SYNOPSIS

Study Title:	An open, comparative, within patient controlled multicentre study of repeated subcutaneous injections of methotrexate 50 mg/ml and 10 mg/ml to compare patient satisfaction and local tolerability in patients with active rheumatoid arthritis
Sponsor's Study Number	MC-MTX.10/RH
Name of Finished Product:	metex® 50 mg/ml Injektionsloesung, Fertigspritze
Name of Active Ingredient:	Methotrexate
Indication Studied:	Rheumatoid arthritis
Publication (Reference):	Not applicable.
Phase of Development:	Phase III
Name of Sponsor:	Headquarter: medac Gesellschaft fuer klinische Spezialpraeparate mbH Fehlandtstrasse. 3, D-20354 Hamburg, Germany Business address: Theaterstrasse 6 D-22880 Wedel Germany
Co-ordinating Investigator:	[redacted] Kerckhoff-Klinik GmbH, [redacted], D-61231 Bad Nauheim, Germany
Study Centres:	Multicentre study (Germany)
Study Period:	First patient in: 22-Nov-2007 Last patient out: 18-Nov-2008

Objectives:

Primary Objective: to quantify the patient's decision for future methotrexate (MTX) treatment (50 mg/ml syringe vs. 10 mg/ml syringe) following repeated subcutaneous injections of 10 mg/ml and 50 mg/ml syringes.

Secondary Objectives: to evaluate/assess

- Patient satisfaction with the 50 mg/ml syringe and with the 10 mg/ml syringe at the end of the study (Day 43) rated by the patient.
- Any potential advantages of the fixed needle attached to the 50 mg/ml MTX pre-filled syringe in comparison to the pre-filled syringe without fixed needle (10 mg/ml) by the patient.
- Any potential advantages of the 0.4 ml volume of the 50 mg/ml syringe in comparison to 2 ml volume of the 10 mg/ml syringe by the patient.
- The usability of the 10 mg/ml syringe at the first injection and the usability of the 50 mg/ml syringe at the fourth injection rated by the physician on a visual analogue scale.
- The usability of the 10 mg/ml syringe at the 2nd and 3rd injection and the usability of the 50 mg/ml syringe at the 5th and 6th injection rated by the patient on a visual analogue scale.
- The local tolerability 30 minutes after administration of the 1st injection (MTX 10 mg/ml) and 4th injection (1st injection with MTX 50 mg/ml) based on the local symptoms occurring at injection site according to the physician.
- The local tolerability of subcutaneous injections of MTX 10 mg/ml and 50 mg/ml syringe, based on the local symptoms occurring at the injection site rated at every injection by patients 2 hours, 24 hours and 48 hours after injection and additionally 30 minutes after administration of the 2nd, 3rd, 5th and 6th injections.

Methodology:

This was an open, comparative, within patient controlled, multicentre phase III clinical trial in patients with rheumatoid arthritis to quantify the patient's decision for future MTX treatment (50 mg/ml syringe vs. 10 mg/ml syringe) following repeated subcutaneous injections of 10 mg/ml and 50 mg/ml syringes.

Treatment was:

- 20 mg MTX administered as 2 ml of 10 mg MTX/ml solution (1st, 2nd and 3rd injection).
- 20 mg MTX administered as 0.4 ml of 50 mg MTX/ml solution (4th, 5th and 6th injection).

Number of Patients:
Planned: 130.
Enrolled: 132.
Valid for safety analysis: 131.
Valid for full analysis: 128.

Inclusion Criteria:
- Written informed consent.
- Age between 18 and 75 years.
- Diagnosis of rheumatoid arthritis according to the American College of Rheumatology (ACR) criteria.
- Patient currently receiving oral MTX for at least 6 weeks and requiring an intensification of therapy due to remaining RA activity (Disease Activity Score 28 [DAS28] >2.6).

