An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP)

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Title: A 52-week double-blind placebo-controlled study of an intensified dosing schedule of subcutaneous methotrexate in patients with moderate-to-severe plaque-type psoriasis (METOP)

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Abstract: Background: We report the study of an intensified dosing schedule of subcutaneous methotrexate (MTX) in patients with moderate-to-severe psoriasis.

Methods: In this prospective, double-blind, multicentre phase 3 study (METOP) eligible patients were 18 years or older with a diagnosis of chronic plaque psoriasis at least 6 months before baseline, had a psoriasis area and severity index (PASI) of 10 or more or 10% or greater body-surface area involvement or a dermatology life quality index (DLQI) of 10 or more and were naïve to treatment with MTX. Participants were randomly assigned 3:1 by computer-generated random sequence integrated in the electronic data capture system to receive either MTX at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by open-label MTX treatment of all patients up to 52 weeks (MTX/MTX and PLC/MTX groups, respectively). Dose escalation to 22.5 mg/week was allowed after 8 weeks of MTX therapy if patients failed to achieve an at least 50% improvement of their baseline PASI (PASI50); blinding was maintained by a corresponding volume increase of placebo injections. Treatment was combined with folic acid 5 mg/week. The primary efficacy endpoint was the proportion of patients achieving a PASI75 response at week 16 analysed by intention to treat with non-responder imputation. This study is registered with the European Medicines Agency, EudraCT number 2012-002716-10.

Findings: Between February 2013 and May 2015 120 patients were randomly assigned to receive subcutaneous MTX (n=91) or placebo (n=29). The primary endpoint was met; the PASI75 response rate at week 16 was 41% (n=37) in the MTX group compared to 10% (n=3) in the placebo group [p=0.0026; effect size 30.3% (95% CI 15.3– 45.3) MTX vs placebo]. Subcutaneous MTX was generally well tolerated; no cases of serious infections, malignancies, major adverse cardiovascular events or deaths were noted. Serious adverse events were observed in 3 patients started on MTX during the 52-week study period.

Interpretation: The study documents a favourable 52-week benefit-risk profile of subcutaneous MTX in psoriasis. The route of administration and the intensified dosing schedule should be considered when using MTX in patients with psoriasis.

A 52-week double-blind placebo-controlled study of an intensified dosing schedule of subcutaneous methotrexate in patients with moderate-to-severe plaque-type psoriasis (METOP)

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Role of the funding source (see also below)

The study was an investigator-initiated trial supported by a grant from Medac to K.R.

Summary

Background: We report the study of an intensified dosing schedule of subcutaneous methotrexate (MTX) in patients with moderate-to-severe psoriasis.

Methods: In this prospective, double-blind, multicentre phase 3 study (METOP) eligible patients were 18 years or older with a diagnosis of chronic plaque psoriasis at least 6 months before baseline, had a psoriasis area and severity index (PASI) of 10 or more or 10% or greater body-surface area involvement or a dermatology life quality index (DLQI) of 10 or more and were naïve to treatment with MTX. Participants were randomly assigned 3:1 by computer-generated random sequence integrated in the electronic data capture system to receive either MTX at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by open-label MTX treatment of all patients up to 52 weeks (MTX/MTX and PLC/MTX groups, respectively). Dose escalation to 22.5 mg/week was allowed after 8 weeks of MTX therapy if patients failed to achieve an at least 50% improvement of their baseline PASI (PASI50); blinding was maintained by a corresponding volume increase of placebo injections. Treatment was combined with folic acid 5 mg/week. The primary efficacy endpoint was the proportion of patients achieving a PASI75 response at week 16 analysed by intention to treat with non-responder imputation. This study is registered with the European Medicines Agency, EudraCT number 2012-002716-10.

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Interpretation: The study documents a favourable 52-week benefit-risk profile of subcutaneous MTX in psoriasis. The route of administration and the intensified dosing schedule should be considered when using MTX in patients with psoriasis.

Word count 347

Introduction

Psoriasis today is perceived as an inflammatory disease complex that primarily affects the skin with erythematous and scaly plaques and requires early and continuous disease control similar to other chronic inflammatory conditions such as rheumatoid arthritis (RA) and inflammatory bowel disease. In 2014, the World Health Organisation recognized psoriasis as a serious non-communicable disease and its report from 2016 highlighted the life running nature of the disease and the need to urgently research and make accessible cost effective medicines throughout the world.¹

The development of monoclonal antibodies that target cytokines central to the psoriatic disease cascade including $\text{TNF}\alpha$, IL-23, and IL-17A, has significantly broadened the therapeutic armamentarium²⁻⁴ however, recent surveys indicate restricted usage of these expensive therapies in less than 10% of patients with moderate-to-severe disease even in Western countries.⁵ For over 50 year's methotrexate (MTX) has been used in the treatment of psoriasis and psoriatic arthritis and is recommended as first-line systemic agent for the treatment of moderate-to-severe psoriasis in US and European guidelines⁶ mainly based on experience and health economic considerations. However, in the absence of modern, well-designed clinical trials,⁷ uncertainties remain regarding the optimal dosing scheme, route of administration and the safety profile with appropriate monitoring in place. Only recently has high-quality data on MTX in psoriasis become available from three studies that tested MTX in comparison to the biologics adalimumab,⁸ briakinumab,⁹ and infliximab.¹⁰ While these studies differed in their dosing schemes, using MTX starting doses of 5 mg/week in conjunction with either a slower⁸ or more rapid uptitration scheme⁹ as well as a starting dose of 15 mg/week in one study,¹⁰ they all showed similar induction therapy PASI75 response rates of 36% to 42% after 16 to 24 weeks of treatment. Longer term data showed a low stability of MTX response with high drop-out rates due to loss of efficacy in up to 70% of patients over a one-year period.⁹ Interestingly, the safety profile of MTX in these studies was similar with different dosing schemes in the first months of therapy, and generally similar to the compared biologic during longer-term treatment with regard to events perceived as of special concern with MTX such as hepatopathy and leukopenia. In all these studies MTX was given orally, which may be suboptimal in light of a recent trial in RA indicating superiority of subcutaneous (s.c.) over oral MTX after a 24-week treatment period.¹¹

The aim of this study was to test an intensified s.c. dosing scheme of MTX in psoriasis with a starting dose of 17.5 mg/week and a possible dose increase to 22.5 mg/week against placebo over a 16-week induction period with a second MTX treatment period over a total of 52 weeks to better understand the potential of the drug in the treatment of this condition. Since the exact mechanism of action of MTX in psoriasis is unknown, we also investigated pairs of skin biopsies obtained before therapy and at week 16 with the intention to obtain insight into the effects of the drug on selected inflammatory disease pathways.

Methods

Study design and participants

METOP was conducted as a double-blind, placebo-controlled randomised investigator-initiated trial. Eligible participants were aged 18 years or older, were naïve to MTX and had a diagnosis of plaque-type psoriasis for at least 6 months with currently moderate-to-severe disease based on the definition by Finlay.¹² Patients were required to have a normal chest x-ray within 6 months prior to study entry and were excluded if hepatic enzymes (ALT, AST, or γ GT) were elevated above 2x the upper limit of normal or total leukocyte counts were below $3.0 \times 10^9/L$ in screening laboratory tests. Previous treatment with biologics had to be discontinued at least 5 times their half-life, other systemic therapies and phototherapies used for the treatment of psoriasis at least 4 weeks and topical therapies at least 2 weeks before study entry. Bland emollients were allowed during the study. Patients with a previous diagnosis of psoriatic arthritis (PsA) could be enrolled; however, patients with currently active PsA as defined by 5 or more tender or swollen joints and peripheral C-reactive protein levels above 2x the upper limit of normal were excluded. The complete list of inclusion and exclusion criteria is available in supplementary table S1.

The study was conducted according to the protocol and in conformance with the ICH-guideline “Note for Good Clinical Practice” (CPMP/ICH/135/95). Study documents were approved by a master ethical committee (University of Kiel, Germany) and investigational review boards at each site. All patients signed an informed consent before undergoing study-related procedures. In total 16 sites were selected in Germany (13 sites), France, Netherlands, and the UK (1 site each).

Randomisation and masking

The randomisation list was generated using the randomisation software randlist 1.2 and the randomisation number assigned at the baseline visit in an ascending order to subjects eligible for treatment after inclusion and exclusion criteria had been checked and the investigator had confirmed the randomisation of the patient. Eligible patients were randomised in a ratio of 3:1 to receive either MTX or placebo (PLC) injections for the first 16 weeks. Between week 16 and week 52 patients from both treatment groups were entitled to receive MTX injections, i.e. either continued on MTX (MTX/MTX group) or crossed-over from placebo (PLC/MTX group).

The trial was performed in a double-blind manner from the time of randomisation until an interim database lock for the data up to and including week 16. All trial drugs were supplied in identical packages. The syringes for placebo and active drug were not distinguishable and fully coated to prevent identification of colour differences between MTX and placebo injections. From week 16 on, MTX injections were open-label.

Procedures

From week 0 to week 16 patients received once weekly s.c. injections of 17.5 mg MTX (metex®, metoject®; concentration 50 mg/ml) in a volume of 0.35 mL or 0.35 mL placebo injections. If PASI50 was not reached after 8 weeks, patients received injections with 22.5 mg MTX/week in a volume of 0.45 mL or 0.45 mL placebo injections. The first injection at day 0 and the injection at day 112 were given at the study sites; all other injections were self-administered by the patient.

From week 16 to week 52 patients originally started on MTX remained on the same dose unless they were receiving 17.5 mg MTX/week and at week 24 had failed to reach PASI 75, in which case they could be dose-escalated to 22.5 mg MTX/week. If patients were already dosed with 22.5 mg

MTX/week at week 24 and PASI50 was not reached, patients were excluded from continuing with study treatment.

Patients originally started on placebo and switched to MTX at week 16 received 17.5 mg of s.c. MTX weekly with possible dose-escalation to 22.5 mg MTX/week at week 24 if PASI50 was not achieved. According to protocol, patients originally treated with placebo and achieving a PASI75 response at week 16 received no further injections until the disease relapsed, when they were treated with 17.5 mg MTX/week as described above.

Patients from all treatment groups received 5 mg of oral folic acid 24 hours after each injection.

Outcomes

The primary endpoint was the percentage of patients achieving an at least 75% improvement of the baseline PASI (PASI75) at week 16. Key secondary endpoints included the PASI75 response rate at week 52, and the following outcomes assessed at weeks 16 and 52: PASI50 and PASI90 response rates, a static physicians' global assessment (sPGA) measured on a 7-point scale ranging from 0=clear to 6=severe, the Nail Psoriasis Severity Index (NAPSI) of the finger nails, the dermatology life quality index (DLQI) and the EQ-5D with 5 levels ranging from level 1 (no problems) to level 5 (extreme problems) .

Safety was assessed based on reported adverse events (AEs), laboratory values, vital signs, physical examinations, and assessments of local drug tolerability collected and observed at study visits during the 52-week study period. AEs were classified as drug-related if the relationship was classified as "related" or "possible" by the investigator. All AEs appeared during treatment and fulfilled the criterion of treatment-emergent AEs. Levels of the amino-terminal propeptide of type-III procollagen (PIIINP) were assessed at baseline, week 16, week 32, and week 52.

Biopsy sub-study

Two punch biopsies (3 mm in diameter) were obtained from 27 patients from the edge of a representative psoriatic plaque, each at baseline and from the same plaque at week 16. One biopsy taken at each time point was immediately transferred to 4% buffered formalin, the other was fixed in RNAlater® solution (Qiagen, Hilden, Germany) for subsequent RNA extraction. All biopsies were handled and analysed by personnel blinded to treatment and time points. RNA was isolated by means of the RNeasy® Fibrous Tissue Mini Kit (Qiagen). Briefly, cDNA was synthesized using the Applied Biosystems® High Capacity cDNA Reverse Transcription Kit (Life Technologies, Grand Island, NY, USA). Quantitative real-time PCRs were carried out in duplicate using a Bio-Rad iQ5 Cyclor (Bio-Rad Laboratories, Hercules, CA, USA) as described.¹³ Results for IL17A, IFNG and TNFA were evaluated using the iQ5 Optical System Software, Version 2.0 (Bio-Rad Laboratories). Quantification was based on $\Delta\Delta CT$ calculations. Samples were normalized based on 2 reference genes, B2M and UBC. Psoriatic micro-anatomical features (epidermal thickness, parakeratosis, presence of epidermal microabscesses) and immunohistochemical markers (CD3-positive T cells, CD1a- and CD11c-positive dendritic cells, Ki-67-positive keratinocytes) were investigated and semi-quantitatively assessed on paraffin-embedded sections using the AxioVision SE64 Rel. 4.8 system (Zeiss, Oberkochen, Germany) on digitally scanned images as described.¹³

Statistical analysis

The METOP study intended to show that an intensified s.c. MTX dosing scheme is superior to PLC in inducing a PASI75 response at week 16 based on two-sided Pearson's Chi-square test with an alpha level of 0.05 of the mITT population with non-responder imputation. The sample size estimation of n=120 treated patients was based on this statistical approach, an assumed PASI75 response rate among MTX-treated patients at week 16 of 35% and among patients receiving placebo of 10%, a power of 80%, and a 3:1 randomization of active drug vs. placebo.

All outcomes were analysed based on the intention to treat population of all patients who had received at least one injection with study drug (modified ITT; mITT) with non-responder imputation (NRI), i.e. missing data were handled as indicating "no response". The mITT population included n=120 patients (n=91 patients started on MTX and n=29 patients started on PLC). All randomised patients received at least one injection of study drug. Post-hoc comparisons of secondary and non pre-specified endpoints at week 16 were also based on the mITT population with non-responder imputation and were performed using the two-sided Pearson's Chi-Square test with an alpha level of 0.05. These analyses were considered exploratory and no adjustment for multiple testing was made. Selected clinical outcomes at week 52 are also presented based on an as-observed analysis.

Two-sided 95% confidence intervals for PASI response rates over time were calculated according to Clopper-Pearson. For the relative risk and the effect size to achieve a PASI75 response at week 16 in response to MTX therapy vs placebo a two-sided asymptotic 95% confidence interval was calculated.

Safety analyses were based on the dataset of all patients who received at least one dose of study medication. Safety data are reported both prior to and after week 16.

