UNIVERSITÄTSmedizin.
MAINZ
Klinik und Poliklinik für Kinder- und
Jugendpsychiatrie und -psychotherapie

SYNOPSIS

Name of Sponsor/Company: Name: Universitätsmedizin Mainz Klinik und Poliklinik für Kinder- und Jugend- psychiatrie und -psychotherapie Address: Langenbeckstrasse 1 55131 Mainz	(For National Authority Use only)
Name of Finished Product: Test product: Medikinet® Reference therapy: Medikinet® retard	
Name of Active Ingredient: Methylphenidatheydrochloride	
Title of Study: Adherence to stimulant treatment in ADHD-patients (ASTA) Effect of methylphenidate formulation on ADHD-patients' adherence to medical treatment. A comparison of Medikinet retard® (ER) once daily and Medikinet® (IR) twice daily in children and adolescents diagnosed with ADHD	
Investigators: Prof. Dr. med. Dipl.-Psych. Michael Huss, Dr. med. Helmut Peters, Dr. med. Andreas Stein	
Study centres: Study site 1: Prof. Dr. med. Dipl.-Psych. Huss Rheinhessen-Fachklinik Mainz, Kinder- und Jugendpsychiatrie -psychosomatik und -psychotherapie Hartmühlenweg 2-4, 55122 Mainz, Tel: 06131 378 2300 Study site 2: Dr. med. Peters Kinderneurologisches Zentrum Mainz (KINZ) Hartmühlenweg 2-4, 55122 Mainz, Tel: 06131 - 378-151 Study site 3: Dr. med. Stein Rheinhessen Fachklinik Alzey, Abteilung für Kinder- und Jugendpsychiatrie, -psychotherapie und -psychosomatik Dautenheimer Landstr. 66, 55232 Alzey, Tel: 06731 - 501600	
Publication (reference): up to now, no publications of the outcomes of this study was published. A recent overview of the topic is provided by: Gajria K. et al. (2014). Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder – a systematic literature review. Neuropsychiatr Dis Treat.10:1543-69.	
Studied period (years): First subject in: 25.03.2009 Last subject out: 19.11.2013 Duration of the trial: 57 months, For the individual patient: 28-35 treatment days run-in phase and 100±5 treatment days under controlled study conditions (clinical trial)	**Phase of development:** Phase 4 trial

Objectives:

Primary objective:

- To measure non-adherence assessed by the number of non-adherent treatment days' during the clinical trial of 100 treatment days using the Medication Event Monitoring System (MEMS).

Secondary Objectives:

- To measure the duration of regular intake of the medication referring to the concept of retention (time until 30 cumulative treatment days of nonadherence) assessed by MEMS
- To measure non-adherence assessed by pill count
- To measure Quality of Life assessed by the Child Health Illness Profile -Child Edition (CHIP-CE)
- To measure ADHD symptoms assessed by ADHD-Rating Scale IV-Parent Version (18 Items) To measure adverse events

Methodology:

The study was designed as a prospective, multi-centric, open-label, randomized, active-controlled trial. ADHD-children and adolescents of both sexes, 6-17 of age, effectively treated with stimulants should be recruited in three centres (actually only one site (study site 1) recruited patients). Over a naturalistic run-in phase of 28-35 days adherence to medication taken before randomisation was measured. In the subsequent controlled clinical trial 50% of the participants were randomized to extended release (ER) methylphenidate (Medikinet retard®) applied with breakfast, 50% are randomized to immediate release (IR) methylphenidate (Medikinet®) in the morning and 3-4 h later (clinical trial). To optimize ecological validity, no double-dummy technique was applied; the allocation to either study arm was non-blinded. The total duration of the study was 57 months. Starting with a run-in visit, each eligible patient was observed in the naturalistic run-in phase for four treatment weeks. Subsequently, patients participated 100±5 treatment days in the clinical trial starting with a baseline visit, an in between-visit and a final visit. Medical care was provided in the routine program of both study centres. To record the adherence, medication events were counted by MEMS. The MEMS-data were cross-validated by classical pill-counts during the study visits. Efficacy of the medication, adverse events and Quality of Life were also assessed during visits using the ADHD Rating Scale-Parent Version, Barkley's Side Effects Scale and the Child Health Illness Profile-Child Editon (CHIP-CE) as well as the opportunity for free reports. The instruments to assess adherence (MEMS, pill count), adverse events (Barkley's Side Effect Scale, spontaneous reports), Quality of life (CHIP-CE), and efficacy (ADHD rating scale) were also applied during the run-in phase.

