SYNOPSIS

Name of Sponsor: medac Gesellschaft für klinische Spezialpräparate mbH Fehlandtstrasse 3, 20354 Hamburg, Germany	
Name of finished product: Metoject®	
Name of active ingredient: methotrexate	
Title of study:	An open-label, randomised, two-period crossover study of repeated subcutaneous injections of methotrexate 50 mg/mL solution either by a pre-filled syringe (reference) or by a disposable pre-filled pen (test) to assess patients' preference and self-injection experience and to compare the local tolerability in patients with active rheumatoid arthritis
Investigators:	Coordinating Investigator: [redacted] Kerkhoff-Klinik GmbH, Bad Nauheim, Germany Principal investigators: [redacted]
Study centre(s):	The clinical study was performed at 12 study sites in Germany.
Publication (reference):	None.
Studied period (years):	date of first randomisation: 04-Jul-2012 date of last completed: 11-Apr-2013
Phase of development:	Phase III/IV
Objectives:	
Primary:	The primary objective was to assess the number of patients preferring the methotrexate (MTX) pre-filled pen to the pre-filled syringe after six weeks of treatment
Secondary:	• To assess the number of patients preferring the MTX pre-filled pen at the end of study based on a six-item questionnaire related to the overall ease of use, acceptability and satisfaction • To compare the self-injection experience of the patients after each treatment period using the Self-Injection Assessment Questionnaire (SIAQ) • To compare the local tolerability of subcutaneous injections by pre-filled syringes and disposable pre-filled pens at the injection site rated by the investigator 30 minutes after the first and fourth injection • To compare the local tolerability of subcutaneous injections by pre-filled syringes and disposable pre-filled pens at the injection site rated by the patient 30 minutes (except first and fourth injection), and 2 hours, 24 hours and 48 hours after injection. • To assess the incidence of adverse events during the study • To assess the number of study nurses and investigators preferring the MTX pre-filled pen at the end of the study (last patient last visit) • To document dysfunction of the pre-filled pen with respect to any information identifying and describing incidents in which the pre-filled pen was misused, broken, incapable of being activated, or did not deliver the appropriate dose

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Methodology:	Prospective, multicentre, open label, active controlled, randomised, two-period, two-sequence, crossover study
Number of patients (planned and analysed):	planned: 120 enrolled: 120 withdrawn: 8 completed: 112 analysed (safety): 120 analysed (efficacy): 111
Diagnosis and main criteria for inclusion:	Rheumatoid Arthritis diagnosed according to the American College of Rheumatology (ACR) Criteria (1987) or ACR/ European League Against Rheumatism (EULAR, 2010)
Test products, dose and mode of administration, batch number:	Using a pre-filled pen (pre-filled syringe sealed in an auto-injector), MTX was administered subcutaneously at a dose of 15, 17.5 or 20 mg weekly for three weeks. The administered dose had to remain stable during the course of the study. The batch numbers used during the course of this study were K110547AB (15 mg), L110541BA (17.5 mg) and L110540BA (20 mg).
Duration of treatment:	Patients were treated once weekly for six weeks.
Reference therapy, dose and mode of administration, batch number:	Using a pre-filled syringe, methotrexate was administered subcutaneously at a dose of 15, 17.5 or 20 mg weekly for three weeks. The administered dose had to remain stable during the course of the study. The batch numbers used during the course of this study were I 119108BB (15 mg), M 110770BA (17.5 mg) and E 119078CA (20 mg).
Criteria for evaluation:	
Efficacy:	Assessment of the primary objective, i.e. the number of patients preferring MTX pre-filled pen to the pre-filled syringe after six weeks of treatment, was based on the question 'Overall, if you could choose, which of both self-injection systems would you prefer for future MTX treatment?". The patients could choose between the answers 'I prefer the pre-filled pen" and 'I prefer the pre-filled syringe. The assessment of the number of patients preferring MTX pre-filled pen to the pre-filled syringe at the end of study regarding the overall ease of use, acceptability and satisfaction was based on a six-item questionnaire. The comparison of the self-injection experience of the patients after each treatment period was based on the SIAQ, v 2.0. The assessment of the number of study nurses / investigators preferring the MTX pre-filled pen at the end of the study was based on the question 'Overall, how would you rate the experience made by the patients with the pre-filled pen during the study?" The answers were given on a five-point semantic Likert-type scale. Additionally the study nurses / investigators were asked which of both self-injection systems they would recommend to their patients for future MTX treatment. The answers to be chosen were "pre-filled pen" or "pre-filled syringe". After each use of the pre-filled pen patients were to answer four questions in order to document any information identifying and describing incidents where the pre-filled pen was misused, broken, incapable of being activated or did not deliver the appropriate dose. The answers were documented by the patients in the patient diaries.
Safety:	The local tolerability of subcutaneous injections with pre-filled syringes and pre-filled pens was rated by the investigators 30 minutes after the first and after the fourth injection and documented on the CRF. In addition, the patients rated the local tolerance symptoms pain, redness, swelling, haematoma and itching using a four-point scale (none, mild, moderate, severe) 30 minutes (except first and fourth injection), 2 hours, 24 hours and 48 hours after injection and documented the results in the patient diary. Adverse events and serious adverse events were documented between Day 1 (first injection) and seven days after the last application of the investigational product. Thereafter, only serious adverse events with suspected relationship to the investigational product were to be reported. At Screening, the medical history focussing on rheumatoid arthritis and its associated treatment with MTX, body height, body weight, body temperature, systolic and diastolic blood pressure, and heart rate were to be assessed and documented. In addition, a physical examination was to be performed. All abnormal findings of the physical examination present at Screening which worsened after first