Exclusion Criteria:
- Prior treatment with parenteral MTX or biologicals.
- Concomitant treatment with another disease-modifying antirheumatic drug (DMARD) or a biological.
- Renal insufficiency (creatinine in serum >1.5 x ULN).
- History or acute signs of hepatic insufficiency (AST or ALT >2 x ULN, bilirubin >5 mg/dl).
- Impaired haematopoiesis (platelets <100 x 10^9/l, leukocytes <3.5 x 10^9/l), significant anaemia (haemoglobin <10 g/dl).
- Known severe, acute or chronic infection like hepatitis B or C, tuberculosis or HIV.
- Ulcer of oral cavity or known ulcer of gastrointestinal tract.
- History or diagnosis of a dermatological disease in the area of the injection-site, which could interfere with a proper assessment.
- Malignant disease.
- Alcohol or drug addiction.
- Patients with a known history of any previous generalised allergic reactions or serious adverse reactions to the study medication or other components of the injection solution.
- Women with child-bearing potential who do not use a highly effective method of contraception (pearl index <1%) such as combined oral contraceptive, hormone IUCD, vaginal hormone ring, transdermal contraceptive patch, contraceptive implant or depot contraceptive injection in combination with a second method of contraception like a condom or a cervical cap / diaphragm with spermicide during the study and at least 6 months thereafter.
- Men who have a partner with child-bearing potential and do not use a condom or a cervical cap / diaphragm with spermicide during the study and at least 6 months thereafter.
- Pregnant or breast feeding women.
- Patients simultaneously participating or having participated in another clinical trial in the 8 weeks before study start.
- Patients with any form of psychiatric disorder or other conditions which in the opinion of the investigator might invalidate or complicate communication with the patient.
- Any subcutaneous administered drug (insulin, heparin, etc.).
- Concurrent vaccination with live vaccines.

Investigational Product, Dose and Mode of Administration, Batch Number:
Methotrexate solution; 20 mg; subcutaneous injection
Pre-filled syringe containing 0.4 ml of a 50 mg/ml MTX solution for injection (corresponding to 21.94 mg/ml MTX disodium equivalent to 20 mg MTX)
Batch number: M70716A/1 and M70716A/3

Duration of Treatment:
2 ml of a 10 mg/ml MTX solution for 3 weeks followed by therapy with 0.4 ml of a 50 mg/ml MTX solution for 3 weeks.
One subcutaneous injection per week.

Reference Therapy:
Methotrexate solution (Metex® 10 mg/ml Injektionsloesung); 20 mg; subcutaneous injection
Pre-filled syringe containing 2 ml of a 10 mg/ml MTX solution for injection
Batch number: M70716A/1 and M70716A/3

Criteria for Evaluation:

Efficacy: The primary variable was to quantify the patient's decision for future MTX treatment (50 mg/ml syringe vs. 10 mg/ml syringe) following repeated subcutaneous injections of 10 mg/ml and 50 mg/ml syringes. At the end of the study the patient was asked to decide on his further therapy (10 mg/ml vs. 50 mg/ml) by means of a patient questionnaire ("which of the pre-filled syringes would you prefer from now on?").

Secondary efficacy variables included assessments of:

- Patient satisfaction with the 50 mg/ml syringe and with the 10 mg/ml syringe at the end of study (Day 43) rated by the patient. The patient was asked: "How would you assess, all in all, the small/large syringe at the end of the study?" For the rating 5 categories were available: "very bad" / "bad" / "no preference" / "good" / "very good".
- Any potential advantages of the fixed needle attached on the 50 mg/ml MTX pre-filled syringe in comparison to the pre-filled syringe without a fixed needle (10 mg/ml) by the patient. The patient was to answer to the question: "How do you find the fixed needle (small syringe) in comparison to one that still has to be attached (large syringe)?" 5 possible categories were provided: "very disadvantageous" / "disadvantageous" / "no difference" / "advantageous" / "very advantageous".
- Any potential advantages of the 0.4 ml volume of the 50 mg/ml syringe in comparison to 2 ml volume of the 10 mg/ml syringe by patient. The patient was asked: "Does it suit you that the injection liquid is 5 times less in the small syringe than in the large syringe?" The patient had to complete the following sentence: In comparison to the solution in the large syringe it is: "very disagreeable" / "disagreeable" / "indifferent" / "agreeable" / "very agreeable".
- Usability of the 10 mg/ml syringe at the 1st injection and of the usability of the 50 mg/ml syringe at the 4th injection rated by the physician on a visual analogue scale from 0 ("not convenient") to 10 ("very convenient").
- Usability of the 10 mg/ml syringe at the 2nd and 3rd injection and of the 50 mg/ml syringe at the 5th and 6th injection rated by the patient on a visual scale from 0 ("not convenient") to 10 ("very convenient").