Number of patients (planned and analyzed):
It was planned to enroll a sufficient number to randomize 106 subjects (53 in each treatment group). De facto 30 patients were enrolled of which 22 regularly completed the study. One subject completed the screening process, but was not included in the study due to the end of the study without the possibility of partaking in the study for the entire time, five subjects dropped out during run-in, two subjects during the study period.

Overview of number of allotment failures, screening failures, dropouts, and completers. (N=48)

ID	Allotment Failure	Screening Failure	Dropout RI- Phase	Dropout V1-V2	Dropout V2-V3	Completer	Reason for dropout
1001						x	
1002						x	
1003						x	
1004						x	
1005						x	
1006						x	
1007			x				adverse events (motor tic[1])
1008			x				at own request
1009						x	
1010						x	
1011	x						not interested
1012	x						not interested
1013						x	
1014	x						not interested
1015						x	
1016						x	
1017						x	
1018	x						not interested
1019						x	
1020				x			at own request
1021	x						no longer interested
1022	x						long journey to visits
1023						x	
1024				x			at own request
1025	x						not interested
1026						x	
1027	x						not interested
1028						x	
1029						x	
1030			x				adverse events (heart racing)
1031						x	
1032						x	
1033	x						other psychiatric disorder in the foreground
1034	x						other psychiatric disorder in the foreground
1035	x						no more MPH intake
1036						x	

[1] Single motor tics, no tic disorder.

Overview of number of allotment failures, screening failures, dropouts, and completers.(continued)

ID	Allotment Failure	Screening Failure	Dropout RI- Phase	Dropout V1-V2	Dropout V2-V3	Completer	Reason for dropout
1037			x				at own request, lacking/insufficient efficacy
1038	x						not interested
1039	x						not interested
1040	x						not interested
1041						x	
1042	x						not interested
1043	x						not interested
1044	x						no more contact
1045			x				at own request, insufficient compliance of patient, other reason: did not want to take test medication midday
1046						x	
1047	x						not interested
1048		x*					
Sum	**18**	**1**	**5**	**2**	**0**	**22**	

**Patient was not included due to time constraints towards the end of the study.*

Diagnosis and main criteria for inclusion:

- Written informed consent (separately for children aged 6-11 years and 12-17 years)
- Children and adolescents of both sexes aged 6 -17 years
- Confirmed diagnosis of ADHD by semi structured-clinical interview K-SADS
- ADHDRS-IV-Parent Version (18-ltem-Scale) raw score ~ 1,5 SD above norm under non-medicated conditions (either drug holiday or prior to medication within the past 6 months)
- Effective treatment with a stable dose of methylphenidate for at least one month (max. 60 mg/day) proved by a 25% symptom reduction in ADHD-RS under medication, compared to retrospective ADHD-RS without medication within the past 6 months.
- Acceptance and capability to swallow capsules of product size, proved by an equally sized placebo provided by Medice®.
- Sufficient knowledge of the German language
- Adequate contraception in case of sexual activity

Test product, dose and mode of administration, batch number:

Medikinet®:

20 Tbl. (N1) 5 mg	PZN 1208642
50 Tbl. (N2) 5 mg	PZN 1208694
20 Tbl. (N1) 10 mg	PZN 0943807
50 Tbl. (N2) 10 mg	PZN 1348188
100 Tbl. (N3) 10 mg	PZN 2387807
50 Tbl. (N2) 20 mg	PZN 1208777

Duration of treatment:
Medikinet® was distributed in three different dosage forms: 5, 10, and 20 mg. The medial daily dose assigned to patients in the immediate release condition amounted to $M = 27.5$ mg ($SD = 11.39$, $Mdn = 25.00$ mg, $N = 14$) for a duration of 100±5 days.

Medikinet® retard was distributed in four different dosage forms: 10, 20, 30, and 40 mg. The medial daily dose assigned to patients in the extended release condition amounted to $M = 29.00$mg ($SD = 11.37$, $Mdn = 30$mg, $N = 15$) for a duration of 100±5 days.

