Clinical trial results:
Vergleich der Wirksamkeit von Medikinet retard mit Concerta bei Kindern mit ADHS
Comparison of the efficacy of Medikinet® retard with Concerta in children with ADHD

Summary

EudraCT number	2005-003295-38
Trial protocol	DE
Global end of trial date	27 March 2009

Results information

Result version number	v1 (current)
This version publication date	20 July 2016
First version publication date	20 July 2016

Trial information

Trial identification

Sponsor protocol code	6520-0650-07

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MEDICE Arzneimittel Pütter GmbH & Co. KG
Sponsor organisation address	Kuhloweg 38, Iserlohn, Germany, 58638
Public contact	Medical Department, MEDICE Arzneimittel Pütter GmbH & Co KG, info@medice.de
Scientific contact	Medical Department, MEDICE Arzneimittel Pütter GmbH & Co KG, info@medice.de

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	27 March 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2009
Global end of trial reached?	Yes
Global end of trial date	27 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study was to compare Medikinet® retard in various doses with Concerta® in relation to efficacy variables in children with ADHD

Protection of trial subjects:

Safety assessments included of monitoring and recording all adverse events and serious adverse events, the regular measurement of vital signs and using a questionnaire about possible side effects of drugs (ADHS-TAP)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 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	Germany: 113
Worldwide total number of subjects	113
EEA total number of subjects	113

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)	81
Adolescents (12-17 years)	32
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female patients were included aged 6 to 17 years 11 months. A prerequisite was that the patient attended a primary, secondary or special school and had a class teacher, or attended the HEBO School in Bonn or had been attending a hospital school in a paediatric psychiatry clinic for at least 3 weeks.

Pre-assignment

Screening details:

122 subjects were screened and 113 subjects were enrolled in this study from 9 study center.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer

Blinding implementation details:

For Concerta and Medikinet retard, capsules were made to order so they appeared identically.

Arms

Are arms mutually exclusive?	No
Arm title	Medikinet retard equivalent dose

Arm description:

Medikinet retard in a approximately equivalent dose to Concerta per dose per day (20 or 30 mg)

Arm type	Experimental
Investigational medicinal product name	Medikinet retard 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg methylphenidate hydrochloride

Investigational medicinal product name	Medikinet retard 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30 mg methylphenidate hydrochloride

Arm title	Medikinet retard lower dose

Arm description:

Medikinet retard in lower daily dose (10 or 20 mg)

Arm type	Experimental
Investigational medicinal product name	Medikinet retard 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: 20 mg m ethylphenidate hydrochloride	
Investigational medicinal product name	Medikinet retard 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 10 mg methylphenidate hydrochloride	
Arm title	Concerta
Arm description: Concerta (18 or 36 mg)	
Arm type	Active comparator
Investigational medicinal product name	Concerta 18 mg or 36 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 18 mg methylphenidatehydrochloride	

Number of subjects in period 1	Medikinet retard equivalent dose	Medikinet retard lower dose	Concerta
Started	108	106	110
Completed	106	99	104
Not completed	2	7	6
Adverse event, non-fatal	-	3	1
Teacher ill	-	1	-
Lack of compliance of the teacher	-	1	3
Protocol deviation	1	2	2
Lack of efficacy	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Period
Reporting group description:	
86 of 113 patients were male. The mean Age was 10	

Reporting group values	Overall Period	Total	
Number of subjects	113	113	
Age categorical			
Units: Subjects			
Children (6-9)	51	51	
Children (10-12)	43	43	
Adolescents (13-17)	19	19	
Age continuous			
Units: years			
arithmetic mean	10.2		
standard deviation	± 2.3	-	
Gender categorical			
86 males and 27 females			
Units: Subjects			
Male	86	86	
Female	27	27	

End points

End points reporting groups

Reporting group title	Medikinet retard equivalent dose
Reporting group description:	
Medikinet retard in a approximately equivalent dose to Concerta per dose per day (20 or 30 mg)	
Reporting group title	Medikinet retard lower dose
Reporting group description:	
Medikinet retard in lower daily dose (10 or 20 mg)	
Reporting group title	Concerta
Reporting group description:	
Concerta (18 or 36 mg)	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Every patient who had taken the investigational drug at least once and for whom there were data for the pairwise intraindividual comparison relating to a SKAMP-D score was accepted into the cohort for confirmatory analysis. In the following text, deviating from the usual definitions, this sample of 107 patients is called the ITT cohort. If, in tables, smaller numbers of cases than n=107 appear, they refer in each case to the data available for the particular variable.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The 91 patients who did not discontinue the study and who could be evaluated as "per protocol" are called the PP cohort in the following text. If, in tables, smaller numbers of cases than n=91 appear, they refer in each case to the data available for the particular variable	