Data of the biopsy sub-study were analysed using descriptive statistics. Scores of cutaneous cells positive for CD3, CD11c, or Ki67 in biopsies from week 16 were compared with values from paired biopsies taken at baseline using the Stuart-Maxwell test. Ratios of post- vs. pre-treatment cutaneous mRNA levels of INFG, IL17A, and TNFA were analysed for a difference from a median of "1" using the Wilcoxon test. Statistical tests were two-sided and performed at an alpha level of 0.05.

Role of the funding source

METOP was an investigator-initiated trial supported by a grant from Medac Germany to KR. Medac also supplied study medication, but had no influence on study conduct or interpretation. The study was designed by consultant experts in psoriasis (RBW, UM and KR) and by employees of SCIderm GmbH, Germany, which served as the clinical research organisation (CRO) for study management, data collection and statistical analysis. Data analysis was done by RBW, UM and KR. Safety data were reviewed at regular intervals by an independent data monitoring committee. RBW and KR prepared the manuscript. All co-authors participated in the collection and final interpretation of the data, reviewed the final manuscript and made the decision to submit for publication.

Results

Clinical findings

Recruitment took place between February 2013 and May 2015 at 13 sites; 11 in Germany, 1 site each in Netherlands, France and United Kingdom. In total 120 patients in METOP were randomly assigned to receive weekly s.c. injections of either placebo (n=29) or MTX (n=91). The majority of patients were middle-aged white males with long-standing psoriasis and a mean weight above 90 kg and a mean BMI around 30 (table 1). Main baseline disease activity characteristics were balanced between the groups with a mean PASI around 15 and a mean DLQI around 12 indicating moderate-to-severe disease with a major impact on health-related quality of life according to severity definitions used in clinical trials and guidelines.¹⁴ Disease duration tended to be longer in patients started on MTX and a previous diagnosis of PsA was documented more frequently in this treatment arm.

77 (85%) of patients in the MTX group and 22 (76%) in the placebo group completed the study through to 16 weeks (figure 1). Of those, 73% (n=56) continuing on MTX and 68% switching from placebo (n=22) completed the study through to 52 weeks.

Significantly more patients in the MTX group (37/91; 40.7%) than in the placebo group (3/29; 10.3%) met the criterion for the primary end point of an at least 75% improvement in the baseline PASI at week 16 ($p=0.0026$; relative risk 3.93 [95% CI 1.31-11.81]; figure 2 and table 2). Dose escalation to 22.5 mg/week at week 8 was documented in 30.8% of patients (28/91) in the MTX group. A sPGA of clear or almost clear (sPGA 0/1) was observed in 27.5% at week 16 (25/91) and a PASI90 response in approximately 1/6 patients (16/91; 17.6%) treated with MTX compared to 6.9% (2/29) and 0%, respectively, in the placebo group (figure 2 and table 2). Based on a non-responder imputation (NRI) analysis of the mITT population PASI75 response rates at week 52 were 45.1% in the MTX/MTX group (41/91) and 34.5% in the patients crossed over from placebo (19/29; figure 2 and table 2). Among patients crossed over from placebo dose escalation to 22.5 mg/week was documented in 22.7% (5/22) at week 24, i.e. 8 weeks after the initiation of active treatment. Five patients in the MTX/MTX group dose-escalated to 22.5 mg/week at week 24 (no PASI75 response). Response levels increased with continuous MTX therapy; PASI90 responses were seen in almost 28% and sPGA 0/1 responses in almost 40% of patients in both the MTX/MTX (25/91 and 36/91, respectively) and PLC/MTX (8/29 and 11/29, respectively) groups at week 52 (figure 2 and table 2). 78.4% (29/37) of patients achieving a PASI75 response at week 16 with MTX therapy still had this response at week 52. Among patients receiving MTX over the full 52-week treatment period PAS75/90/100 responses were seen in 73.2% (41/56)/44.6% (25/56)/17.9% (10/56) of patients and 64.3% (36/56) achieved a sPGA 0/1 response (as observed analyses; table 2). MTX reduced the activity of nail psoriasis within 16 weeks as measured by the NAPSI of the worst fingernail as a target nail while placebo had no effect (table 2). After 52 weeks of MTX treatment 13.6% of all patients with an active target nail at baseline showed complete clearance of that nail.

Improvements in the signs of psoriasis were paralleled by improvements in the health-related quality of life as assessed by the DLQI. An absolute DLQI ≤ 5 (mild effect of psoriasis on DLQI domains) and a DLQI of 0 or 1 (no effect of psoriasis on DLQI domains) at week 16 was found in 59.3% (54/91) and 42.9% (39/91) of patients treated with MTX, respectively, compared to 34.5% (10/29) and 10.3% (3/29) of patients receiving placebo (table 2). 71.4% (40/56) of patients

continuously treated with MTX throughout the study period (as observed analysis) had a DLQI 0/1 response at week 52 (table 2). The difference in the percentage of patients reporting “no problems” across the 5 dimensions assessed with the EQ-5D at week 16 compared to baseline indicated different effects of MTX compared to placebo. For example, 13.2% (12/91) more patients stated “no problems” with usual activities in the MTX arm compared to 13.8% less patients (4/29) in the placebo arm. Similarly, 6.6% (6/91) more individuals receiving MTX reported “no problems” with anxiety and depression at week 16 compared to baseline, but 17.2% less (5/29) among patients receiving placebo. A more detailed analysis is shown supplementary table S2.

Biopsy sub-study

Pairs of baseline and week-16 biopsies were available from 27 patients of whom 23% (6/27) received placebo (none with a PASI75 response), 26% (7/27) were MTX PASI75 non-responders, and 52% (14/27) were MTX PASI75 responders. In the latter group, clinical effects were associated with prominent reductions of numbers of skin-infiltrating CD3-positive T cells (supplementary figure S1) and CD11c-positive dendritic cells (not shown) with week-16 numbers almost returning to values in normal skin. These changes were associated with effects on the expression of specific Th17- and Th1 cytokines. Compared to baseline values, cutaneous mRNA levels of IL-17A at week 16 were largely reduced among MTX PASI75 responder, but not significantly altered among MTX PASI75 non-responder and patients receiving placebo (supplementary figure S1). Individual changes in cutaneous IL-17A mRNA levels correlated well with individual PASI responses (Spearman correlation coefficient -0.74; $p < 0.0001$). Similarly, levels of IFN- γ mRNA were reduced in responders to MTX with no major effects in the MTX non-responder group or patients receiving placebo, while expression levels of TNF- α remained unaffected (not shown), irrespective of the clinical response. Immunologic effects coincided with effects on selected epidermal parameters; the most pronounced reductions among MTX PASI75 responder were seen for numbers of Ki-67-positive (proliferating) keratinocytes and numbers of epidermal micro-abscesses (data not shown).

Safety findings

There were no deaths, malignancies or major adverse cardiovascular events (MACE) in this study and no SAEs related to treatment with MTX (table 3). During the placebo-controlled study phase, nasopharyngitis, headache, gastrointestinal disorders, and hepatic enzyme increase were the most frequently reported AEs (tables 3 and S3), of which the latter two types of AEs were more common in the MTX than in the placebo group (table 3). Among patients treated with MTX nausea and/or vomiting accounted for the majority of gastrointestinal events in the first 16 weeks and during the overall study period (table 3). Gastrointestinal AEs were usually mild or moderate and led to permanent discontinuations of study drug in 3 patients taking MTX (week 0 – 52). During the 1-year study period elevation of hepatic enzymes was reported as AE in 23.1% of the patients started on MTX and in approximately half of these cases led to permanent discontinuation of study drug (table 3). Hepatic enzyme increase was not associated with elevated levels of PIIINP, which were detected in 5 patients at baseline and in 5 patients at week 52 (1 was identical, 4 were different patients). Leukopenia was reported in 5.5% of patients started on MTX, but there was no case with leukopenia grade 3 or 4 and only one case with lymphopenia grade 3 (table 3). Rates of infections were similar between MTX- and placebo-treated patients with nasopharyngitis accounting for >50% of all

infectious events (tables 3 and S3). One case of severe nasopharyngitis was reported in study phase I in a patient receiving placebo. No serious and no severe infectious AEs were recorded during MTX therapy in this study.

Discussion

To the best of our knowledge this is the first double blind, placebo-controlled study to investigate s.c. MTX in patients with moderate to severe psoriasis and should help to close the gap, identified in a recent systematic review,⁷ in generating high quality data on a drug that has been in use for over 50 years. The study used an intensified dosing scheme with a higher starting dose of 17.5 mg/week compared to previous studies and a dose escalation to 22.5 mg/week after 8 weeks of MTX if PASI50 was not achieved. MTX was combined with 5 mg of oral folic acid given 24 h after the injection. The starting dosing was based on the results of three previous trials in which starting doses between 5 to 15 mg with different subsequent up-titration schemes were not associated with differences in the safety profile.⁸⁻¹⁰ Subcutaneous administration was chosen because of improved adherence, lower risk of accidental overdosing and higher concentration of MTX-polyglutamates (MTX-PG), the active MTX metabolite.^{15,16} The dose escalation scheme followed pharmacokinetic considerations to establish a stable pool of MTX-PG as well as a result of previous clinical observations in psoriasis. In particular, dose escalation beyond 22.5 mg/week was not tested as PASI50 non-responders to 20 mg did not benefit from further up-titration to 25 mg/week.⁸ In RA higher MTX-PG levels and improved outcomes have been observed after switching from oral to s.c. MTX¹⁷ and is supported by retrospective clinical data collected among patients with psoriasis that also suggest advantageous efficacy of s.c. MTX.^{18,19} Limitations of the study primarily relate to the relatively small number of patients enrolled and the lack of an active comparator arm with oral MTX. Additionally, the study population was mainly white so further study in non-white participants might be necessary to fully understand the efficacy and safety in a more genetically diverse population.

The induction efficacy observed in the present study is similar to previous findings with oral MTX in that approximately four out of ten patients achieve a PASI75 response by week 16 [this study 41% (37/91); three previous studies 36% to 42%].⁸⁻¹⁰ Different study populations and study designs, however, limit the value of this indirect comparison. In particular two of the previous trials with oral MTX were not placebo-, but active comparator-controlled,^{9,10} and one of them was an open-label study.¹⁰ Efficacy tended to increase up to week 24 in this study [PASI75/90=50.5% (46/91)/24.2% (22/91) among patients started on MTX], but this delayed response is difficult to distinguish from effects related to the termination of the blinding and open-label treatment with active drug from week 16 on. The main difference to oral dosing, in addition to a more rapid onset of efficacy [PASI75 response at week 8 approximately 30% (25/91) in this placebo-controlled study compared to approximately 20% in the previous active comparator-controlled study⁸], appeared to be a superior and more stable long-term response beyond week 16 and up to 52 weeks of therapy. In particular, based on ITT-NRI analyses, the PASI75 response rate at week 52 was 24% in the only previous 1-year trial with oral MTX using doses of up to 25 mg/week in combination with 5 mg folic acid per week⁹ compared to 45% (41/91) in this study. Similarly, higher levels of response at week 52 such as PASI90 and PGA 0/1 were seen in approximately 18% and 20% of patients in the previous trial with oral MTX⁷ compared to 28% (25/91) and 40% (36/91), respectively, in the present trial with s.c. MTX. While the overall dropout rate was above 70% (118/163) during the one-year study period among patients receiving oral MTX, with lack of response being the main reason (n=95), the dropout rate

over 52 weeks was 39% (35/91) in this study with n=8 patients discontinuing for lack of efficacy. Among patients started on s.c. MTX permanent study drug discontinuation due to adverse events was reported in 21% (19/91) of the subjects and elevation of liver enzymes was the single most common AE reported as the reason for permanent study drug discontinuation (11/91; 12%). All of these patients had elevations $> 3 \times \text{ULN}$ of at least one the tested parameters (ALT, AST, γGT). The distribution of age, weight and BMI among patients experiencing liver enzymes increase $> 3 \times \text{ULN}$ was similar to those in the overall patient population. Furthermore, levels of the amino-terminal propeptide of type III procollagen (PIIINP), which is regarded as a useful early marker of MTX-induced liver damage in psoriasis,²⁰ were not associated with liver enzyme increase. Gastrointestinal AEs including nausea and diarrhoea occurred in approximately 30% of the patients, but were usually mild and did not lead to study drug discontinuation (only n=4 affected patients terminated prematurely). Whether the s.c. administration of MTX or the setting of a clinical trial has influenced the low dropout rate due to GI problems remains to be further investigated. No severe or serious infections, no malignancies, or major adverse cardiovascular events and no deaths were observed during therapy with s.c. MTX.

The exact mechanisms of action of MTX in psoriasis are not clear at present, but immunomodulatory effects rather than direct anti-proliferative effects through inhibition of dihydrofolate reductase are assumed to play a role. There is increasing evidence that immunomodulatory effects are mediated at least partially *via* agonistic effects of MTX on the adenosine A2A receptor²¹ and inhibitory effects on NF- κB activation through depletion of tetrahydrobiopterin.²² More recently, a modulation of T cell motogenic pathways by MTX has been described.²³ We here present preliminary evidence that the clinical response to s.c. MTX involves inhibitory effects on key cellular components of the inflammatory infiltrate in psoriasis, namely CD11c-positive dendritic cells and T cells, as well as the cutaneous expression of cytokines central to helper T cells type 1 and type 17 (Th1/Th17) pathways.²⁴ These immunologic effects were paralleled by an at least partial normalization of epidermal changes characteristic for psoriasis such as keratinocyte hyperproliferation. Our results support and extend previous findings on a suppression of Th cytokine expression in patients responding to treatment with MTX.²⁵ While the observed changes are unlikely to represent a unique pattern induced by successful MTX therapy,^{13, 25} they add to the emerging concept of a spectrum of cutaneous immunologic effects mediated by the drug that warrant further investigation including the analysis of early skin responses before the onset of a marked clinical improvement.

MTX meets the WHO remit of being accessible throughout the world. This study encourages s.c. injections of MTX for the treatment of psoriasis and suggests long-term clinical outcomes better than previously reported for oral administration, although this warrants final confirmation in a direct head-to-head trial between s.c. and oral dosing. The study may also contribute to guide future recommendations on the optimal dosing of the drug. Our trial in concert with earlier trials with oral MTX as well as recent results from patient registries²⁶ support an acceptable benefit-risk profile of MTX, but appropriate patient selection and monitoring are mandatory, particularly with regard to gastrointestinal and hepatic side effects. There is growing evidence that genetic profiling of enzyme and transporter variants involved in MTX metabolism^{27, 28} as well as phenotyping of certain T cell populations²⁹ may in the future help to better predict patients responding to and tolerating MTX therapy.