Dose combinations of Medikinet® and number of patients assigned to each combination.

Dose combination		Number of patients
Morning	Noon	
5mg	5mg	1
10mg	5mg	1
10mg	10mg	4
10+5mg	10mg	2
10+5mg	10+5mg	1
20mg	10mg	1
20mg	20mg	2
20+5mg	20mg	1
20+10mg	10+5mg	1

Dose combinations of Medikinet® retard and number of patients assigned to each combination.

Dose combination	Number of patients
10mg	1
20mg	5
30mg	4
40mg	4
30mg+20mg	1

Reference therapy, dose and mode of administration, batch number:
Medikinet® retard:

50 hard capsule, retard. (N2) 5 mg	PZN 0734802
50 hard capsule, retard. (N2) 10 mg	PZN 2388126
50 hard capsule, retard. (N2) 20 mg	PZN 2388155
50 hard capsule, retard. (N2) 30 mg	PZN 2388190
50 hard capsule, retard. (N2) 40 mg	PZN 2388215

Criteria for evaluation:

Efficacy:

Primary endpoint:

- Primary endpoint was the number of (non-)adherent treatment days during the clinical trial measured by MEMS.

Secondary endpoints:

- Number of non-adherent treatment days during the clinical trial measured by pill count
- The time interval until a total number of 30 treatment days of nonadherence (treatment days with deviant intake behaviour) is reached cumulatively during the clinical trial, measured by MEMS.
- Quality of life during the clinical trial measured by Child Health Illness Profile -Child Edition (CHIP-CE) Score
- The efficacy of stimulant treatment during the clinical trial measured by ADHD-Rating Scale-Parent Version Sum Score

Safety:

Frequencies of subjects experiencing adverse events (AE), duration, whether the AE was serious, intensity, relationship to trial treatment, action taken and clinical outcome.

Statistical methods:

Primary endpoint:

For each patient the relative number of non-adherent and adherent treatment days during the clinical trial, referring to the individual study duration was determined. The relative number of adherent treatment days was compared between treatments by the t-test on a two-sided alpha-level=0.05 because data was adequate normal-distributed. The primary analysis was a two-folded approach with firstly evaluating a completer-population and secondly an intent-to-treat population, following a last observation carried forward method.

Safety:

Frequencies of subjects experiencing at least one adverse event (AE) were displayed by body system and preferred term according to MedDRA terminology. Further analyses of adverse events comprised duration, whether the AE was serious, intensity, relationship to trial treatment, action taken and clinical outcome.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Patients assigned to the extended-release condition showed significantly higher adherence rates than those assigned to the immediate-release condition.

Mean adherence values for the extended release condition (ER) compared to the immediate release condition (IR)during the study period analyzing patients who regularly completed the study as well as patients who dropped out at visit 2.

	Group				
	IR	ER	*t*	*df*	*d*
Completers	43.70	75.68	-3.18*	11.29	1.44
$N_{(IR)} = 9$	(27.46)	(14.93)			
$N_{(IR)} = 13$					
Incl. dropout V2	43.70	74.34	-3.06*	11.20	1.51
$N_{(ER)} = 10$	(27.46)	(15.20)			
$N_{(ER)} = 14$					

Note. * = $p < .05$, *** = $p < .001$. Standard Deviations appear in parentheses below means.

SAFETY RESULTS:
All frequencies and durations of adverse events were calculated only for the trial period with intake of clinical trial medication. Adverse events that occurred during the run in-period were not taken into account, as patients' took their previous methylphenidate preparation or dosage and no study medication, which created the possibility of different preparations being taken within the sample and thus making a comparison of potential adverse events irrelevant for this study's purpose.

Frequencies of adverse events that occurred during trial period displayed by body system and preferred term according to MedDRA terminology.