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	administration of MTX were to be documented as adverse events. Laboratory values (haematology and serum chemistry) were to be assessed at Screening, on Day 22, and at the End of Study Visit.
Statistical methods:	All data recorded on the case report forms describing the sample, the efficacy and the safety were first analysed descriptively. Descriptive statistics provided frequencies and percentages for categorical data. Continuous data were summarised with number of patients, with non-missing observations, arithmetic mean, standard deviation, minimum, median, maximum, 25% percentile (Q1) and 75% percentile (Q3). Preplanned confirmatory analysis consisted of showing that the rate of patients preferring the MTX pre-filled pen was significantly above 50%. A one-sided single-arm chi-square test on a significance level of 2.5% was applied. For exploratory analysis of six-item questionnaire methods rates were estimated and 95% confidence intervals were provided. Exploratory subgroup analyses taking into account potentially relevant covariates such as age, gender, body mass index (BMI), previous oral MTX treatment and activity of RA were foreseen. SIAQ was analysed by means of descriptive statistics and Analysis of Variance (ANOVA) models. For safety analysis, methods of descriptive statistics were applied. To allow for by-device analysis, adverse events were attributed to the last preceding device. Local tolerability was analysed separately and was therefore not included in AE-tables.
SUMMARY OF RESULTS **EFFICACY RESULTS:**	In 111 patients qualifying for Full Analysis Set, the rate of patients favouring the pre-filled pen was 74.8% with a 95% C.I. of [65.6%; 82.5%]. The one-sided single-arm chi-square test revealed that this rate was significantly above 50% ($p < 0.0001$). The preference rate in the Per Protocol Set was numerically equal. Exploratory subgroup analysis did not show relevant differences with respect to age, gender, body mass index, previous oral MTX treatment, and DAS28. For all subgroup categories, the rate of patients preferring the MTX pre-filled pen ranged from approximately 71.7% to 84.6% and the lower limits of the associated 95% confidence intervals were well above 50%. The assessment of the number of patients preferring MTX pre-filled pen to the pre-filled syringe at the end of study regarding the overall ease of use, acceptability and satisfaction was based on a six-item questionnaire. For all but one item, the rate of patients preferring the pen ranged from 73.0 to 75.7%. For the item 'It does not take much effort to overcome self-injection' the rate of patients preferring the pen reached only 66.7%. Exploratory subgroup analysis did not show relevant differences with respect to age, gender, body mass index, previous oral MTX treatment, and DAS28. A secondary objective was to assess and compare the self-injection experience of the patients after each treatment period based on the SIAQ. The SIAQ PRE module revealed patients' positive attitude towards self-injection at baseline. Both device sequence groups were homogeneously distributed with respect to PRE module domain results. The results of the SIAQ POST modules showed that the experience made by the patients with both device systems during the study was positive. No clinically important differences were found in all domains scores of the SIAQ POST module between both devices. However, exploratory statistical testing showed mean score differences between both devices in two domains: In the domain 'Self-image' the score was significantly higher for the pen (9.14 (pen) versus 8.71 (syringe); $p = 0.0059$), in the domain 'self-confidence' the score was significantly higher for the syringe (7.53 (syringe) versus 7.09 (pen); $p = 0.0444$). In addition, the ANOVA revealed a period effect for the domain 'Self-confidence'. However, focusing statistical analysis of SIAQ POST on the results before fourth injection only did not alter the general results described above. The study nurses/investigators questionnaire were completed (one per site) after the last visit of the last patient at each site. The investigator or study nurse reported positive to best experience made by all patients at their site with the pre-filled pen. All but one site would recommend the pre-filled pen at the end of the study for the future treatment of their patients.