Figure 1: Trial profile of METOP

Study phase 1=baseline to week 16 (double-blind). Study phase 2=week 16 to week 52 (open-label MTX).

	MTX/MTX (n=91)	Placebo/MTX (N=29)
Age at Screening, years		
mean $\pm$ SD	45.9 $\pm$ 12.9	44.4 $\pm$ 10.8
median (range)	48 (18-73)	46 (23-65)
Men, n (%)	65 (71.4)	25 (86.2)
Ethnic origin, n (%)		
White	89 (97.8)	28 (96.6)
Asian	2 (2.2)	0 (0.0)
Other	0 (0.0)	1 (3.4)
Weight, kg	92.4 $\pm$ 18.6	95.9 $\pm$ 20.9
≥ 100 kg, n (%)	26 (28.6)	11 (37.9)
BMI, kg per m ²	30.1 $\pm$ 6.3	30.1 $\pm$ 6.1
Psoriasis duration, years	20.7 $\pm$ 13.8	14.3 $\pm$ 11.3
sPGA ≥ 4 , n (%)	74 (81.3)	22 (75.9)
PASI	15.4 $\pm$ 5.9	15.4 $\pm$ 5.3
BSA	20.0 $\pm$ 11.7	19.6 $\pm$ 12.5
Nail psoriasis*		
Patients with at least one affected nail, n (%)	59 (64.8)	20 (69.0)
Target (worst) nail NAPSI; median (range)	4.0 (1-8)	4.0 (1-8)
DLQI	12.9 $\pm$ 7.7	11.6 $\pm$ 6.7
Confirmed PsA, n (%)	11 (12.1)	2 (6.9)
Previous therapy, n (%)		
Phototherapy	7 (7.7)	1 (3.4)
Conventional systemic**	29 (31.9)	7 (24.1)
Fumaric acid esters	24 (26.4)	7 (24.1)
Other	6 (6.6)	2 (6.9)
Biological	5 (5.5)	1 (3.4)

Values represent mean $\pm$ SD at baseline unless indicated otherwise. Data from single patients were missing for some parameters; BMI could not be calculated for 4 subjects. Confirmed PsA refers to a previous diagnosis by a rheumatologist, but does not indicate currently active PsA *referring to fingernails. **excluding methotrexate (MTX). BMI=Body Mass Index. BSA=Body Surface Area. DLQI=Dermatology Life Quality Index. NAPSI=Nail Psoriasis Severity Index. PASI=Psoriasis Area and Severity Index. PGA=Physicians' Global Assessment (range from 0=clear to 6=severe). PsA=Psoriatic Arthritis

Table 1: Baseline demographics and clinical characteristics

Figure 2. Percent of patients with different levels of clinical improvements over the 52-week treatment period

Shown are mean values and 95%-confidence intervals of mITT analyses with non-responder imputation (NRI). Patients received MTX (n=91) or placebo (n=29) until the primary endpoint at week 16 (red arrowheads); both groups were then continued on MTX.

	Week 16		Week 52	
	MTX mITT, N=91	Placebo mITT, N=29	MTX/MTX mITT, N=91 As observed, N=56	Placebo/MTX mITT, N=29 As observed, N=15
PASI50				
NRI	60 (65.9) ^a	9 (31.0)	53 (58.2)	10 (34.5)
As observed	nd	nd	53 (94.6)	10 (66.7)
PASI75				
NRI	37 (40.7) ^b	3 (10.3)	41 (45.1)	10 (34.5)
As observed	nd	nd	41 (73.2)	10 (66.7)
PASI90				
NRI	16 (17.6) ^c	0 (0.0)	25 (27.5)	8 (27.6)
As observed	nd	nd	25 (44.6)	8 (53.3)
PASI100				
NRI	4 (4.4)	0 (0.0)	10 (11.0)	5 (17.2)
As observed	nd	nd	10 (17.9)	5 (33.3)
PASI ≤3				
NRI	35 (38.5) ^d	3 (10.3)	42 (46.2)	10 (34.5)
As observed	nd	nd	42 (75.0)	10 (66.7)
sPGA 0,1				
NRI	25 (27.5) ^e	2 (6.9)	36 (39.6)	11 (37.9)
As observed	nd	nd	36 (64.3)	11 (73.3)
DLQI				
Absolute change mean ± SD	-9.4 ± 6.58	-2.6 ± 5.83	-11.6 ± 7.50	-5.5 ± 6.09
median (range)	-9.0 (-29-1)	-3.0 (-11-10)	-11.0 (-30-1)	-3.0 (-20-0)
DLQI ≤5, n (%)	54 (59.3) ^f	10 (34.5)	50 (54.9)	13 (44.8)
DLQI 0/1, n (%)				
NRI	39 (42.9) ^g	3 (10.3)	40 (44.0)	13 (44.8)
As observed	nd	nd	40 (71.4)	13 (86.7)
NAPSI^h	N=59 ^s	N=20 ^s	N=59 ^s	N=20 ^s
Absolute change mean ± SD	-0.86 ± 2.02	0.47 ± 1.46	-1.83 ± 2.05	-1.40 ± 2.12
median (range)	-1.00 (-8.0-3.0)	0.00 (-1.0-4.0)	-2.0 (-6.0-5.0)	-2.0 (-5.0-2.0)
Total clearance; n (%)	3 (5.1)	0 (0.0)	8 (13.6)	5 (25.0)

Values represent n (%) of patients in the respective group unless indicated otherwise; ^ap=0.0009; ^bp=0.0026; ^cp=0.015; ^dp=0.0046; ^ep=0.02; ^fp=0.02; ^gp=0.0014 MTX vs. placebo at week 16 (exploratory analyses for outcomes other than PASI75); ^hall nail data are NRI analyses of target nail (=worst finger nail) changes; ^spatients with at least one target nail (NAPSI≥1) at baseline.

DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; nd, not done; NRI, non responder imputation; PASI, Psoriasis Area and Severity Index; PGA, Physicians' Global Assessment (0=clear, 1=almost clear)

Table 2: Clinical responses at week 16 and week 52

	Week 0-16		Week 16-52		Week 0-52
	MTX (N=91)	PLC (N=29)	MTX/MTX (N=76)	PLC/MTX (N=22)	MTX/MTX (N=91)
Any AE	75 (82.4)	27 (93.1)	59 (77.6)	17 (77.3)	86 (94.5)
Any drug-related AE*	55 (60.4)	14 (48.3)	35 (46.1)	12 (54.5)	66 (72.5)
Any SAE	1 (1.1)	4 (13.8)	2 (2.6)	1 (4.5)	3 (3.3)
Any drug-related SAE*	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events of special interest					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any infection	40 (44.0)	13 (44.8)	31 (40.8)	11 (50.0)	58 (63.7)
Serious infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe infections	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MACE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (1.1)	1 (3.4)	1 (1.3)	0 (0.0)	2 (2.2)
White blood count decreased					
Any	4 (4.4)	1 (3.4)	1 (1.3)	0 (0.0)	5 (5.5)
Leukopenia Grade 3**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia Grade 3**	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.1)
Permanent discontinuation [§]	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Hepatic enzyme increased [¶]	12 (13.2)	2 (6.9)	10 (11.0)	5 (17.2)	21 (23.1)
>2 x ULN	10 (11.0)	1 (3.4)	7 (7.7)	5 (17.2)	17 (18.7)
>3 x ULN	8 (8.8)	1 (3.4)	6 (6.6)	3 (10.3)	14 (15.4)
Permanent discontinuation [§]	6 (6.6)	1 (3.4)	5 (5.5)	2 (6.9)	11 (12.1)
Gastrointestinal disorders					
Any	22 (24.2)	3 (10.3)	10 (13.2)	7 (31.8)	30 (33.0)
Nausea/vomiting	13 (14.3)	1 (3.4)	7 (9.2)	3 (13.6)	20 (22.0)
Diarrhoea	3 (3.3)	1 (3.4)	4 (5.2)	3 (13.6)	6 (6.6)
Abdominal pain	3 (3.3)	1 (3.4)	0 (0.0)	1 (4.5)	3 (3.3)
Mouth ulceration	3 (3.3)	0 (0.0)	0 (0.0)	1 (4.5)	3 (3.3)
Permanent discontinuation [§]	1 (1.1)	1 (3.4)	2 (2.6)	0 (0.0)	3 (3.3)

All values represent n (%) of patients with events receiving treatment in the indicated study phase. Adverse events (AEs) are assigned to the study phase in which they started. Severe infections are infectious AEs requiring systemic treatment. *AEs and serious AEs (SAEs) were classified as “drug-related” if the relationship was classified as “related” or “possibly related” by the investigator. **According to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 with grade 3 lymphopenia $<500 - 200/\text{mm}^3$ and grade 3 leukopenia $<2000 - 1000/\text{mm}^3$; case had 467 lymphocytes/ mm^3 , no grade 4 lymphopenia or leukopenia were observed. [¶]Hepatic enzymes included aspartate and alanine aminotransferase (ALT, AST) and γ -glutamyltransferase (γ GT). [§]Permanent study drug discontinuations due to the respective AEs of interest are assigned to the actual time of discontinuation. MACE=major cardiovascular adverse event (myocardial infarction, stroke, death due to cardiovascular event). ULN=upper limit or normal.

Table 3: Adverse events of special interest for METOP

References

1. Global Report on Psoriasis, World Health Organization.
www.who.int/iris/handle/10665/204417 DOA 10/05/2016
2. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**: 1367-74.
3. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675-84.
4. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; **371**: 326-38.
5. Lebwohl MG, Kavanaugh A, Armstrong AW, Van Voorhees AS. US Perspectives in the Management of Psoriasis and Psoriatic Arthritis: Patient and Physician Results from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. *Am J Clin Dermatol* 2016; **17**: 87-97.
6. Warren RB, Chalmers RJ, Griffiths CE, Menter A. Methotrexate for psoriasis in the era of biological therapy. *Clin Exp Dermatol* 2008; **33**: 551-4.
7. West J, Ogston S, Foerster J. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. *PLoS One* 2016;**11**:e0153740.
8. Saurat JH, Langley RG, Reich K, Unnebrink K, Sasso EH, Kampman W. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. *Br J Dermatol* 2011; **165**: 399-406.
9. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med* 2011; **365**: 1586-96.
10. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011; **165**: 1109-17.
11. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58**: 73-81.
12. Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005; **152**: 861-7.
13. Reich K, Papp KA, Matheson RT, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol* 2015; **24**: 529-35.
14. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1-10.

15. Hawwa AF, AlBawab A, Rooney M, Wedderburn LR, Beresford MW, McElnay JC
Methotrexate polyglutamates as a potential marker of adherence to long-term therapy in children with juvenile idiopathic arthritis and juvenile dermatomyositis: an observational, cross-sectional study. *Arthritis Res Ther* 2015; **17**:295.
16. Dervieux T, Furst D, Lein DO, et al. Pharmacogenetic and metabolite measurements are associated with clinical status in patients with rheumatoid arthritis treated with methotrexate: results of a multicentred cross sectional observational study. *Ann Rheum Dis* 2005; **64**: 1180-5.
17. Stamp LK, Barclay ML, O'Donnell JL, et al. Effects of changing from oral to subcutaneous methotrexate on red blood cell methotrexate polyglutamate concentrations and disease activity in patients with rheumatoid arthritis. *J Rheumatol* 2011; **38**: 2540-7.
18. Yesudian PD, Leman J, Balasubramaniam P, et al. Effectiveness of Subcutaneous Methotrexate in Chronic Plaque Psoriasis. *J Drugs Dermatol* 2016; **15**: 345-9.
19. West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. *Br J Dermatol*. 2016;**174**:1407-10
20. Montaudié H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. *J Eur Acad Dermatol Venereol* 2011; **25**: Suppl 2:2-11.
21. Vincenzi F, Padovan M, Targa M, et al. A(2A) adenosine receptors are differentially modulated by pharmacological treatments in rheumatoid arthritis patients and their stimulation ameliorates adjuvant-induced arthritis in rats. *PLoS One* 2013; **8**: e54195.
22. Spurlock CF 3rd, Tossberg JT, Matlock BK, Olsen NJ, Aune TM. Methotrexate-mediated inhibition of nuclear factor κ B activation by distinct pathways in T cells and fibroblast-like synoviocytes. *Rheumatology* 2015; **54**: 178-87.
23. Talme T, Bergdahl E, Sundqvist KG. Methotrexate and its therapeutic antagonists, caffeine and theophylline, target a motogenic T-cell mechanism driven by thrombospondin-1 (TSP-1). *Eur J Immunol* 2016; **46**:1279-90.
24. Zaba LC, Fuentes-Duculan J, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol* 2009; **129**:79-88.
25. Goldminz AM, Suárez-Fariñas M, Wang AC, et al. CCL20 and IL22 Messenger RNA Expression After Adalimumab vs Methotrexate Treatment of Psoriasis: A Randomized Clinical Trial. *JAMA Dermatol* 2015; **151**:837-46.
26. Reich K, Mrowietz U, Radtke MA, Thaci D, Rustenbach SJ, Spehr C, Augustin M. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res*. 2015 Dec;**307**(10):875-83

27. Warren RB, Smith RL, Campalani E, et al. Genetic variation in efflux transporters influences outcome to methotrexate therapy in patients with psoriasis. *J Invest Dermatol* 2008; **128**: 1925-9.
28. Becker ML, Gaedigk R, van Haandel L, et al. The effect of genotype on methotrexate polyglutamate variability in juvenile idiopathic arthritis and association with drug response. *Arthritis Rheum* 2011; **63**: 276-85.
29. Peres RS, Liew FY, Talbot J, et al. Low expression of CD39 on regulatory T cells as a biomarker for resistance to methotrexate therapy in rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2015; **112**: 2509-14.

A 52-week double-blind placebo-controlled study of an intensified dosing schedule of subcutaneous methotrexate in patients with moderate-to-severe plaque-type psoriasis (METOP)

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Summary

Background: We report the [study of](#) an intensified dosing schedule of subcutaneous methotrexate (MTX) in patients with moderate-to-severe psoriasis.