Primary: Skamp-D in the first 3 school hours; Test H0A Test for non-inferiority of Medikinet retard in equivalent dose vs. Concerta

End point title	Skamp-D in the first 3 school hours; Test H0A Test for non-inferiority of Medikinet retard in equivalent dose vs. Concerta[1]
End point description:	
In patients with ADHD, diagnosed using DCL-HKS, an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives the same or insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school, accepting a non-inferiority limit of Delta=+0.167. The null hypothesis H0A could be ruled out at a level of significance of alpha0.025 (one-sided) (p<0.0001; test according to Duchateau et al., 2002). Consequently it could be demonstrated that an approximately equivalent daily dose of Medikinet® retard compared with an appropriate dose of Concerta® gave the same and/or insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school. The one-sided 97.5% confidence interval was (minus infinity;-0.217). Handling for missing data is described in detail in the free available publication.	
End point type	Primary
End point timeframe:	
Baseline and after each visit	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to cross-over design. Almost all patients were included in each Group/Treatment Arm

End point values	Medikinet retard equivalent dose	Concerta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[2]	101[3]		
Units: points				
arithmetic mean (standard error)	0.6 (± 0.06)	0.76 (± 0.05)		

Notes:

[2] - Teacher did not complete the SKAMP

[3] - Teacher did not complete the SKAMP

Statistical analyses

Statistical analysis title	H0A: non-inferiority equivalent dose of Medikinet®

Statistical analysis description:

Null hypothesis A: H0A
In patients with ADHD, diagnosed using DCL-HKS, an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school, accepting a non-inferiority limit of Delta0.167.

Comparison groups	Medikinet retard equivalent dose v Concerta
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	< 0.0001
Method	Duchateau 2002
Parameter estimate	Effect estimators
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-0.217

Notes:

[4] - The null hypothesis H0A could be ruled out at a level of significance of alpha=0.025 (one-sided) (p<0.0001; test according to Duchateau et al., 2002). Consequently it could be demonstrated that an approximately equivalent daily dose of Medikinet® retard compared with an appropriate dose of Concerta® gave the same and/or insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school. The one-sided 97.5% confidence interval was (-infinity, -0.217.

Primary: SKAMP-D in the first 3 school hours H0B1 Test for superiority of Medikinet retard in approximately equivalent daily dose vs. Concerta

End point title	SKAMP-D in the first 3 school hours H0B1 Test for superiority of Medikinet retard in approximately equivalent daily dose vs. Concerta[5]

End point description:

In patients with ADHD, diagnosed using DCL-HKS, an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives the same or poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school.
Alternative hypothesis B1: H1B1
In patients with ADHD, diagnosed using DCL-HKS, an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives better results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school.
The null hypothesis H0B1 could be ruled out (p=0.0009; test according to Duchateau et al., 2002). It could thus be shown that an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives better results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school.
Handling for missing data is described in detail in the free available publication.

End point type	Primary

End point timeframe:

reported at each visit

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to cross-over design. Almost all patients were included in each Group/Treatment Arm

End point values	Medikinet retard equivalent dose	Concerta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[6]	101[7]		
Units: points				
arithmetic mean (standard error)	0.6 (± 0.06)	0.76 (± 0.05)		

Notes:

[6] - Teacher did not complete the SKAMP

[7] - Teacher did not complete the SKAMP

Statistical analyses

Statistical analysis title	H0B1 Medikinet ret.in equivalent dose vs. Concerta

Statistical analysis description:

Once the non-inferiority (hypotheses A) could be shown, hypothesis B1 (the superiority of the virtually equivalent daily dose of Medikinet® retard over an appropriate dose of Concerta®) and hypothesis B2 (the non-inferiority of the lower daily dose of Medikinet® retard to an appropriate dose of Concerta® with a non-inferiority limit of =0.167) were tested hierarchically, for the primary parameter, the SKAMP-D teacher ratings taken as mean values for the first 3 hours of school.

Comparison groups	Concerta v Medikinet retard equivalent dose
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0009
Method	Duchateau

Notes:

[8] - The null hypothesis H0B1 could be ruled out (p=0.0009; test according to Duchateau et al., 2002). It could thus be shown that an equivalent dose of Medikinet® retard compared with an appropriate dose of Concerta® gives better results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school.