Safety: Local tolerability at injection site, incidence of adverse events, determination of laboratory safety parameters (haematology and biochemistry).

Statistical Methods:

All data were subjected to descriptive analyses. Continuous data were to be summarised with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Descriptive analyses were to be summarised based on the specific patient set.

The primary efficacy variable (proportion of patient deciding in favour of the 50 mg/ml syringe after repeated subcutaneous injections of three 10 mg/ml and three 50 mg/ml syringes) was subjected to statistical testing according to the hypothesis system defined applying a two-sided one-group chi-square test on significance level of 5%. For all secondary variables evaluating the satisfaction and usability of the small 50 mg/ml syringes compared to the large 10 mg/ml syringes absolute and relative frequencies were provided. Safety endpoints were analysed descriptively.

Summary - Conclusions

Efficacy Results:

Demographics

- In total, 132 subjects were enrolled at 16 centres in Germany. Of these patients, one was excluded from the safety-analysis set and 4 were excluded from the full-analysis set.
- Of the 128 patients included in the full-analysis set, 34 were men and 94 women. Mean age was 55 years, mean weight 78 kg, mean height 167 cm, systolic blood pressure 131 mmHg, diastolic blood pressure 81 mmHg, heart rate 74 beats/min and mean body temperature 36.3°C.
- The mean baseline Disease Activity Score of 28 joints (DAS28) was 4.4 and the mean duration of rheumatoid arthritis in the patients was 5.6 years
- Of the 128 patients, 63 (49.2%) had previously received treatment with MTX in dosages which differ from those given at study start. At study start, methotrexate dosages ranged between 7.5 to 25 mg/week. 85.1% of the patients received dosages of 15 or 20 mg/week.
- Seventeen (13.3%) patients had a history of a relevant medical condition. The most frequent concomitant medical conditions were surgical and medical procedures (4.7%), followed be gastrointestinal disorders, infections and infestations, benign/malignant/unspecified neoplasms, nervous disorders and psychiatric disorders (1.6% each).
- Ninety-eight (76.6%) patients had a relevant concomitant illness. The most frequent illnesses were vascular disorders (39.1%) and musculoskeletal and connective tissue disorders (37.5%) followed by endocrine disorders (14.1%), metabolism and nutrition disorders (12.5%) and respiratory, thoracic and mediastinal disorders (10.2%).

Efficacy

The primary efficacy variable was to quantify the patient's decision for future MTX treatment (50 mg/ml syringe vs. 10 mg/ml syringe) following repeated subcutaneous injections of 10 mg/ml and 50 mg/ml syringes. At the end of the study, 93.0% of all patients stated that from now on they would prefer the small syringes (IMP) to Metex® (2.3%). The result was highly statistically significant ($p<0.0001$) and the primary study endpoint was met.

Secondary efficacy variables included physician's and patient's global assessment of syringe usability as well as patient's assessment of usability and preference of treatments:

- Physician's and patient's global assessment of syringe usability stratified by visit decreased from 77.0 to 65.5 mm from 1st to 3rd injection (Day 1 vs. Day 15) with Metex® treatment indicating deterioration and improved to 89.0, 85.6 and 86.7 mm with 4th, 5th and 6th injection when using small syringes (IMP). The differences between 1st and 4th as well as 3rd and 6th injection were statistically significant ($p<0.0001$) in favour of the IMP. However, it should be noted that assessments of the 1st and 4th injection were made by the physician and all others by the patient.
- Physician's and patient's global assessment of syringe usability stratified by filling volume was 69.7 mm with Metex® treatment and 87.3 mm with the small syringes (IMP). The difference was statistically significant ($p<0.0001$) in favour of the IMP.

