-treat (ITT) population			
Subject group type	Subject analysis set			
Number of subjects analysed	507[2]			
Units: percentage of subjects				
number (confidence interval 95%)	59.6 (55.3 to 63.8)			

Notes:

[2] - ITT Population

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Optimal Response as per the Dose of OROS Methylphenidate

End point title	Percentage of Subjects With Optimal Response as per the Dose of OROS Methylphenidate[3]

End point description:

Subjects with optimal response as per dose of OROS methylphenidate (18, 36 and 54 mg per day) were reported. Optimal response is defined as a score of 0 or 1 on each of the first 18 Attention-deficit/hyperactivity disorder (ADHD) items in Swanson, Nolan and Pelham-Fourth Edition (SNAP-IV) rating scale. SNAP-IV rating scale consists of 18 ADHD items and 8 Oppositional Defiant Disorder (ODD) items. Each item was scored for severity on a 4-point scale ranging from 0-3, where 0=not at all and 3=very much.

End point type	Primary

End point timeframe:

Up to Week 10

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: Statistical analysis was not reported for this endpoint as inferential analysis was not planned.

End point values	Intent-to-treat (ITT) population			
Subject group type	Subject analysis set			
Number of subjects analysed	507[4]			
Units: Percentage of subjects				
number (not applicable)				
18 mg of OROS Methylphenidate	9.9			
36 mg of OROS Methylphenidate	15.4			
54 mg of OROS methylphenidate	15.2			

Notes:

[4] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Swanson, Nolan, and Pelham Questionnaire (SNAP-IV) Total Score at Week 10

End point title	Change from Baseline in Swanson, Nolan, and Pelham Questionnaire (SNAP-IV) Total Score at Week 10

End point description:

SNAP-IV rating scale consists of 18 ADHD items and 8 Oppositional Defiant Disorder (ODD) items. Each item was scored for severity on a 4-point scale ranging from 0-3, where 0=not at all and 3=very much.

End point type	Secondary

End point timeframe:

Baseline and Week 10

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	439[5]			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline	37.9 (± 14.87)			
Change at week 10	-21.52 (± 14.02)			

Notes:

[5] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression (CGI) Scale Score

End point title	Change From Baseline in Clinical Global Impression (CGI) Scale Score

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. CGI Improvement scale is a 7 point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

End point type	Secondary

End point timeframe:

Baseline, Week 10

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	439[6]			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline: Clinical Global Impression-Severity	3.9 (± 0.93)			
Change at Week 10: Clinical Global Impression-Seve	-1.57 (± 1.16)			
Baseline: Clinical Global Impression-Improvement	4 (± 0)			
Change at Week 10: Clinical Global Impression-Impr	-1.78 (± 0.92)			

Notes:

[6] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Satisfaction at Week 10

End point title	Change From Baseline in Global Satisfaction at Week 10

End point description:

Global satisfaction included ratings from parent/caregiver, subjects/patients rationings, observations during study period and adverse effects. This scale ranges from 1=completely dissatisfied to 5=complete satisfied.Global satisfaction was assessed by parent/caregiver and subject.

End point type	Secondary

End point timeframe:

Baseline and Week 10

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	439[7]			
Units: Unit on a scale				
arithmetic mean (standard deviation)				
Baseline: Parents/Caregivers Global Satisfaction	3.3 (± 0.86)			
Change At Week 10: Parents/Caregivers Global Satis	0.74 (± 1.13)			
Baseline: Subject Global Satisfaction	3.3 (± 0.99)			
Change at Week 10: Subject Global Satisfaction	0.61 (± 1.25)			

Notes:

[7] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to end of treatment (week 10)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	OROS Methylphenidate

Reporting group description:

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Serious adverse events	OROS Methylphenidate		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 507 (0.59%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 507 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 507 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 507 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 507 (0.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 507 (0.20%)		
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	OROS Methylphenidate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	260 / 507 (51.28%)		
Nervous system disorders			
Headache			
subjects affected / exposed	35 / 507 (6.90%)		
occurrences (all)	36		
Somnolence			
subjects affected / exposed	13 / 507 (2.56%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	25 / 507 (4.93%)		
occurrences (all)	25		
Dry Mouth			
subjects affected / exposed	59 / 507 (11.64%)		
occurrences (all)	61		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	25 / 507 (4.93%)		
occurrences (all)	25		
Communication Disorder			
subjects affected / exposed	26 / 507 (5.13%)		
occurrences (all)	29		
Daydreaming			

subjects affected / exposed	16 / 507 (3.16%)		
occurrences (all)	16		
Decreased Interest			
subjects affected / exposed	20 / 507 (3.94%)		
occurrences (all)	20		
Depressed Mood			
subjects affected / exposed	24 / 507 (4.73%)		
occurrences (all)	24		
Inappropriate Affect			
subjects affected / exposed	20 / 507 (3.94%)		
occurrences (all)	21		
Insomnia			
subjects affected / exposed	104 / 507 (20.51%)		
occurrences (all)	108		
Nightmare			
subjects affected / exposed	18 / 507 (3.55%)		
occurrences (all)	19		
Onychophagia			
subjects affected / exposed	12 / 507 (2.37%)		
occurrences (all)	12		
Tic			
subjects affected / exposed	11 / 507 (2.17%)		
occurrences (all)	11		
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	20 / 507 (3.94%)		
occurrences (all)	22		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	186 / 507 (36.69%)		
occurrences (all)	195		

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