Primary: Skamp-D in the first 3 school hours H0B2 Test for non-inferiority of Medikinet retard in the reduced daily dose vs. Concerta

End point title	Skamp-D in the first 3 school hours H0B2 Test for non-inferiority of Medikinet retard in the reduced daily dose vs. Concerta[9]

End point description:

In patients with ADHD, diagnosed using DCL-HKS, a lower dose of Medikinet® retard compared with an appropriate dose of Concerta® gives the same or insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school, accepting a non-inferiority limit of Delta =0.167.
The null hypothesis H0B2 could be ruled out (p=0.0001; test according to Duchateau et al., 2002). It could thus be shown that a lower dose of Medikinet® retard gives the same or only insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school. The one-sided 97.5% confidence interval was (minus infinity;+ 0.051.
To sum up it can be said that all the null hypotheses were rejected in the confirmatory analysis and that Medikinet® retard proved to be – at least in the first 3 hours of school and referring to the SKAMP-D – as effective as Concerta®.

End point type	Primary

End point timeframe:

reported at each visit

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to cross-over design. Almost all patients were included in each Group/Treatment Arm

End point values	Medikinet retard lower dose	Concerta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104[10]	101[11]		
Units: points				
arithmetic mean (standard error)	0.67 (± 0.06)	0.76 (± 0.05)		

Notes:

[10] - Teacher did not complete the SKAMP

[11] - Teacher did not complete the SKAMP

Statistical analyses

Statistical analysis title	H0B2 Medikinet retard in reduced dose vs. Concerta

Statistical analysis description:

In patients with ADHD, diagnosed using DCL-HKS, a lower dose of Medikinet® retard compared with an appropriate dose of Concerta® gives poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school, accepting a non-inferiority limit of Delta =0.167.

Comparison groups	Medikinet retard lower dose v Concerta
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	< 0.0001
Method	Duchateau 2002
Confidence interval	
level	Other: 97.4 %
sides	1-sided
upper limit	0.051

Notes:

[12] - The null hypothesis H0B2 could be ruled out (p=0.0001; test according to Duchateau et al., 2002). It could thus be shown that a lower dose of Medikinet® retard compared with an appropriate dose of Concerta® gives the same or only insignificantly poorer results in SKAMP-D teacher ratings taken as mean values over the first 3 hours of school. The one-sided 97.5% confidence interval was (minus infinity, + 0.051.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall including baseline

Adverse event reporting additional description:

In addition to the AEs documented by the doctors, side effects were systematically recorded using the ADHD-TAP. These weekly rating forms for the teachers and parents contain the essential aspects of the Observer Rating form for ADHD, the Observer Rating form for Social Conduct Disorders and the Side Effect Rating Scale. These are not reported here

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups

Reporting group title	Medikinet retard in equivalent dose
Reporting group description: -	
Reporting group title	Medikinet in lower dose
Reporting group description: -	
Reporting group title	Concerta

Reporting group description: -

Serious adverse events	Medikinet retard in equivalent dose	Medikinet in lower dose	Concerta
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 108 (0.00%)	0 / 106 (0.00%)	0 / 110 (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: 4.4 %

Non-serious adverse events	Medikinet retard in equivalent dose	Medikinet in lower dose	Concerta
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 108 (30.56%)	40 / 106 (37.74%)	39 / 110 (35.45%)
Investigations			
Weight loss			
subjects affected / exposed	0 / 108 (0.00%)	3 / 106 (2.83%)	2 / 110 (1.82%)
occurrences (all)	0	3	2
Nervous system disorders			
Headache			

subjects affected / exposed	8 / 108 (7.41%)	3 / 106 (2.83%)	10 / 110 (9.09%)
occurrences (all)	8	3	10
Disturbance in attention			
subjects affected / exposed	0 / 108 (0.00%)	3 / 106 (2.83%)	5 / 110 (4.55%)
occurrences (all)	0	3	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 108 (0.00%)	4 / 106 (3.77%)	3 / 110 (2.73%)
occurrences (all)	0	4	3
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	6 / 108 (5.56%)	7 / 106 (6.60%)	5 / 110 (4.55%)
occurrences (all)	6	7	5
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	3 / 108 (2.78%)	3 / 106 (2.83%)	6 / 110 (5.45%)
occurrences (all)	3	3	6
Aggression			
subjects affected / exposed	2 / 108 (1.85%)	3 / 106 (2.83%)	5 / 110 (4.55%)
occurrences (all)	2	3	5
Restlessness			
subjects affected / exposed	1 / 108 (0.93%)	5 / 106 (4.72%)	2 / 110 (1.82%)
occurrences (all)	1	5	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 108 (1.85%)	2 / 106 (1.89%)	1 / 110 (0.91%)
occurrences (all)	2	2	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 108 (2.78%)	3 / 106 (2.83%)	7 / 110 (6.36%)
occurrences (all)	3	3	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2006	Inclusion criteria "The patient was taking at least methylphenidate rapid release twice daily or Concerta or Medikinet retard once daily" was changed in: "The patient was taking at least methylphenidate rapid release twice daily or a methlyphenidate retard preparation once daily (e.g. Medikinet retard, / Ritalin SR / Metadate CD)"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21790298