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	In the Full Analysis Set, 18 patients reported dysfunction or misuse of the pre-filled pen or other difficulties at any injection. Three patients reported 'defects in the pen like cracks or breaks'. Seven patients reported their incapacity or difficulties to 'activate the injection by pushing the knob'. Nine patients reported that the 'solution could not be injected completely'. Finally, nine patients reported 'any other difficulties using the pre-filled pen'. Among those issues, review of individual comments revealed that in six patients, one injection per patient could not be performed due to a reported dysfunction of the pen. For these injections the pens had to be replaced. All other patients' reports concerned observations, incorrect use of the pen or difficulties encountered when using it.
SAFETY RESULTS:	Both MTX pen and syringe treatments were generally well tolerated. In 120 patients qualifying for the safety analysis no serious adverse events and no device related adverse events were reported during the course of this study. A total of 38 patients (31.7%) reported adverse events: 24 patients (20.7%) using the pen and 19 patients (16.2%) using the syringe. The severity of adverse events was mild in six patients (5.2%) using the pen and 12 patients (10.3%) using the syringe. It was moderate in 15 patients (12.9%) using the pen and in seven patients (6.0%) using the syringe. Only three patients (2.5%) using the pen reported severe adverse events. No relevant differences between the two devices were present with regard to number and type of adverse events. The adverse events that were reported most often were of the System Organ Classes 'Infections and infestations' (pen: 8.6%, syringe: 6.8%),'Gastrointestinal disorders' (pen: 8.6%, syringe: 2.6%), 'Nervous system disorders' (pen: 3.4%, syringe: 0.9%) and 'Skin and subcutaneous tissue disorders' (pen: 0.9%, syringe: 3.4%). More patients reported drug related adverse events using the pen (17 patients, 14.7%) compared to patients using the syringe (4 patients, 3.4%). A total of seven patients experienced adverse events that led to permanent discontinuation of MTX treatment. Adverse events leading to permanent MTX discontinuation were predominantly nausea in five patients and individual adverse events (experienced by one patient only: vomiting, dizziness, headache, pruritus, pruritus generalised, rash macular, swelling face, tachycardia, pyrexia, weight decreased, decreased appetite, and cough). More patients discontinued temporarily the MTX treatment when using the pen (four patients) compared to patients using the syringe (one patient). The associated AEs were influenza like illness, malaise, cystitis, gastrointestinal infection, hepatic enzyme increased, constipation, headache, and restlessness. The most frequently observed abnormal haematological parameters after Screening were increased white blood cells (14% of the patients) with increased neutrophils (15.7%) and reduced lymphocytes (10.8%) as well as reduced red blood cells (8.8 % of the patients). Elevated transaminases were the most frequently observed abnormal clinical chemistry parameters after screening (ALT: 16.7% of patients; AST 6.4%). All adverse reactions and abnormal laboratory values were in line with known undesirable effects of MTX or conditions associated with RA. With 48 hours of the injection 52 patients (44.8%) using the pen and 54 patients (46.2%) using the syringe experienced local symptoms as rated by the patient or the investigator. In the majority of patients the symptoms reported by patients were mild with both devices. Patients using the pen experienced the symptom haematoma most often (28.4%) followed by pain (21.6%), redness (16.4%), itching (8.6%) and swelling (6.9%). Patients using the syringe experienced the symptom haematoma (22.2%), redness (30.8%), pain and itching (8.5%, each), and swelling (7.7%). Exploratory analysis revealed differences in local intolerance symptoms between both devices for pain (21.6% for the pen versus 8.5% for the syringe, $p = 0.0019$) and redness (30.8% syringe versus 16.4% pen, $p = 0.0421$).

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CONCLUSION:

- The primary objective of the study was met. The majority of the patients preferred the pens over the syringes. In a total of 111 patients qualifying for Full Analysis Set, the rate of the patients favouring the pre-filled pen was 74.8% with a 95% C.I. of [65.6%; 82.5%]. The one-sided single-arm chi-square test revealed that this rate was significantly above 50% ($p < 0.0001$).
- The overall preference of the patient for the pen was confirmed by the results obtained with a six-item questionnaire regarding the overall ease of use, acceptability and satisfaction at the end of study. For all but one item, the rate of patients preferring the pen ranged from 73.0% to 75.7%. For the item "It does not take much effort to overcome self-injection" the rate of patients preferring the pen reached only 66.7%.
- The results of the SIAQ demonstrated the positive experience of the patients with the pen. These results were not clinically different between pen and syringe regarding all domains scores of the SIAQ POST module. Testing for difference in the mean scores between both devices revealed two domains with significantly different scores: The score of the domain 'Self-image' was significantly higher for the pen and the score of the domain 'self-confidence' was significantly higher for the syringe.
- The nurses and investigators reported positive to best experience made by all patients at their site with the pre-filled pen. All but one site would recommend the pre-filled pen at the end of the study for the future treatment of their patients.
- In the Full Analysis Set, 18 patients reported dysfunction or misuse of the pre-filled pen or other difficulties at any injection. A review of individual comments revealed that in six patients, one injection per patient could not be performed due to a reported dysfunction of the pen. For these injections the pens had to be replaced. All other patients' reports concerned observations, incorrect use of the pen or difficulties.
- The pre-filled pen and the pre-filled syringe were well tolerated at the injection site. 46.2% of the patients reported local tolerance symptoms; these were of mild severity in the majority of patients with both devices. On an exploratory perspective, significant differences in local intolerance symptoms between both devices were found for pain (21.6% for the pen versus 8.5% for the syringe, $p = 0.0019$) and redness (30.8% syringe versus 16.4% pen, $p = 0.0421$).
- In general, both MTX pen and syringe were well tolerated. No serious adverse events occurred during the course of this clinical study. No adverse events occurred which were considered to be device related. Reported adverse reactions were in line with the known undesirable effects of MTX.

Date of the report: 20-Dec-2013