Methods: [In this prospective, double-blind, multicentre phase 3 study \(METOP\) eligible patients were 18 years or older with a diagnosis of chronic plaque psoriasis at least 6 months before baseline, had a psoriasis area and severity index \(PASI\) of 10 or more or 10% or greater body-surface area involvement or a dermatology life quality index \(DLQI\) of 10 or more and were naïve to treatment with MTX. Participants](#) were randomly assigned 3:1 by computer-generated random sequence integrated in the [electronic data capture](#) system to receive either MTX at a starting dose of 17.5 mg/week or placebo for the first 16 weeks, followed by [open-label](#) MTX treatment [of all patients](#) up to 52 weeks (MTX/MTX and PLC/MTX groups, respectively). Dose escalation to 22.5 mg/week was allowed after 8 weeks of MTX therapy if patients failed to achieve an at least 50% improvement of their [baseline PASI \(PASI50\)](#); [blinding was maintained by a corresponding volume increase of placebo injections](#). Treatment was combined with folic acid 5 mg/week. [The primary efficacy endpoint was the proportion of patients achieving a PASI75 response at week 16 analysed by intention to treat with non-responder imputation. This study is registered with the European Medicines Agency, EudraCT number 2012-002716-10.](#)

Findings: [Between February 2013 and May 2015 120 patients were randomly assigned to receive subcutaneous MTX \(n=91\) or placebo \(n=29\). The primary endpoint was met; the PASI75 response rate at week 16 was 41% \(n=37\) in the MTX group compared to 10% \(n=3\) in the placebo group \[p=0.0026; effect size 30.3% \(95% CI 15.3– 45.3\) MTX vs placebo\].](#) Subcutaneous MTX was generally well tolerated; [no cases of serious infections, malignancies, major adverse cardiovascular events or deaths were noted. Serious adverse events were observed in 3 patients started on MTX during the 52-week study period.](#)

Interpretation: The study documents a favourable 52-week benefit-risk profile of subcutaneous MTX in psoriasis. The route of administration and the intensified dosing schedule should be considered when using MTX in patients with psoriasis.

Introduction

Psoriasis today is perceived as an inflammatory disease complex that primarily affects the skin with erythematous and scaly plaques and requires early and continuous disease control similar to other chronic inflammatory conditions such as rheumatoid arthritis (RA) and inflammatory bowel disease. In 2014, the World Health Organisation recognized psoriasis as a serious non-communicable disease and its report from 2016 highlighted the life running nature of the disease and the need to urgently research and make accessible cost effective medicines throughout the world.¹

The development of monoclonal antibodies that target cytokines central to the psoriatic disease cascade including $\text{TNF}\alpha$, IL-23, and IL-17A, has significantly broadened the therapeutic armamentarium²⁻⁴ however, recent surveys indicate restricted usage of these expensive therapies in less than 10% of patients with moderate-to-severe disease even in the Western countries.⁵ For over 50 year's methotrexate (MTX) has been used in the treatment of psoriasis and psoriatic arthritis and is recommended as first-line systemic agent for the treatment of moderate-to-severe psoriasis in US and European guidelines⁶ mainly based on experience and health economic considerations. However, in the absence of modern, well-designed clinical trials,⁷ uncertainties remain regarding the optimal dosing scheme, route of administration and the safety profile with appropriate monitoring in place. Only recently has high-quality data on MTX in psoriasis become available from three studies that tested MTX in comparison to the different biologics including adalimumab,⁸ briakinumab,⁹ and infliximab.¹⁰ While these studies differed in their dosing schemes, using MTX starting doses of 5 mg/week in conjunction with either a slower⁸ or more rapid uptitration scheme⁹ as well as a starting dose of 15 mg/week in one study,¹⁰ they all showed similar induction therapy PASI75 response rates of 36% to 42% after 16 to 24 weeks of treatment. Longer term data showed a low stability of MTX response with high drop-out rates due to loss of efficacy in up to 70% of patients over a one-year period.⁹ Interestingly, the safety profile of MTX in these studies was similar with different dosing schemes in the first months of therapy, and generally similar to the compared biologic during longer-term treatment with regard to events perceived as of special concern with MTX such as hepatopathy and leukopenia. In all these studies MTX was given orally, which may be suboptimal in light of a recent trial in RA indicating superiority of subcutaneous (s.c.) over oral MTX after a 24-week treatment period.¹¹

The aim of this study was to test an intensified s.c. dosing scheme of MTX in psoriasis with a starting dose of 17.5 mg/week and a possible dose increase to 22.5 mg/week against placebo over a 16-week induction period with a second MTX treatment period over a total of 52 weeks to better understand the potential of the drug in the treatment of this condition. Since the exact mechanism of action of MTX in psoriasis is unknown, we also investigated pairs of skin biopsies obtained before therapy and at week 16 with the intention to obtain insight into the effects of the drug on selected inflammatory disease pathways.

Methods

Study design and participants

METOP was conducted as a double-blind, placebo-controlled randomised investigator-initiated trial. Eligible participants were aged 18 years or older, were naïve to MTX and had a diagnosis of plaque-type psoriasis for at least 6 months with currently moderate-to-severe disease based on the definition by Finlay.¹² Patients were required to have a normal chest x-ray within 6 months prior to study entry and were excluded if hepatic enzymes (ALT, AST, or γ GT) were elevated above 2x the upper limit of normal or total leukocyte counts were below $3.0 \times 10^9/L$ in screening laboratory tests. Previous treatment with biologics had to be discontinued at least 5 times their half-life, other systemic therapies and phototherapies used for the treatment of psoriasis at least 4 weeks and topical therapies at least 2 weeks before study entry. Bland emollients were allowed during the study. Patients with a previous diagnosis of psoriatic arthritis (PsA) could be enrolled; however, patients with currently active PsA as defined by 5 or more tender or swollen joints and peripheral C-reactive protein levels above 2x the upper limit of normal were excluded. The complete list of inclusion and exclusion criteria is available in supplementary table S1.

The study was conducted according to the protocol and in conformance with the ICH-guideline “Note for Good Clinical Practice” (CPMP/ICH/135/95), ~~the German Drug Law (Arzneimittelgesetz; including its 15th and 16th amendment) and the corresponding Directive 2001/20/EC.~~ Study documents were approved by a master ethical committee (University of Kiel, Germany) and investigational review boards at each site. All patients signed an informed consent before undergoing study-related procedures. In total 16 sites were selected in Germany (13 sites), France, Netherlands, and the UK (1 site each).

Randomisation and masking

The randomisation list was generated using the randomisation software randlist 1.2 and the randomisation number assigned at the baseline visit in an ascending order to subjects eligible for treatment after inclusion and exclusion criteria had been checked and the investigator had confirmed the randomisation of the patient. Eligible patients were randomised in a ratio of 3:1 to receive either MTX or placebo (PLC) injections for the first 16 weeks. Between week 16 and week 52 patients from both treatment groups were entitled to receive MTX injections, i.e. either continued on MTX (MTX/MTX group) or crossed-over from placebo (PLC/MTX group).

The trial was performed in a double-blind manner from the time of randomisation until an interim database lock for the data up to and including week 16. All trial drugs were supplied in identical packages. The syringes for placebo and active drug were not distinguishable and fully coated to prevent identification of colour differences between MTX and placebo injections. From week 16 on, MTX injections were open-label.

Procedures

From week 0 to week 16 patients received once weekly s.c. injections of 17.5 mg MTX (metex®, metoject®; concentration 50 mg/ml) in a volume of 0.35 mL or 0.35 mL placebo injections. If PASI50 was not reached after 8 weeks, patients received injections with 22.5 mg MTX/week in a volume of 0.45 mL or 0.45 mL placebo injections. The first injection at day 0 and the injection at day 112 were given at the study sites; all other injections were self-administered by the patient.

From week 16 to week 52 patients originally started on MTX remained on the same dose unless they were receiving 17.5 mg MTX/week and at week 24 had failed to reach PASI 75, in which case they could be dose-escalated to 22.5 mg MTX/week. If patients were already dosed with 22.5 mg MTX/week at week 24 and PASI50 was not reached, patients were excluded from continuing with study treatment.

Patients originally started on placebo and switched to MTX at week 16 received 17.5 mg of s.c. MTX weekly with possible dose-escalation to 22.5 mg MTX/week at week 24 if PASI50 was not achieved. According to protocol, patients originally treated with placebo and achieving a PASI75 response at week 16 received no further injections until the disease relapsed, when they were treated with 17.5 mg MTX/week as described above.

Patients from all treatment groups received 5 mg of oral folic acid 24 hours after each injection.

Outcomes

The primary endpoint was the percentage of patients achieving an at least 75% improvement of the baseline PASI (PASI75) at week 16. Key secondary endpoints included the PASI75 response rate at week 52, and the following outcomes assessed at weeks 16 and 52: PASI50 and PASI90 response rates, a static physicians' global assessment (sPGA) measured on a 7-point scale ranging from 0=clear to 6=severe, the Nail Psoriasis Severity Index (NAPSI) of the finger nails, and the dermatology life quality index (DLQI) and the EQ-5D with 5 levels ranging from level 1 (no problems) to level 5 (extreme problems). ~~Non pre-specified analyses presented in this paper include patients achieving a PASI100 response or an absolute PASI $\leq$ 3 at weeks 16 and 52, and analyses of PASI75 response rates at week 16 in subgroups defined by weight, previous therapy or their clinical response at week 8. All outcomes were analysed based on the population with non-responder imputation (NRI), i.e. missing data were handled as indicating "no response".~~

Safety was assessed based on reported adverse events (AEs), laboratory values, vital signs, physical examinations, and assessments of local drug tolerability collected and observed at study visits during the 52-week study period. AEs were classified as drug-related if the relationship was classified as "related" or "possible" by the investigator. All AEs appeared during treatment and fulfilled the criterion of treatment-emergent AEs. Levels of the amino-terminal propeptide of type-III procollagen (PIIINP) were assessed at baseline, week 16, week 32, and week 52.

Biopsy sub-study

Two punch biopsies (3 mm in diameter) were obtained from 27 patients from the edge of a representative psoriatic plaque, each at baseline and from the same plaque at week 16. One biopsy taken at each time point was immediately transferred to 4% buffered formalin, the other was fixed in RNAlater® solution (Qiagen, Hilden, Germany) for subsequent RNA extraction. All biopsies were handled and analysed by personnel blinded to treatment and time points. RNA was isolated by means of the RNeasy® Fibrous Tissue Mini Kit (Qiagen). Briefly, cDNA was synthesized using the Applied Biosystems® High Capacity cDNA Reverse Transcription Kit (Life Technologies, Grand Island, NY, USA). Quantitative real-time PCRs were carried out in duplicate using a Bio-Rad iQ5 Cyclor (Bio-Rad Laboratories, Hercules, CA, USA) as described.¹³ Results for IL17A, IFNG and TNFA were evaluated using the iQ5 Optical System Software, Version 2.0 (Bio-Rad Laboratories). Quantification

was based on $\Delta\Delta CT$ calculations. Samples were normalized based on 2 reference genes, B2M and UBC. Psoriatic micro-anatomical features (epidermal thickness, parakeratosis, presence of epidermal microabscesses) and immunohistochemical markers (CD3-positive T cells, CD1a- and CD11c-positive dendritic cells, Ki-67-positive keratinocytes) were investigated and semi-quantitatively assessed on paraffin-embedded sections using the AxioVision SE64 Rel. 4.8 system (Zeiss, Oberkochen, Germany) on digitally scanned images as described.¹³

Statistical analysis

The METOP study intended to show that an intensified s.c. MTX dosing scheme is superior to PLC in inducing a PASI75 response at week 16 based on two-sided Pearson's Chi-square test with an alpha level of 0.05 of the mITT population with non-responder imputation. The sample size estimation of n=120 treated patients was based on this statistical approach, an assumed PASI75 response rate among MTX-treated patients at week 16 of 35% and among patients receiving placebo of 10%, a power of 80%, and a 3:1 randomization of active drug vs. placebo.

All outcomes were analysed based on the intention to treat population of all patients who had received at least one injection with study drug (modified ITT; mITT) with non-responder imputation (NRI), i.e. missing data were handled as indicating "no response". The mITT population included n=120 patients (n=91 patients started on MTX and n=29 patients started on PLC). All randomised patients received at least one injection of study drug. Post-hoc comparisons of secondary and non pre-specified endpoints at week 16 were also based on the mITT population with non-responder imputation and were performed using the two-sided Pearson's Chi-Square test with an alpha level of 0.05. These analyses were considered exploratory and no adjustment for multiple testing was made. Selected clinical outcomes at week 52 are also presented based on an as-observed analysis.

Two-sided 95% confidence intervals for PASI response rates over time were calculated according to Clopper-Pearson. For the relative risk and the effect size to achieve a PASI75 response at week 16 in response to MTX therapy vs placebo a two-sided asymptotic 95% confidence interval was calculated.

Safety analyses were based on the dataset of all patients who received at least one dose of study medication. Safety data are reported both prior to and after week 16.

Data of the biopsy sub-study were analysed using descriptive statistics. Scores of cutaneous cells positive for CD3, CD11c, or Ki67 in biopsies from week 16 were compared with values from paired biopsies taken at baseline using the Stuart-Maxwell test. Ratios of post- vs. pre-treatment cutaneous mRNA levels of INFG, IL17A, and TNFA were analysed for a difference from a median of "1" using the Wilcoxon test. Statistical tests were two-sided and performed at an alpha level of 0.05.

Role of the funding source

METOP was an investigator-initiated trial supported by a grant from Medac Germany to KR. Medac also supplied study medication, but had no influence on study conduct or interpretation. The study was designed by consultant experts in psoriasis (RBW, UM and KR) and by employees of SCIderm GmbH, Germany, which served as the clinical research organisation (CRO) for study management, data collection and statistical analysis. Data analysis was done bytogether-with RBW, UM and KR. Safety data were reviewed at regular intervals by an independent data monitoring committee. RBW

220 and KR prepared the manuscript. All co-authors participated in the collection and final interpretation
221 of the data. ~~All authors~~ reviewed the final manuscript and made the decision to submit for
222 publication.

Results

Clinical findings

Recruitment took place between February 2013 and May 2015 at 13 sites; 11 in Germany, 1 site each in Netherlands, France and United Kingdom. In total 120 patients in METOP were randomly assigned to receive weekly s.c. injections of either placebo (n=29) or MTX (n=91). The majority of patients were middle-aged white males with long-standing psoriasis and a mean weight above 90 kg and a mean BMI around 30 (table 1). Main baseline disease activity characteristics were balanced between the groups with a mean PASI around 15 and a mean DLQI around 12 indicating moderate-to-severe disease with a major impact on health-related quality of life according to severity definitions used in clinical trials and guidelines.¹⁴ Disease duration tended to be longer in patients started on MTX and a previous diagnosis of PsA was documented more frequently in this treatment arm.