MedDRA SOC MedDRA LLT	MedDRA LLT code	Frequency
Cardiac disorders		**1**
Heart racing	10066996	1
Gastrointestinal disorders		**3**
Abdominal pain	10000081	2
Stomach ache	10042076	1
General disorders and administration site conditions		**2**
Fever	10016558	1
Lassitude	10023929	1
Infections and infestations		**6**
Bronchitis	10006451	1
Cold	10009851	1
Gastrointestinal infection	10017964	1
Herpes NOS	10019944	1
Febrile infection	10051998	1
Acute respiratory tract infection	10066740	1
Injury, poisoning and procedural complications		**1**
Auricular haematoma	10003797	1
Musculoskeletal and connective tissue disorders		**1**
Shoulder pain	10040617	1
Nervous system disorders		**5**
Attention concentration difficulty	10003729	1
Headache	10019211	4
Psychiatric disorders		**2**
Depressive episode	10012402	1
Sleep disorder	10040984	1
Respiratory, thoracic and mediastinal disorders		**2**
Nose bleed	10029792	1
Tonsillar inflammation	10065169	1
Skin and subcutaneous tissue disorders		**2**
Blisters	10005216	1
Neurodermatitis	10029263	1

Overview of duration of AE, intensity, relationship to trial treatment, and clinical outcome of AE that occurred during trial period:

Description of AE	Continuous	Number of AE-days trial period	Number of AE-days RI-period	Connection with medication	Clinical outcome
Headache	yes	**55**	0	possible	not recovered
Cold	yes	0	**12**	not assessable	
Light headache	no	0	**2**	none	improved
High fever	no	**4**	0	none	recovered
Feverish infection	no	**41**	0	unlikely	recovered
Hematoma right ear	n.k.	**n.k.**	**n.k.**	none	unknown
Gastrointestinal infection	no	**7**	0	none	recovered
Stomachache	no	0	**1**	unlikely	recovered
Light stomachache	no	**2**	0	unlikely	recovered
Headache	no	**2**	0	unlikely	recovered
Shoulder pain	no	**n.k.**	**n.k.**	unlikely	recovered
Heart Racing	n.k.	**n.k.**	**n.k.**	likely	unknown
Neurodermatitis	no	**8**	0	none	unknown
Herpes blister	no	**54**	0	none	recovered
Acute infection of upper respiratory tracts; Mucosolvan registered once as concurrent medication on Sept. 22nd 2011	no	0	**1**	none	recovered
Concentration problems with IR medication in school	yes	0	**1**	likely	recovered
Nose bleed	no	0	**2**	unlikely	recovered
Stomachache	yes	**101**	**1**	possible	unknown
Headache	yes	**101**	**1**	possible	unknown
Nausea	no	**n.k.**	**n.k.**	none	recovered
Tonsillitis and bronchitis	no	**7**	0	unlikely	recovered
Depressive Episode	no	**13**	0	none	improved
Sleep disturbances	yes	**n.k.**	**n.k.**	possible	not recovered

No Serious adverse events occurred over the course of the study.

CONCLUSION:
The study was conducted according to the scheduled investigational plan, medication was prepared by the pharmacy of the university medicine in Mainz, guaranteeing a high standard of quality. The study was monitored closely by the IZKS (Interdisziplinäres Zentrum für Klinische Studien in Mainz) and only very few and minor protocol deviations took place. Therefore a high level of reliability in means of efficacy and reliability was achieved.

In line with literature, a significant difference in adherence to stimulant treatment emerged between the group taking immediate release methylphenidate and the group taking extended release methylphenidate. The immediate release group had relatively low adherence scores in relation to the extended release group. This difference was significant with a large effect size with d=1.44, respectively 1.51 in the intent-to-treat-analysis.

Derived from literature a sample size of 106 patients was calculated. The recruitment process was much more complicated than expected, mainly because the benefit for study patients was negligible and two of the three study cites didn't recruit patients at all.
Taking the large effect size and the substantial difference between the two groups in a monocentric randomized approach the study was prematurely stopped due to both answering scientific hypothesis with a smaller patient group and ethical reasons. This was concerted with the IZKS and the ethics' committee in advance and reported to all regulatory authorities in time.

Using fully licensed drugs in a phase 4 study, adverse events were rare. Noted adverse events in the study were corresponding to adverse events described in the prescribing information. No serious adverse events occurred. One patient who developed symptoms of an adverse event, as described under withdrawal criteria, was excluded from treatment as soon as the adverse event became known to study investigators at the next visit. In summary, the safety for patients was very good.

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