Sponsor	MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37, 58638 Iserlohn, Germany	
Name of Finished Product	Medikinet® adult (10mg / 20 mg / 30 mg)	
Name of Active Substance	Methylphenidate Hydrochloride	
Title of study:	Placebo-controlled multi-center double-blind trial for adults with extended-release methylphenidate for ADHD with an open extension phase (QUMEA)	
EudraCT number	2008-000942-29	
Principal Investigator	Prof. Dr. Michael Rösler, Uniklinikum des Saarlandes, Institut für Gerichtliche Psychologie und Psychiatrie, 66421 Homburg/Saar	
Trial sites	• Dr. Barbara Alm, Zentralinstitut für Seelische Gesundheit, Psychiatrie Ambulanz, J5, 68159 Mannheim • Dr. Marc-Andreas Edel, Klinikum der Ruhr Universität Bochum, Klinik für Psychiatrie, Psychotherapie und Präventivmedizin, Alexandrinenstr. 1, 44791 Bochum • Prof. Dr. Victor-Felix Mautner, Universitätsklinikum Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg • Johannes Fuhr, Laustr. 30, 34537 Bad Wildungen • Dr. Thomas Wirth, Benzengasse 11/1, 71636 Ludwigsburg • Dr. Alexandra Philipsen, Universitätsklinikum Freiburg, Abteilung für Psychiatrie und Psychotherapie, Hauptstr. 5, 79104 Freiburg • Dr. Klaus-Ulrich Oehler,Medizinisches Studienzentrum Würzburg, Augustinerstr. 15, 97070 Würzburg • Prof. Dr. Michael Huss, Klinik und Poliklinik für Kinder- und Jugendpsychiatrie und –psychotherapie, Langenbeckstr. 1, 55131 Mainz Further trial sites[1]: • 22527 Hamburg • 10789 Berlin • 10117 Berlin	
Publication	Retz et al., Multiscale assessment of treatment efficacy in adults with ADHD: A randomized placebo-controlled, multi-centre study with extended-release methylphenidate. World J. Biol. Psychiatry: 1-12, 2010.	
Study period	First patient in: 05-09-2008	Last patient out: 23-09-2009
Phase of development	III	
Trial objective	To investigate the efficacy and safety of extended-release MPH in the treatment of adult ADHD. The primary outcome measure is the standardised and validated Wender-Reimherr-Interview (WRAADDS) total score at week 8	
Methods	Multicenter clinical trial in which adult ADHD outpatients, after central review of eligibility followed by randomization, underwent an 8-week double-blind, parallel-group treatment. All patients were offered participation in the following 12-week open extension phase with verum. Dosage was individually titrated	

[1] Consent to publish name and address of the investigator is not available

	during the first 2 weeks both in the double-blind and open phase. Decisive for the assessment of efficacy was the comparison at week 8.
Number of patients	201
Diagnostic and main inclusion criteria	• Female and male patients age 18 or older, treated as outpatients • Diagnosis of ADHD according to ADHD-DC (DSM IV) and WRAADDS total score > 35 points at screening • ADHD symptoms present since childhood (WURS-k ≥ 30) • No concomitant disease and/or therapy where methylphenidate is contra-indicated
Investigational substance	Extended-release methylphenidate hydrochloride (MPH-ER) 10, 15, 20 or 30 mg capsules (1 mg / kg body weight) 2 capsules after breakfast and after lunch. 10 mg Ch.-B.: 4620, 4609 15 mg Ch.-B.: 4622, 4610 20 mg Ch.-B.: 4621, 4611 30 mg Ch.-B.: 4623, 4612
Control substance	Placebo capsules, after breakfast and after lunch
Duration of treatment	8 weeks double-blind + 12 weeks open phase
Criteria for evaluation	
Efficacy	Primary endpoint: • Standardised and validated Wender-Reimherr-Interview (WRAADDS) total score in week 8 Secondary endpoints: • Number of responders according to WRAADDS • WRAADDS subscales and overall interviewer assessments • CAARS Self Report: Long Version (CAARS-S:L) • Adverse Event List (AEL) • CGI (Clinical Global Impressions) • Sheehan Scale • BDI
Safety	• AE assessment • Side effects based on an Adverse Event List (AEL) documented on sheet 5 of the Association for Methodology and Documentation in Psychiatrics (AMDP System) • Laboratory parameters and vital signs
Statistical methods	The Wender Reimherr interview (WRAADDS) consists of 28 items. The total score is the sum of all items (in case of missing items the sum was divided by the number of items answered and multiplied by 28). This total score after 8 weeks was analysed as primary endpoint. Missing data were imputed using the last-observation carried forward (LOCF) procedure (only one measurement was missing). The confirmatory analysis was performed on the intent-to-treat (ITT) population using a linear mixed effects model with fixed effect treatment, covariate baseline WRAADDS and random effect center. We applied a significance level of $\alpha=0.05$ for the primary confirmatory test (F-test of the fixed effect). Additional sensitivity analyses were performed to test the robustness of the primary analyses with regard to the imputed data (under a best- and a worst-case scenario). All secondary endpoints were analysed exploratively accounting