77 (85%) of patients in the MTX group and 22 (76%) in the placebo group completed the study through to 16 weeks (figure 1). Of those, 73% (n=56) -continuing on MTX and 68% switching from placebo (n=22) completed the study through to 52 weeks.

Significantly more patients in the MTX group (37/91; 40.7%) than in the placebo group (3/29; 10.3%) met the criterion for the primary end point of an at least 75% improvement in the baseline PASI at week 16 (p=0.0026; relative risk 3.93 [95% CI 1.31-11.81]; figure 2 and table 2). Dose escalation to 22.5 mg/week at week 8 was documented in 30.8% of patients (28/91) in the MTX group. A sPGA of clear or almost clear (sPGA 0/1) was observed in 27.5% at week 16 (25/91) and a PASI90 response in approximately 1/6 patients (16/91; 17.6%) treated with MTX compared to 6.9% (2/29) and 0%, respectively, in the placebo group (figure 2 and table 2). ~~Significantly different responses occurred early with 27.5% of patients in the MTX group achieving a PASI50 response at week 4 compared to 3.4% in the placebo group (p=0.0062; post-hoc analysis).~~ Based on a non-responder imputation (NRI) analysis of the mITT population PASI75 response rates at week 52 were 45.1% in the MTX/MTX group (41/91) and 34.5% in the patients crossed over from placebo (19/29; figure 2 and table 2). Among patients crossed over from placebo dose escalation to 22.5 mg/week was documented in 22.7% (5/22) at week 24, i.e. 8 weeks after the initiation of active treatment. Five patients in the MTX/MTX group dose-escalated to 22.5 mg/week at week 24 (no PASI75 response). Response levels increased with continuous MTX therapy; PASI90 responses were seen in almost 28% and sPGA 0/1 responses in almost 40% of patients in both the MTX/MTX (25/91 and 36/91, respectively) and PLC/MTX (8/29 and 11/29, respectively) groups at week 52 (figure 2 and table 2). 78.4% (29/37) of patients achieving a PASI75 response at week 16 with MTX therapy still had this response at week 52. Among patients receiving MTX over the full 52-week treatment period PAS75/90/100 responses were seen in 73.2% (41/56)/44.6% (25/56)/17.9% (10/56) of patients and 64.3% (36/56) achieved a sPGA 0/1 response (as observed analyses; table 2). ~~Post-hoc analyses showed trends for similar PASI75 response rates at week 16 among MTX-treated patients <100 kg (41.5%) compared to individuals ≥100 kg (38.5%) and higher responses at week 16 among patients naïve to previous conventional or biologic therapy (PASI75/90: 43.5%/21.0%) compared to those with prior systemic therapy (PASI75/90: 34.5%/10.3%).~~ MTX reduced the activity of nail psoriasis within 16 weeks as measured by the NAPS of the worst fingernail as a target nail while placebo had no effect (table 2).

After 52 weeks of MTX treatment 13.6% of all patients with an active target nail at baseline showed complete clearance of that nail.

Improvements in the signs of psoriasis were paralleled by improvements in the health-related quality of life as assessed by the [Dermatology Life Quality Index \(DLQI\)](#). An absolute DLQI ≤ 5 (mild effect of psoriasis on DLQI domains) and a DLQI of 0 or 1 (no effect of psoriasis on DLQI domains) at week 16 was found in 59.3% (54/91) and 42.9% (39/91) of patients treated with MTX, respectively, compared to 34.5% (10/29) and 10.3% (3/29) of patients receiving placebo (table 2). 71.4% (40/56) of patients continuously treated with MTX throughout the study period (as observed analysis) had a DLQI 0/1 response at week 52 (table 2). The difference in the percentage of patients reporting “no problems” across the 5 dimensions assessed with the EQ-5D at week 16 compared to baseline indicated different effects of MTX compared to placebo. For example, 13.2% (12/91) more patients stated “no problems” with usual activities in the MTX arm compared to 13.8% less patients (4/29) in the placebo arm. Similarly, 6.6% (6/91) more individuals receiving MTX reported “no problems” with anxiety and depression at week 16 compared to baseline, but 17.2% less (5/29) among patients receiving placebo. A more detailed analysis is shown supplementary table S2.

Biopsy sub-study

Pairs of baseline and week-16 biopsies were available from 27 patients of whom 23% (6/27) received placebo (none with a PASI75 response), 26% (7/27) were MTX PASI75 non-responders, and 52% (14/27) were MTX PASI75 responders. In the latter group, clinical effects were associated with prominent reductions of numbers of skin-infiltrating CD3-positive T cells ([supplementary figure S13](#)) and CD11c-positive dendritic cells (not shown) with week-16 numbers almost returning to values in normal skin. These changes were associated with effects on the expression of specific Th17- and Th1 cytokines. Compared to baseline values, cutaneous mRNA levels of IL-17A at week 16 were largely reduced among MTX PASI75 responder, but not significantly altered among MTX PASI75 non-responder and patients receiving placebo ([supplementary figure S13](#)). Individual changes in cutaneous IL-17A mRNA levels correlated well with individual PASI responses (Spearman correlation coefficient -0.74; $p < 0.0001$). Similarly, levels of IFN- γ mRNA were reduced in responders to MTX with no major effects in the MTX non-responder group or patients receiving placebo, while expression levels of TNF- α remained unaffected (not shown), irrespective of the clinical response. Immunologic effects coincided with effects on selected epidermal parameters; the most pronounced reductions among MTX PASI75 responder were seen for numbers of Ki-67-positive (proliferating) keratinocytes and numbers of epidermal micro-abscesses (data not shown).

Safety findings

There were no deaths, malignancies or major adverse cardiovascular events (MACE) in this study and no SAEs related to treatment with MTX (table 3). During the placebo-controlled study phase, nasopharyngitis, headache, gastrointestinal disorders, and hepatic enzyme increase were the most frequently reported AEs (tables 3 and S32), of which the latter two types of AEs were more common in the MTX than in the placebo group (table 3). frequent in the MTX than in the placebo group mainly due to an increased rate of overall laboratory abnormalities (MTX 22.0%, PLC 13.8%) and gastrointestinal AEs (MTX 24.2%, PLC 10.3%). Higher dropout rates due to adverse events during the

~~placebo-controlled part were seen in the placebo group with no specific pattern identifiable. "Psoriasis" as an AE was more frequently reported in the placebo group (13.8%) than in the MTX group (1.1%).~~ Among patients treated with MTX nausea and/or vomiting accounted for the majority of gastrointestinal events in the first 16 weeks and during the overall study period (table 3). Gastrointestinal AEs were usually mild or moderate and led to permanent discontinuations of study drug in 3 patients taking MTX (week 0 – 52). During the 1-year study period elevation of hepatic enzymes was reported as AE in 23.1% of the patients started on MTX and in approximately half of these cases led to permanent discontinuation of study drug (table 3). Hepatic enzyme increase was not associated with elevated levels of PIIINP, which were detected in 5 patients at baseline and in 5 patients at week 52 (1 was identical, 4 were different patients). Leukopenia was reported in 5.5% of patients started on MTX, but there was no case with leukopenia grade 3 or 4 and only one case with lymphopenia grade 3 (table 34). Rates of infections were similar between MTX- and placebo-treated patients with nasopharyngitis accounting for >50% of all infectious events (tables 3 and S324). One case of severe nasopharyngitis was reported in study phase I in a patient receiving placebo. No serious and no severe infectious AEs were recorded during MTX therapy in this study.

Discussion

To the best of our knowledge this is the first double blind, placebo-controlled study to investigate s.c. MTX in patients with moderate to severe psoriasis and should help to close the gap, identified in a recent systematic review,⁷ in generating high quality data on a drug that has been in use for over 50 years. The study used an intensified dosing scheme with a higher starting dose of 17.5 mg/week compared to previous studies and a dose escalation to 22.5 mg/week after 8 weeks of MTX if PASI50 was not achieved. MTX was combined with 5 mg of oral folic acid given 24 h after the injection. The starting dosing was based on the results of three previous trials in which starting doses between 5 to 15 mg with different subsequent up-titration schemes were not associated with differences in the safety profile.⁸⁻¹⁰ Subcutaneous administration was chosen because of improved adherence, lower risk of accidental overdosing and higher concentration of MTX-polyglutamates (MTX-PG), the active MTX metabolite.^{15,16} The dose escalation scheme followed pharmacokinetic considerations to establish a stable pool of MTX-PG as well as a result of previous clinical observations in psoriasis. In particular, dose escalation beyond 22.5 mg/week was not tested as PASI50 non-responders to 20 mg did not benefit from further up-titration to 25 mg/week.⁸ In RA higher MTX-PG levels and improved outcomes have been observed after switching from oral to s.c. MTX¹⁷ and is supported by retrospective clinical data collected among patients with psoriasis that also suggest advantageous efficacy of s.c. MTX.^{18,19} Limitations of the study primarily relate to the relatively small number of patients enrolled and the lack of an active comparator arm with oral MTX. Additionally, the study population was mainly white so further study in non-white participants might be necessary to fully understand the efficacy and safety in a more genetically diverse population.

The induction efficacy observed in the present study is similar to previous findings with oral MTX in that approximately four out of ten patients achieve a PASI75 response by week 16 [this study 41% (37/91); three previous studies 36% to 42%].⁸⁻¹⁰ Different study populations and study designs, however, limit the value of this indirect comparison. In particular two of the previous trials with oral MTX were not placebo-, but active comparator-controlled,^{9,10} and one of them was an open-label study.¹⁰ Efficacy tended to increase up to week 24 in this study [PASI75/90=50.5% (46/91)/24.2% (22/91) among patients started on MTX], but this delayed response is difficult to distinguish from

effects related to the termination of the blinding and open-label treatment with active drug from week 16 on. The main difference to oral dosing, in addition to a more rapid onset of efficacy [PASI75 response at week 8 approximately 30% (25/91) in this placebo-controlled study compared to approximately 20% in the previous active comparator-controlled study⁸], appeared to be a superior and more stable long-term response beyond week 16 and up to 52 weeks of therapy. In particular, based on ITT-NRI analyses, the PASI75 response rate at week 52 was 24% in the only previous 1-year trial with oral MTX using doses of up to 25 mg/week in combination with 5 mg folic acid per week⁹ compared to 45% (41/91) in this study. Similarly, higher levels of response at week 52 such as PASI90 and PGA 0/1 were seen in approximately 18% and 20% of patients in the previous trial with oral MTX⁷ compared to 28% (25/91) and 40% (36/91), respectively, in the present trial with s.c. MTX. While the overall dropout rate was above 70% (118/163) during the one-year study period among patients receiving oral MTX, with lack of response being the main reason (n=95), the dropout rate over 52 weeks was 39% (35/91) in this study with n=8 patients discontinuing for lack of efficacy. Among patients started on s.c. MTX permanent study drug discontinuation due to adverse events was reported in 21% (19/91) of the subjects and elevation of liver enzymes was the single most common AE reported as the reason for permanent study drug discontinuation (11/91; 12%). All of these patients had elevations > 3 x ULN of at least one the tested parameters (ALT, AST, γ GT). The distribution of age, weight and BMI among patients experiencing liver enzymes increase >3 x ULN was similar to those in the overall patient population. Furthermore, levels of the amino-terminal propeptide of type III procollagen (PIIINP), which is regarded as a useful early marker of MTX-induced liver damage in psoriasis,²⁰¹⁹ were not associated with liver enzyme increase. Gastrointestinal AEs including nausea and diarrhoea occurred in approximately 30% of the patients, but were usually mild and did not lead to study drug discontinuation (only n=4 affected patients terminated prematurely). Whether the s.c. administration of MTX or the setting of a clinical trial has influenced the low dropout rate due to GI problems remains to be further investigated. No severe or serious infections, no malignancies, or major adverse cardiovascular events and no deaths were observed during therapy with s.c. MTX.

~~Evaluation of the effects of dose escalation was not part of the pre-specified analyses. The exploratory finding that 64% of patients with a PASI50 response at week 8 (48/53) achieved a PASI75 response at week 16 without dose escalation compared to 8% (3/38) of patients with no PASI50 response at week 8 who were dose-escalated may be taken as preliminary evidence that a) early partial clinical response is a marker of later response to MTX and that b) the value of dose escalation in patients with no early partial response to 17.5 mg s.c. MTX is not supported by the findings of this study.~~

The exact mechanisms of action of MTX in psoriasis are not clear at present, but immunomodulatory effects rather than direct anti-proliferative effects through inhibition of dihydrofolate reductase are assumed to play a role. There is increasing evidence that immunomodulatory effects are mediated at least partially *via* agonistic effects of MTX on the adenosine A2A receptor²¹⁹ and inhibitory effects on NF- κ B activation through depletion of tetrahydrobiopterin.²²¹ More recently, a modulation of T cell motogenic pathways by MTX has been described.²³² We here present preliminary evidence that the clinical response to s.c. MTX involves inhibitory effects on key cellular components of the inflammatory infiltrate in psoriasis, namely CD11c-positive dendritic cells and T cells, as well as the cutaneous expression of cytokines central to helper T cells type 1 and type 17 (Th1/Th17) pathways.²⁴³ These immunologic effects were paralleled by an at least partial normalization of

epidermal changes characteristic for psoriasis such as keratinocyte hyperproliferation. Our results support and extend previous findings on a suppression of Th cytokine expression in patients responding to treatment with MTX.²⁵⁴ While the observed changes are unlikely to represent a unique pattern induced by successful MTX therapy,^{13, 254} they add to the emerging concept of a spectrum of cutaneous immunologic effects mediated by the drug that warrant further investigation including the analysis of early skin responses before the onset of a marked clinical improvement.

MTX meets the WHO remit of being accessible throughout the world. This study encourages s.c. injections of MTX for the treatment of psoriasis and suggests long-term clinical outcomes better than previously reported for oral administration, although this warrants final confirmation in a direct head-to-head trial between s.c. and oral dosing. The study may also contribute to guide future recommendations on the optimal dosing of the drug. Our trial in concert with earlier trials with oral MTX as well as recent results from patient registries²⁶⁵ support an acceptable benefit-risk profile of MTX, but appropriate patient selection and monitoring are mandatory, particularly with regard to gastrointestinal and hepatic side effects. There is growing evidence that genetic profiling of enzyme and transporter variants involved in MTX metabolism^{276, 287} as well as phenotyping of certain T cell populations²⁹⁸ may in the future help to better predict patients responding to and tolerating MTX therapy.

Figure 1: Trial profile of METOP

Study phase 1=baseline to week 16 (double-blind). Study phase 2=week 16 to week 52 (open-label MTX).