Usability and preference of treatment with Metex® and the small syringes (IMP) as assessed by patients were:

- 99.1% of the patients assessed the convenience of having a fixed needle with the small syringe (IMP) as "advantageous" and "very advantageous" and 3.1% as "disadvantageous" and "very disadvantageous".
- 87.5% of the patients found that the smaller volume in the IMP was more suitable ("agreeable" and "very agreeable") compared to the larger volume with Metex®. 1.6% of the patients disagreed in this regard.
- At the end of the study, the patients' overall assessment of the small syringes (IMP) was "good" and "very good" in 90.6% of the patients compared to 1.6% with a "bad" and "very bad" overall assessment.
- The patients' overall assessment of Metex® was "good" and "very good" in 34.4% of the patients compared to 17.2% with a "bad" and "very bad" overall assessment.

Usability and preference of treatment with Metex® and the IMP as assessed by study nurse/investigator:

- All study nurses and investigators assessed the convenience of having a fixed needle with the small syringe (IMP) as "advantageous" and "very advantageous".
- 87.5% found that the smaller volume in the IMP was more suitable ("agreeable" and "very agreeable") compared to the larger volume with Metex®. 12.5% saw no difference in this regard.
- At the end of the study, study nurses' and investigators' overall assessment of the IMP was "good" (18.8%) and "very good" (81.3%).
- The overall assessment of Metex® was "good" in 31.3% of cases, "very good" in 12.5% and no preference in 50%.

Safety Results:

- Adverse events were reported in 25 (19.1%) of the 131 patients valid for safety analysis. The number of patients experiencing adverse events was 14 (10.7%) and 15 (11.5%) with 10 mg/ml and 50 mg/ml filling volume, respectively.
- Drug-related adverse events were reported in 24 (18.3%) patients. The number of patients experiencing such events was 14 (10.7%) in each treatment sequence.
- The most frequent adverse events and drug-related adverse events were gastrointestinal disorders (6.1%), investigations (3.8%) and general disorders and administration site conditions (3.1%).
- Adverse events were of severe intensity in 3 patients. All others were of mild and moderate intensity. Of all drug-related adverse events, 2 events were of severe intensity in 2 patients.
- No relevant differences were observed between the 2 MTX formulations with the exception of 5 cases of investigations occurring during IMP treatment compared to none during Metex® treatment.
- Three serious adverse events were reported, of which one occurred until the final examination and two within 28 days after the final examination. Two (cheek bone fracture and back pain) were considered unrelated to study drug and one case (mastoiditis) possibly related to study medication.
- No deaths were reported.
- Adverse events led to discontinuation of study participation in three patients. None of the possibly drug-related events was serious.
- Overall local tolerability as assessed by the absence of redness, swelling, itching, pain, and haematoma at the injection site was numerically greater with small syringe (IMP) treatment compared to Metex® treatment. Only few cases of moderate or severe intensity were reported, the incidences of these not being different between the 2 treatments to a relevant degree.
- For all laboratory categories (haematology and biochemistry), the number of patients with available measurements differed slightly with regard to the respective laboratory parameters and the time points of measurements. Absolute mean changes from baseline on the time of the 4th injection (Day 22) and study end were small and standard deviations were large. Mean changes from baseline vs. end of study were minor and tended to slightly decrease for all haematology parameters except for monocytes and basophils. Mean biochemistry parameter changes were also minor including those in liver function tests. Except for a mean decrease in CRP by 4 mg/l, mean changes were of no clinical relevance.

Conclusions:

The majority (93.0%) of the patients preferred the small syringes (IMP) to the large syringe (Metex®) (2.3%) at the end of the study and thus the primary study endpoint was met. The small syringe (IMP) was also valued higher by physicians, study nurses and patients with regard to usability and preference. A smaller volume of administered drug, the convenience of being able to use a fixed needle with the small syringe and a slightly improved local tolerability were the main reasons for the majority of patients to prefer the small syringe (IMP) used for subcutaneous MTX administration. This assessment was supported by similar assessments made by physicians and study nurses. Quality and quantity of adverse events did not differ between the two formulations.

Date of report:	20 Apr 2009