	for the variable scale.
Summary of results	
Efficacy	The difference of the WRAADDS total score between the two groups (at week 8) was 6.8 (95% confidence interval 3.2-10.4; p=0.0003), significant at the level α=0.05 and in favour of the investigational substance. These results were consistent across a number of sensitivity analyses (in the PP population, under the best-case and worst-case scenarios and for selected subgroups). Regarding the exploratively assessed secondary endpoint (CAARS-S: L) the results in week 8 were similar to those of the WRAADDS (Wilcoxon U-Test, p=0.008). Moreover, the other secondary endpoints (subscales of WRAADDS and CAARS-S:L, ADHD-DC, CGI and Sheehan Scale) all showed differences in favour of verum. However, in the Beck Depression Inventory no difference between the groups was detectable (p=0.53).
Safety	There were 7 drop outs from the study (verum group N=4, placebo group N=3). The most important reason was adverse events (AEs). AEs occurred in 65% of the verum and in 41% of the placebo patients. The total number of AEs was 151 in the verum and 77 in the placebo group. The most frequent System Organ Class was ”psychiatric disorders” followed by ”Gastrointestinal disorders”. According to the investigator, 61% of the AEs in the verum group and 45% of the AEs in the placebo group were classified as probably related, possibly related or related to the study medication. Nobody died during the study period. We observed 3 serious adverse events (SAEs) of which none was rated as related or possibly related to the study medication. Note that we used a documentation system focussed on AEs, which typically occurs during psychopharmacological trials in psychiatric disorders (sheet 5 of the AMDP System, 2006). This system was used in addition to the general AE recording. Finally, the CGI subscale side effects indicated more side effects in the verum group; however, they did not impair for the 94% of the patients in their daily functioning
Conclusion	The study was performed as a consequence of the results of the 24-week ”EMMA” study and their results. One of the main targets of the QUMEA Study was to clarify possible effects of MPH-ER by age and gender. The results of the QUMEA study showed a treatment response in every assessment procedure in favor of MPH-ER as compared with placebo. The results of the expert assessments showed a significant superiority of MPH-ER as well as the patients self-reports by the CAARS-S-L and the global impression of change as measured by the CGI. In the QUMEA study no gender effect was visible. A new aspect of the QUMEA study was the inclusion of an instrument for the detection of functional changes when MPH-ER was administered and compared with placebo. The Sheehan Disability Scale revealed a significant improvement of daily functioning. Therefore we draw the conclusion that MPH retard is an effective agent in adult ADHD. Regarding safety we conclude that this study did not find any symptoms or signs which have not been described so far in earlier trials on children and adolescents. It was not possible to recognize any specific risk in adulthood with regard to vital signs,

	laboratory findings, AE and SAE. In this regard, the data from our trail are consistent with other recent short-term MPH studies in adult ADHD. Therefore we are in the position to say that our 8-week double-blind phase in this study was not able to discover additional risks in comparison to the earlier 6- or 8-week intervention studies. In this study no adverse effects of MPH were seen that would justify a new safety evaluation for adults with ADHD.
Date of report	March 22, 2010

Subsequent substantial amendments	Ammendment February 18, 2008 Addition of proton pump inhibitors (PPI) to the list of concomitant medication not permitted