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	MTX/MTX (n=91)	Placebo/MTX (N=29)
Age at Screening, years		
mean $\pm$ SD	45.9 $\pm$ 12.9	44.4 $\pm$ 10.8
median (range)	48 (18-73)	46 (23-65)
Men, n (%)	65 (71.4)	25 (86.2)
Ethnic origin, n (%)		
White	89 (97.8)	28 (96.6)
Asian	2 (2.2)	0 (0.0)
Other	0 (0.0)	1 (3.4)
Weight, kg	92.4 $\pm$ 18.6	95.9 $\pm$ 20.9
≥ 100 kg, n (%)	26 (28.6)	11 (37.9)
BMI, kg per m ²	30.1 $\pm$ 6.3	30.1 $\pm$ 6.1
Psoriasis duration, years	20.7 $\pm$ 13.8	14.3 $\pm$ 11.3
sPGA ≥ 4 , n (%)	74 (81.3)	22 (75.9)
PASI	15.4 $\pm$ 5.9	15.4 $\pm$ 5.3
BSA	20.0 $\pm$ 11.7	19.6 $\pm$ 12.5
Nail psoriasis*		
Patients with at least one affected nail, n (%)	59 (64.8)	20 (69.0)
Target (worst) nail NAPSI; median (range)	4.0 (1-8)	4.0 (1-8)
DLQI	12.9 $\pm$ 7.7	11.6 $\pm$ 6.7
Confirmed PsA, n (%)	11 (12.1)	2 (6.9)
Previous therapy, n (%)		
Phototherapy	7 (7.7)	1 (3.4)
Conventional systemic**	29 (31.9)	7 (24.1)
Fumaric acid esters	24 (26.4)	7 (24.1)
Other	6 (6.6)	2 (6.9)
Biological	5 (5.5)	1 (3.4)

435 Values represent mean $\pm$ SD at baseline unless indicated otherwise. Data from single patients were missing for
436 some parameters; BMI could not be calculated for 4 subjects. Confirmed PsA refers to a previous diagnosis by
437 a rheumatologist, but does not indicate currently active PsA *referring to fingernails. **excluding
438 methotrexate (MTX). BMI=Body Mass Index. BSA=Body Surface Area. DLQI=Dermatology Life Quality Index.
439 NAPSI=Nail Psoriasis Severity Index. PASI=Psoriasis Area and Severity Index. PGA=Physicians' Global
440 Assessment (range from 0=clear to 6=severe). PsA=Psoriatic Arthritis

441 **Table 1: Baseline demographics and clinical**
442 **characteristics**

Figure 2. Percent of patients with different levels of clinical improvements over the 52-week treatment period

Shown are mean values and 95%-confidence intervals of mITT analyses with non-responder imputation (NRI). Patients received MTX (n=91) or placebo (n=29) until the primary endpoint at week 16 (red arrowheads); both groups were then continued on MTX.

	Week 16		Week 52	
	MTX mITT, N=91	Placebo mITT, N=29	MTX/MTX mITT, N=91 As observed, N=56	Placebo/MTX mITT, N=29 As observed, N=15
PASI50				
NRI	60 (65.9) ^{a**}	9 (31.0)	53 (58.2)	10 (34.5)
As observed	nd	nd	53 (94.6)	10 (66.7)
PASI75				
NRI	37 (40.7) ^{b**}	3 (10.3)	41 (45.1)	10 (34.5)
As observed	nd	nd	41 (73.2)	10 (66.7)
PASI90				
NRI	16 (17.6) ^{c*}	0 (0.0)	25 (27.5)	8 (27.6)
As observed	nd	nd	25 (44.6)	8 (53.3)
PASI100				
NRI	4 (4.4)	0 (0.0)	10 (11.0)	5 (17.2)
As observed	nd	nd	10 (17.9)	5 (33.3)
PASI ≤3				
NRI	35 (38.5) ^{d**}	3 (10.3)	42 (46.2)	10 (34.5)
As observed	nd	nd	42 (75.0)	10 (66.7)
sPGA 0,1				
NRI	25 (27.5) ^{e*}	2 (6.9)	36 (39.6)	11 (37.9)
As observed	nd	nd	36 (64.3)	11 (73.3)
DLQI				
Absolute change mean ± SD	-9.4 ± 6.58	-2.6 ± 5.83	-11.6 ± 7.50	-5.5 ± 6.09
median (range)	-9.0 (-29-1)	-3.0 (-11-10)	-11.0 (-30-1)	-3.0 (-20-0)
DLQI ≤5, n (%)	54 (59.3) ^{f*}	10 (34.5)	50 (54.9)	13 (44.8)
DLQI 0/1, n (%)				
NRI	39 (42.9) ^{g**}	3 (10.3)	40 (44.0)	13 (44.8)
As observed	nd	nd	40 (71.4)	13 (86.7)
NAPSI^h	N=59 [§]	N=20 [§]	N=59 [§]	N=20 [§]
Absolute change mean ± SD	-0.86 ± 2.02	0.47 ± 1.46	-1.83 ± 2.05	-1.40 ± 2.12
median (range)	-1.00 (-8.0-3.0)	0.00 (-1.0-4.0)	-2.0 (-6.0-5.0)	-2.0 (-5.0-2.0)
Total clearance; n (%)	3 (5.1)	0 (0.0)	8 (13.6)	5 (25.0)

Values represent n (%) of patients in the respective group unless indicated otherwise; ^a*p=0.0009; ^bp=0.0026; ^cp=0.015; ^dp=0.0046; ^ep=0.02; ^fp=0.02; ^gp=0.0014 <0.05 and ^h*p<0.005—MTX vs. placebo at week 16 (exploratory analyses for outcomes other than PASI75); ^hall nail data are NRI analyses of target nail (=worst finger nail) changes; [§]patients with at least one target nail (NAPSI≥1) at baseline.

DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; nd, not done; NRI, non responder imputation; PASI, Psoriasis Area and Severity Index; PGA, Physicians' Global Assessment (0=clear, 1=almost clear)

Table 2: Clinical responses at week 16 and week 52

	Week 0-16		Week 16-52		Week 0-52	
	MTX (N=91)	PLC (N=29)	MTX/MTX (N=91)	PLC/MTX (N=29)	MTX/MTX (N=91)	PLC/MTX (N=29)
Any AE	75 (82.4)	27 (93.1)	59 (64.8)	17 (58.6)	86 (94.5)	28 (96.6)
Any drug-related AE*	55 (60.4)	14 (48.3)	35 (38.5)	12 (41.4)	66 (72.5)	21 (72.4)
Any SAE	1 (1.1)	4 (13.8)	2 (2.2)	1 (3.4)	3 (3.3)	5 (17.2)
Any drug-related SAE*	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.9)
Common AEs**						
Nasopharyngitis	25 (27.5)	8 (27.6)	18 (19.8)	5 (17.2)	39 (42.9)	13 (44.8)
Headache	12 (13.2)	5 (17.2)	5 (5.5)	1 (3.4)	16 (17.6)	6 (20.7)
Fatigue	8 (8.8)	1 (3.4)	0 (0.0)	2 (6.9)	8 (8.8)	3 (10.3)
Back pain	6 (6.6)	3 (10.3)	7 (7.7)	1 (3.4)	12 (13.2)	4 (13.8)
Cough	5 (5.5)	1 (3.4)	2 (2.2)	0 (0.0)	7 (7.7)	1 (3.4)
Hypertension	3 (3.3)	0 (0.0)	4 (4.4)	2 (6.9)	6 (6.6)	2 (6.9)
Bronchitis	3 (3.3)	0 (0.0)	3 (3.3)	0 (0.0)	6 (6.6)	0 (0.0)
Sinusitis	3 (3.3)	1 (3.4)	2 (2.2)	0 (0.0)	5 (5.5)	1 (3.4)
Arthralgia	2 (2.2)	0 (0.0)	4 (4.4)	1 (3.4)	5 (5.5)	1 (3.4)
Increase of MCV	2 (2.2)	0 (0.0)	4 (4.4)	1 (3.4)	5 (5.5)	1 (3.4)
Pain in extremity	1 (1.1)	1 (3.4)	0 (0.0)	1 (3.4)	1 (1.1)	2 (6.9)
Influenza	1 (1.1)	1 (3.4)	4 (4.4)	5 (17.2)	4 (4.4)	6 (20.7)
Oropharyngeal pain	1 (1.1)	2 (6.9)	0 (0.0)	1 (3.4)	1 (1.1)	2 (6.9)
Rhinorrhoea	1 (1.1)	1 (3.4)	0 (0.0)	1 (3.4)	1 (1.1)	2 (6.9)
Osteoarthritis	0 (0.0)	0 (0.0)	2 (2.2)	3 (10.3)	2 (2.2)	3 (10.3)
Myalgia	0 (0.0)	1 (3.4)	0 (0.0)	3 (10.3)	0 (0.0)	3 (10.3)

All values represent n (%) of patients with events. *AEs and SAEs are assigned to the study phase in which they started and were classified as “drug-related” if the relationship was classified as “related” or “possibly related” by the investigator. **AEs occurring in at least 5% of patients in either treatment group during 52-week study period by system organ class preferred term excluding hepatic enzyme increase and gastrointestinal disorders, which are given in Table 4. Common AEs are listed according to their frequency in the MTX group week 0 to 16. AE=adverse events. MCV=mean corpuscular volume. SAE=serious adverse events.

Table 3: Common adverse events for METOP

	Week 0-16		Week 16-52		Week 0-52
	MTX (N=91)	PLC (N=29)	MTX/MTX (N=76)	PLC/MTX (N=22)	MTX/MTX (N=91)
Any AE	75 (82.4)	27 (93.1)	59 (77.6)	17 (77.3)	86 (94.5)
Any drug-related AE*	55 (60.4)	14 (48.3)	35 (46.1)	12 (54.5)	66 (72.5)
Any SAE	1 (1.1)	4 (13.8)	2 (2.6)	1 (4.5)	3 (3.3)
Any drug-related SAE*	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events of special interest					
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any infection	40 (44.0)	13 (44.8)	31 (40.8)	11 (50.0)	58 (63.7)
Serious infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe infections	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MACE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (1.1)	1 (3.4)	1 (1.3)	0 (0.0)	2 (2.2)
White blood count decreased					
Any	4 (4.4)	1 (3.4)	1 (1.3)	0 (0.0)	5 (5.5)
Leukopenia Grade 3**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

<u>Lymphopenia Grade 3**</u>	<u>0 (0.0)</u>	<u>0 (0.0)</u>	<u>1 (1.3)</u>	<u>0 (0.0)</u>	<u>1 (1.1)</u>
<u>Permanent discontinuation[§]</u>	<u>2 (2.2)</u>	<u>0 (0.0)</u>	<u>0 (0.0)</u>	<u>0 (0.0)</u>	<u>2 (2.2)</u>
<u>Hepatic enzyme increased[¶]</u>	<u>12 (13.2)</u>	<u>2 (6.9)</u>	<u>10 (11.0)</u>	<u>5 (17.2)</u>	<u>21 (23.1)</u>
<u>>2 x ULN</u>	<u>10 (11.0)</u>	<u>1 (3.4)</u>	<u>7 (7.7)</u>	<u>5 (17.2)</u>	<u>17 (18.7)</u>
<u>>3 x ULN</u>	<u>8 (8.8)</u>	<u>1 (3.4)</u>	<u>6 (6.6)</u>	<u>3 (10.3)</u>	<u>14 (15.4)</u>
<u>Permanent discontinuation[§]</u>	<u>6 (6.6)</u>	<u>1 (3.4)</u>	<u>5 (5.5)</u>	<u>2 (6.9)</u>	<u>11 (12.1)</u>
<u>Gastrointestinal disorders</u>					
<u>Any</u>	<u>22 (24.2)</u>	<u>3 (10.3)</u>	<u>10 (13.2)</u>	<u>7 (31.8)</u>	<u>30 (33.0)</u>
<u>Nausea/vomiting</u>	<u>13 (14.3)</u>	<u>1 (3.4)</u>	<u>7 (9.2)</u>	<u>3 (13.6)</u>	<u>20 (22.0)</u>
<u>Diarrhoea</u>	<u>3 (3.3)</u>	<u>1 (3.4)</u>	<u>4 (5.2)</u>	<u>3 (13.6)</u>	<u>6 (6.6)</u>
<u>Abdominal pain</u>	<u>3 (3.3)</u>	<u>1 (3.4)</u>	<u>0 (0.0)</u>	<u>1 (4.5)</u>	<u>3 (3.3)</u>
<u>Mouth ulceration</u>	<u>3 (3.3)</u>	<u>0 (0.0)</u>	<u>0 (0.0)</u>	<u>1 (4.5)</u>	<u>3 (3.3)</u>
<u>Permanent discontinuation[§]</u>	<u>1 (1.1)</u>	<u>1 (3.4)</u>	<u>2 (2.6)</u>	<u>0 (0.0)</u>	<u>3 (3.3)</u>

All values represent n (%) of patients with events receiving treatment in the indicated study phase. Adverse events (AEs) are assigned to the study phase in which they started. Severe infections are infectious AEs requiring systemic treatment. *AEs and serious AEs (SAEs) were classified as “drug-related” if the relationship was classified as “related” or “possibly related” by the investigator. **According to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 with grade 3 lymphopenia <500 – 200/mm³ and grade 3 leukopenia <2000 – 1000/mm³; case had 467 lymphocytes/mm³, no grade 4 lymphopenia or leukopenia were observed. [¶]Hepatic enzymes included aspartate and alanine aminotransferase (ALT, AST) and γ -glutamyltransferase (γ GT). [§]Permanent study drug discontinuations due to the respective AEs of interest are assigned to the actual time of discontinuation.

MACE=major cardiovascular adverse event (myocardial infarction, stroke, death due to cardiovascular event).
ULN=upper limit or normal.

Table 3: Adverse events of special interest for METOP

	Week 0-16		Week 16-52		Week 0-52	
	MTX (N=91)	PLC (N=29)	MTX/MTX (N=91)	PLC/MTX (N=29)	MTX/MTX (N=91)	PLC/MTX (N=29)
Adverse events of special interest						
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any infection	40 (44.0)	13 (44.8)	31 (34.1)	11 (37.9)	58 (63.7)	22 (75.9)
Serious infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe infections	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Malignancies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MACE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depression	1 (1.1)	1 (3.4)	1 (1.1)	0 (0.0)	2 (2.2)	1 (3.4)
White blood count decreased						
Any	4 (4.4)	1 (3.4)	1 (1.1)	0 (0.0)	5 (5.5)	1 (3.4)
Leukopenia Grade 3*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia Grade 3*	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	0 (0.0)
Permanent discontinuation [§]	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
Hepatic enzyme increased**	12 (13.2)	2 (6.9)	10 (11.0)	5 (17.2)	21 (23.1)	7 (24.1)
>2 x ULN	10 (11.0)	1 (3.4)	7 (7.7)	5 (17.2)	17 (18.7)	6 (20.7)
>3 x ULN	8 (8.8)	1 (3.4)	6 (6.6)	3 (10.3)	14 (15.4)	4 (13.8)
Permanent discontinuation [§]	6 (6.6)	1 (3.4)	5 (5.5)	2 (6.9)	11 (12.1)	3 (10.3)
Gastrointestinal disorders						
Any	22 (24.2)	3 (10.3)	10 (11.0)	7 (24.1)	30 (33.0)	10 (34.5)
Nausea/vomiting	13 (14.3)	1 (3.4)	7 (7.7)	3 (10.3)	20 (22.0)	4 (13.8)
Diarrhoea	3 (3.3)	1 (3.4)	4 (4.4)	3 (10.3)	6 (6.6)	4 (13.8)
Abdominal pain	3 (3.3)	1 (3.4)	0 (0.0)	1 (3.4)	3 (3.3)	2 (6.9)
Mouth ulceration	3 (3.3)	0 (0.0)	0 (0.0)	1 (3.4)	3 (3.3)	1 (3.4)
Permanent discontinuation [§]	1 (1.1)	1 (3.4)	2 (2.2)	0 (0.0)	3 (3.3)	1 (3.4)

All values represent n (%) of patients with events. Adverse events are assigned to the study phase in which they started. Severe infections are infectious AEs requiring systemic treatment. *According to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 with grade 3 lymphopenia <500–200/mm³ and grade 3 leukopenia <2000–1000/mm³; case had 467 lymphocytes/mm³, no grade 4 lymphopenia or leukopenia were observed. **Hepatic enzymes included aspartate and alanine aminotransferase (ALT, AST) and γ -glutamyltransferase (γ GT).[§]Permanent study drug discontinuations due to the respective AEs of interest are assigned to the actual time of discontinuation. MACE=major cardiovascular adverse event (myocardial infarction, stroke, death due to cardiovascular event). ULN=upper limit of normal.

Table 4: Adverse events of special interest for METOP

References

1. Global Report on Psoriasis, World Health Organization.
www.who.int/iris/handle/10665/204417 DOA 10/05/2016
2. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**: 1367-74.
3. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675-84.
4. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; **371**: 326-38.
5. Lebwohl MG, Kavanaugh A, Armstrong AW, Van Voorhees AS. US Perspectives in the Management of Psoriasis and Psoriatic Arthritis: Patient and Physician Results from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) Survey. *Am J Clin Dermatol* 2016; **17**: 87-97.
6. Warren RB, Chalmers RJ, Griffiths CE, Menter A. Methotrexate for psoriasis in the era of biological therapy. *Clin Exp Dermatol* 2008; **33**: 551-4.
7. West J, Ogston S, Foerster J. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. *PLoS One* 2016; **11**: e0153740.
8. Saurat JH, Langley RG, Reich K, Unnebrink K, Sasso EH, Kampman W. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. *Br J Dermatol* 2011; **165**: 399-406.
9. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med* 2011; **365**: 1586-96.
10. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011; **165**: 1109-17.
11. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58**: 73-81.
12. Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005; **152**: 861-7.
13. Reich K, Papp KA, Matheson RT, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. *Exp Dermatol* 2015; **24**: 529-35.

14. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1-10.
15. Hawwa AF, AlBawab A, Rooney M, Wedderburn LR, Beresford MW, McElnay JC
Methotrexate polyglutamates as a potential marker of adherence to long-term therapy in children with juvenile idiopathic arthritis and juvenile dermatomyositis: an observational, cross-sectional study. *Arthritis Res Ther* 2015; **17**:295.
16. Dervieux T, Furst D, Lein DO, et al. Pharmacogenetic and metabolite measurements are associated with clinical status in patients with rheumatoid arthritis treated with methotrexate: results of a multicentred cross sectional observational study. *Ann Rheum Dis* 2005; **64**: 1180-5.
17. Stamp LK, Barclay ML, O'Donnell JL, et al. Effects of changing from oral to subcutaneous methotrexate on red blood cell methotrexate polyglutamate concentrations and disease activity in patients with rheumatoid arthritis. *J Rheumatol* 2011; **38**: 2540-7.
18. Yesudian PD, Leman J, Balasubramaniam P, et al. Effectiveness of Subcutaneous Methotrexate in Chronic Plaque Psoriasis. *J Drugs Dermatol* 2016; **15**: 345-9.
- 18-19. [West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. *Br J Dermatol*. 2016;**174**:1407-10](#)
- 19-20. Montaudie H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. *J Eur Acad Dermatol Venereol* 2011; **25**: Suppl 2:2-11.
- 20-21. Vincenzi F, Padovan M, Targa M, et al. A(2A) adenosine receptors are differentially modulated by pharmacological treatments in rheumatoid arthritis patients and their stimulation ameliorates adjuvant-induced arthritis in rats. *PLoS One* 2013; **8**: e54195.
- 21-22. Spurlock CF 3rd, Tossberg JT, Matlock BK, Olsen NJ, Aune TM. Methotrexate-mediated inhibition of nuclear factor κ B activation by distinct pathways in T cells and fibroblast-like synoviocytes. *Rheumatology* 2015; **54**: 178-87.
- 22-23. Talme T, Bergdahl E, Sundqvist KG. Methotrexate and its therapeutic antagonists, caffeine and theophylline, target a motogenic T-cell mechanism driven by thrombospondin-1 (TSP-1). *Eur J Immunol* 2016; **46**:1279-90.
- 23-24. Zaba LC, Fuentes-Duculan J, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol* 2009; **129**:79-88.
- 24-25. Goldminz AM, Suárez-Fariñas M, Wang AC, et al. CCL20 and IL22 Messenger RNA Expression After Adalimumab vs Methotrexate Treatment of Psoriasis: A Randomized Clinical Trial. *JAMA Dermatol* 2015; **151**:837-46.
- 25-26. Reich K, Mrowietz U, Radtke MA, Thaci D, Rustenbach SJ, Spehr C, Augustin M. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res*. 2015 Dec;307(10):875-83

- 601
602 | ~~26-27.~~ Warren RB, Smith RL, Campalani E, et al. Genetic variation in efflux transporters
603 | influences outcome to methotrexate therapy in patients with psoriasis. *J Invest Dermatol*
604 | 2008; **128**: 1925-9.
605
606 | ~~27-28.~~ Becker ML, Gaedigk R, van Haandel L, et al. The effect of genotype on methotrexate
607 | polyglutamate variability in juvenile idiopathic arthritis and association with drug response.
608 | *Arthritis Rheum* 2011; **63**: 276-85.
609
610 | ~~28-29.~~ Peres RS, Liew FY, Talbot J, et al. Low expression of CD39 on regulatory T cells as a
611 | biomarker for resistance to methotrexate therapy in rheumatoid arthritis. *Proc Natl Acad Sci*
612 | *U S A* 2015; **112**: 2509-14.
613

Necessary additional data

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Supplementary Material

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Figure

An international prospective, double-blind, placebo-controlled phase III RCT in which patients with moderate to severe psoriasis vulgaris are treated with s.c. methotrexate using an optimized treatment schedule.

Author(s):	Christina Kahl, Kristian Reich, Norbert Berenzen	
Document type:	Clinical study protocol	
Sponsor code	165-001	
Protocol no.	165-001	
Phase	III	
EudraCT no.	2012-002716-10	
Version / Date	Final version 3.0	15.Oct.2012

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medac's written consent.

1 Study Synopsis

Study Title	An international prospective, double-blind, placebo-controlled phase III RCT in which patients with moderate to severe psoriasis vulgaris are treated with s.c. methotrexate using an optimized treatment schedule.
Protocol No.	165-001
EudraCT No	2012-002716-10
Clinical Phase	III
Study Design	This is a multicenter, multinational (12 centers planned, in Germany 9 centers and in France, the Netherlands and the UK 1 center in each country respectively), randomized, double-blinded, placebo-controlled study.
Study Objective(s)	The primary objective is to evaluate the efficacy of methotrexate in patients with moderate to severe Psoriasis compared to Placebo as assessed by the primary endpoint PASI 75 during a 16 week treatment phase. As secondary objectives the safety and efficacy of the optimized treatment schedule will be assessed using multiple methods (e.g. (S)AE occurrence and questionnaires)
Duration of Patient Participation	12 months (exclusive screening)
Approximate Duration of Study	The study is estimated to have a duration of approximately 18 months from FPI to LPO.
Number of Visits	12 in the verum/verum-Arm and 13 in the placebo/verum-arm
Approx. Number of Sites	12 (9 sites in Germany and 1 site in the UK, the Netherlands and France respectively)
Number of Patients	150 patients are planned, randomized 3:1 (verum:placebo) In the UK, the Netherlands and France not more than a maximum of 20 patients per site should be enrolled. Enrolment will cease if the target number of patients is reached.
Target Disease	Moderate to severe psoriasis vulgaris

Criteria for Inclusion	<ol style="list-style-type: none"> 1. Are 18 years of age or older at time of informed consent; may be men or women. 2. Are MTX naïve 3. Moderate to severe plaques psoriasis (according rule of ten (PASI ≥ 10 or BSA ≥ 10 or DLQI ≥ 10) for at least 6 months with or without psoriatic arthritis (however, highly active psoriatic arthritis is excluded, defined by. > 5 swollen tender joints or soles and CRP >2 x UNL) . 4. Women of childbearing potential and all men must be using a highly effective method of contraception (pearl index < 1%) as defined below and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 6 months after receiving the last injection of IMP. Highly effective method is defined as: Use of oral, injected or implanted hormonal methods, intrauterine device (IUD) or intrauterine system (IUS), barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. 5. Able to adhere to the study visit schedule and other protocol requirements. 6. Capable of giving informed consent. The informed consent must be obtained prior to any study related procedures. 7. Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study. 8. Must agree not to receive a live virus or live bacterial vaccination 4 weeks prior to the first IMP s.c. administration, during the trial and up to 3 months after the last injection. 9. Chest X-ray investigation within the last 6 months prior to first s.c. administration of IMP and show no clinically relevant abnormalities
Criteria for Exclusion	<ol style="list-style-type: none"> 1. Currently have non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular). 2. Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, (hydroxy-) chloroquine, or lithium). 3. Are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the

	<p>study.</p> <p>4. Have screening laboratory test results for the following parameters outside the stated ranges (please refer also to :</p> <ul style="list-style-type: none"> a. Hemoglobin < 10 g/dL b. White blood cells < 3.0 x 10⁹/L c. Neutrophils < 1.5 x 10⁹/L d. Platelets < 100 x 10⁹/L e. Creatinine clearance (calculated according to Cockcroft-Gault) < 50 mL/min) f. AST, ALT, and γ-GT levels must be > 2 times the upper limit of normal range g. Bilirubin > 5mg/dl (85,5 μmol/l) h. Hypalbuminemia <3,5 g/dl <p>5. Have used any other IMP within the previous 4 weeks or 5 times the half-life of an investigational agent prior to the first s.c. administration of the IMP of this study, whichever is longer.</p> <p>6. Not able or willing to wash out any prohibited medications as listed below.</p> <table border="1"> <tr> <td>Medication / Therapy</td><td>Washout requirements (all times with regard to first s.c. administration of the IMP)</td></tr> <tr> <td>Any biologics</td><td>5 times of half-life</td></tr> <tr> <td>Phototherapy or any systemic medications that could affect the psoriasis (including but not limited to oral or injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, sulfasalazine, hydroxyurea, or fumaric acid derivatives)</td><td>Within 4 weeks</td></tr> <tr> <td>Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives,</td><td>Within 2 weeks</td></tr> </table>	Medication / Therapy	Washout requirements (all times with regard to first s.c. administration of the IMP)	Any biologics	5 times of half-life	Phototherapy or any systemic medications that could affect the psoriasis (including but not limited to oral or injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, sulfasalazine, hydroxyurea, or fumaric acid derivatives)	Within 4 weeks	Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives,	Within 2 weeks
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Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives,	Within 2 weeks								

	retinoids, tazarotene)	
	Any systemic immunosuppressants (e.g. azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus)	Within 4 weeks
	lithium, antimalarial agents	To be stopped directly prior to first s.c. administration of IMP
	Intramuscular gold	Within 4 weeks
<p>Patients who take prohibited medications that cannot be washed out within 4 weeks or at least 5 times of the half-life of the investigational agent prior to first s.c. administration of IMP should not be asked to participate in the trial.</p> <ol style="list-style-type: none"> 7. Have a history of chronic or recurrent infectious disease or had a serious infection or have been hospitalized or received i.v. antibiotics for the treatment of an infection within 2 months prior to screening. 8. History of radiotherapy or planned concomitant radiotherapy 9. Ulcers of the oral cavity (e.g. ulcerative stomatitis) and/or known gastrointestinal ulcer disease 10. A known B12/cobalamin deficiency 11. Known diagnosed ascites or pleural effusions 12. Have a history of latent or active TB (prior to screening). 13. Have current signs or symptoms of severe, progressive, or uncontrolled renal (specifically with calculated creatinine clearance < 20), hepatic (especially with bilirubin > 5mg/dl (85,5 mol/l), hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease. 14. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical 		

	<p>carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent).</p> <p>15. Have shown a previous immediate hypersensitivity response, including anaphylaxis, to the folic acid</p> <p>16. Are unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.</p> <p>17. Are known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.</p> <p>18. Staff or relatives/partner of any clinical research site</p>
Investigational Medicinal Product (Including Placebo and Active Comparator, If Any)	Verum (methotrexate 50 mg/ml) and placebo (0.9 % NaCl solution)
Dosage and Administration	<p>From week 0 to week 16: Once weekly (every 7 days) s.c. administration of 17.5 mg MTX/ 0.35 mL placebo If PASI50 is not reached after 8 weeks (week 8), the dosing will be increased to 22.5 mg MTX / week or 0.45 mL placebo. Primary endpoint to be achieved after 16 weeks.</p> <p>From week 16 to week 52: <u>Verum/verum-arm:</u> The patients will stay on their dose in the verum/verum-arm. However, if at week 24 the patients receive 17.5 mg MTX but PASI75 is still not reached, the dosing will be increased to 22.5 mg MTX. If patients were already dosed with 22.5 mg MTX/week at week 24 and PASI50 is not reached, patients will be excluded from treatment.</p> <p><u>Placebo/verum-arm:</u> The patients will receive from week 16 to week 52 MTX according to the dose schedule of the verum-verum-arm (starting dose 17.5 mg with the possibility of up-titration after 8 weeks (week 24)). However, patients who will reach PASI75 under placebo-treatment after 16 weeks, will be dosed neither with placebo nor with MTX until relapse. After relapse the patients will be dosed with a starting dose of 17.5 mg MTX as described above.</p>

Concomitant Treatment	<p>24 hours following each IMP administration 5 mg folic acid will be administrated;</p> <p>No immunosuppressive or other systemic or topical treatment of the psoriasis will be allowed.</p> <p>Other medication e.g. acetaminophen or antibiotics (with the exception of co-trimoxazole) may be prescribed if needed and only following permission of the investigator.</p>
Efficacy Evaluation	Efficacy will be evaluated by a physical examination such as PASI, BSA, PGA, reduced NAPSI, PsA, as well as patient questionnaires, such as PSAT metex [®] , EQ-5D and DLQI (see also primary and secondary endpoints)
Safety and Tolerability Evaluation	Safety and tolerability will be assessed by laboratory evaluation, physical examination (local tolerability) and (S)AE evaluation
Primary Endpoint	Difference in PASI75 responder rate after week 16 between treatment arms
Secondary Endpoints	<ul style="list-style-type: none"> • PASI75 after 52 weeks treatment • PASI50 and 90 after 15 and 52 weeks treatment • PASI75 after 32 weeks treatment in placebo arm (cross-over) • NAPSI, BSA, PGA, PsA and questionnaires as , PSAT metex[®], DLQI and EQ-5D after 16 and 52 weeks treatment • Safety and tolerability assessed by AE/SAE, laboratory values and local tolerability at the site of administration • Changes of levels of molecular biologic analysis (UBC and B2M as housekeeping gens; TNF-α, IL-17, IL-4, IFN-gamma) and immunohistochemistry analysis (CD3, CD1a, Ki67) at baseline and after 16

	<p>weeks (at 2-3 sites for approx. 30 patients)</p> <p>The data up to and including week 16 will be analyzed regarding the difference between verum and placebo treatment. The data from week 16-52 will be analyzed regarding long term treatment effects in a descriptive manner only.</p>
Ethical Considerations	<p>This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH-GCP guideline and the ethics principles that have their origins in the Declaration of Helsinki. The independent ethics committee and the competent authority must review and approve the study before any patients are enrolled. Consent must be obtained from the patient using the approved informed consent form before any procedures specified in the protocol are performed.</p>

Study Flow Chart

Visits	V0	V1*	V2**	V3	V4	V5	V6***	V6a****	V6b*****	V7	V8	V9	V10
Week	-4 - -1	0	0	4	8	16	16	17	20	24	32	44	52
Day	-28 - -1	0	5	28 ± 2	56 ± 2	110 - 2	112	117	140 ± 2	168 ± 2	224 ± 2	308 ± 7	364 ± 7
Informed consent ¹	x												
In- and Exclusion Criteria	x	x											
Randomisation		x											
Medical history (including psoriasis vulgaris history)	x												
Demography	x												
Physical Examination	x	x	x	x	x	x		x	x	x	x	x	x
Safety Lab ¹	x	X ^{1a}	x	x	x	x		x	x	x	x	x	x
Bilirubin, Serum albumin	x	x ^{1a}											
Pregnancy Test ²	x	X ^{2a}											
Hepatitis A, B, C serology	x												
PIIINP	x					x					x		x
Vital signs	x	x	x	x	x	x		x	x	x	x	x	x
PASI, BSA and PGA	x	x		x	x	x			x	x	x		x
NAPSI ³ ,		x		x	x	x			x	x	x		x
PsA ⁴		x				x							x
DLQI, EQ-5D	x	x		x		x			x		x		x
PSAT metex® ⁵		x				x							x
Sub-Study: Skin Biopsy (optional) (3 Sites in Germany, approx. 30 Patients)		x				x							
Study drug administration ⁶		Once weekly according to dosing schedule (week 0 – week 51)											
Adverse Events / Comed (complete study duration)	Recording of AEs after 1 st injection of IMP till end of study												

*Visit 1: First dosing will be performed by the investigator; patients have to be trained with regard to self-administration at this visit. An emergency card will be handed out to the patients.

** At most 2 days after this visit (day 7, week 2), patients have to be called by phone after receiving the laboratory results to give dosing instructions; thereafter the patients will dose themselves at home.

***Visit 6: Unblinded phase starts. Patients will be informed concerning their treatment allocation. On this visit, study medication (commercial product) will be administered to all patients by the study personnel. Patients of the placebo-verum-arm will be treated with verum for the first time.

**** Visit 6a affects only patients of arm 2. At most 2 days after this visit (day 119, week 17), patients have to be called by phone after receiving the Laboratory results to give dosing instructions; thereafter the patients will dose themselves at home.

*****Visit 6b affects only patients of arm 2.

¹ Laboratory: Complete blood count, Differential blood count, Serum creatinine, calculated creatinine clearance, CRP, γ -GT, ASAT, ALAT, AP, U-Status, U-Sediment if necessary; ^{1a} blood sample for baseline safety lab check (incl. bilirubin, serum albumin) will only be performed in case of more than 8 days between screening (V0) and baseline (V1)

² For females only, at screening from serum and ^{2a} on visit 1 from urine

³ reduced NPSI assessment (only of worst and best finger)

⁴ Short questionnaire to assess status of psoriatic arthritis

⁵ Patient questionnaire to observe the patient's satisfaction with the pre-filled syringe

⁶ At each regular visit used study medication and the medication card will be collected and new study medication and updated medication card will be handed out to the patients.

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3 **Signature Page**

The signatures below document the approval of this protocol, and provide the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to all applicable laws and regulations including, but not limited to, the German Drug Law, the International Good Clinical Practice guideline (ICH-GCP) and the ethics principles that have their origins in the Declaration of Helsinki.

Prof. Dr. med. Kristian Reich
Sponsor

Date

Prof. Dr. med Ulrich Mrowietz
Coordinating Investigator (LKP)

Date

Dr. Ina Zschocke
SCIderm GmbH
Managing Director

Date

4 Statements of Principal Investigator and Sub-investigator(s)

I have thoroughly read this study protocol and have understood the requirements as well as the conditions of this clinical study protocol. I agree to following points:

- To perform the clinical study according to this protocol and all applicable laws and regulations including, but not limited to, the German Drug Law, the international Good Clinical Practice guideline (ICH-GCP) and the ethical principles that have their origins in the Declaration of Helsinki.
- To record accurately all required data on the case report forms (CRFs),
- To provide direct access to source data/documents (source document verification),
- To permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections,
- To use the study material including the medical device only as specified in this protocol,
- To report within 24 hours any adverse event that is serious, whether considered treatment-related or not.

Principal Investigator:

Name

Signature

Date

Site Stamp:

5 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AMG	German Drug Law (Arzneimittelgesetz)
ATC-Code	Anatomic-Therapeutically-Chemical Code
bpm	Beats Per Minute
CPMP	Committee for Proprietary Medicinal Products, now CHMP, Committee for Medicinal Products for Human Use
CRA	Clinical Research Associate (=synonymous to monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
FPI	First Patient In
FS	Fertigspritze (pre-filled syringe)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine Device
LPI	Last Patient In
LPO	Last Patient Out
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetres of Mercury
MTX	Methotrexate
N	Number
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S.C.	Subcutaneous
SOP	Standard Operating Procedure
WHO	World Health Organisation

6 Definitions

Eligible Participant	Any potential participant who upon entrance into the treatment phases of the study meets all of the inclusion criteria and none of the exclusion criteria set forth in the protocol and had signed a valid IRB/IEC approved informed consent form.
Informed Consent Form	The form prepared in conformance with the regulations (as hereinafter defined), in consultation with the sponsor, and the IRB/IEC (as hereinafter defined), approved by the IRB/IEC and signed by all patients before they begin to participate in the study.
Regulations	Any relevant legislation, codes or guidelines directly or indirectly related to the conduct of the study including but not limited to (as applicable) the Clinical Trials Directive 2001/20/EC and its transforming legislation in the relevant countries of the European Union, the ICH-GCP guideline (July 2002) ("ICH-GCP"), and/or any other relevant applicable legislation, codes or guidelines issued by any regulatory authority. For the avoidance of doubt such legislation, codes or guidance shall include those related to the protection and privacy of the personal data of individuals.
Regulatory Authority	Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.
Serious Adverse Event	<p>Any untoward medical occurrence that at any dose:</p> <ul style="list-style-type: none">• results in death• is life-threatening• requires in-patient hospitalisation or results in prolongation of existing hospitalisation• results in persistent or significant disability/incapacity,• is a congenital anomaly/birth defect,• is another medically important event or reaction. <p>Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.</p>
Site	The location where study-related activities are actually conducted.
Study	The clinical study known as protocol no. XXX to be conducted according to the protocol.

7 Introduction

7.1 Background

With a prevalence of 1.5 - 2% psoriasis vulgaris is one of the most common chronic inflammatory skin diseases in Western industrialized countries (Nevitt 1996). It has a chronic relapsing progressive course and often a major impact on patients' lives. The disease requires a severity adjusted treatment, which should take into account both the skin symptomatic and the deteriorations of the patient's quality of life (QoL).

As one of the conventional and comparatively cheap therapy options, methotrexate (MTX) is recommended as first line therapy by the "german guideline on treatment of psoriasis vulgaris" for the (induction) therapy of moderate to severe psoriasis vulgaris in adults (Nast 2011).

MTX is a folic acid analogue, which competitively inhibits the enzyme dihydrofolate reductase and other folate-dependent enzymes. Administration of MTX thus leads to a reduced synthesis of thymidylate and purine, in a decreased production of DNA and RNA. In activated T cells and in keratinocytes, this mechanism is believed to lead to the antiproliferative and immunomodulatory effects of MTX, which are decisive in the treatment of psoriasis (Pathirana 2009). In contrast to subcutaneous application, the bioavailability after oral dosing is difficult to predict, due to variable resorption. Furthermore, the clinical efficacy of MTX is dependent on the intracellular glutamation of this 'prodrug' to MTX-Glu_n, where n can be up to 6 glutamate moieties. The rate and extend of glutamation is increased after switching from oral to subcutaneous dosing (Dervieux 2010). It has been shown, that the clinical response in rheumatoid arthritis correlates with the degree of MTX polyglutamation (Dervieux 2009). Hence, due to its better efficacy and also due to its increased gastrointestinal tolerability, subcutaneous administration of MTX should be favoured.

Administration of MTX comprises the risk of hepatotoxicity due to the reduced purine synthesis. Combination of folic acid demonstrably reduces this risk. A study in Psoriasis patients showed, that a dose of 20mg folic acid per week tended to decrease the efficacy of MTX (Chládek 2008). However, a study in rheumatoid arthritis showed that, administration of 5mg folic acid per week successfully reduced the hepatotoxicity without loss of efficacy (Morgan 1994). Thus, administration of 5 mg folic acid 24 hours after application of MTX is recommended (Pathirana 2009).

In contrast to the world-wide clinical experience with MTX, it has been used for the treatment of psoriasis for over 50 years (Edmundson 1958, Smith 2000), the evidence for its efficacy in psoriasis is limited.

The "European S3-Guidelines on the systemic treatment of psoriasis vulgaris" (Pathirana 2009) only includes three studies on MTX monotherapy (Heyendael 2003, Nyfors 1970, Weinstein 1971) into their evaluation.

In one study with 88 patients, the efficacy and safety of methotrexate was compared to cyclosporine (Heydendael 2003). Initially, 15 mg methotrexate divided into three portions administered after an interval of 12-hour each was given orally per week according to the schedule of Weinstein and Frost (Weinstein 1971). After four weeks of treatment, the dose was increased up to 22.5 mg if no PASI25 response was achieved. No folic acid was administered. After 16 weeks, 60% of methotrexate treated patient achieved a PASI75 response. Methotrexate treatment had to be discontinued in 12 of 43 patients due to hepatotoxicity.

A study from 1970 with a clearly lower evidence grade revealed a clearing of skin lesions in 62% of the patients, *i.e.* 31 patients and a lesion reduction of at least 50% in 1/5, *i.e.* 10 of 50 MTX treated patients (Nyfors 1970). Another small study showed an improvement of skin lesions of at least 75% in 77% of 25 MTX treated patients (Weinstein 1971).

Recently, three larger studies have been conducted comparing MTX to the biological briakinumab (Reich 2011), adalimumab (Saurat 2011) and infliximab (Barker 2011) treatments respectively.

In the comparative study with briakinumab, the initial oral MTX dose was 5 mg per week. The dose was increased by 5 mg in week 2 and 3 until a dose of 15 mg was reached. After 10 weeks, dosing of MTX was increased to 20 mg per week, and after 16 weeks to 25 mg per week in those patients who had not achieved a PGA < 2 or PASI75. All patients treated with MTX received 5 mg oral folate every week.

After 24 weeks of treatment, 39.9% of all MTX treated patients achieved a PASI75 response. Overall, the MTX treatment was well tolerated: Until week 52, 6% of the MTX treated patients discontinued the study due to adverse events (Reich 2011).

In the comparative study with adalimumab, the initial oral MTX dose was 7.5 mg per wk (per os). Additionally, all patients received 5 mg oral folate per week given at least 48 hours after dosing MTX. After two weeks, the MTX dose was increased to 10 mg per week and after two further weeks to 15 mg per week. After 8 weeks, dosing of MTX was increased to 20 mg per week and after 12 weeks to 25 mg per week in these patients that had not achieved a PASI50 response

After 16 weeks of treatment, 35.5% of all MTX treated patients achieved a PASI75 response. In this study, a considerable part of patients profited from a dose increase to 20 mg MTX per week, but only very few from a further dose increase to 25 mg MTX per week. Consequently, nearly all of the patients with a PASI75 response at week 16 already had a PASI50 response at week 8 or 12 with a maximum weekly MTX dose of 15 or 20 mg (Saurat 2008).

In the comparative study with infliximab, the start-up dose of MTX was 15 mg per week administered orally. At week 6, the dose was increased to 20 mg per week if no PASI50 response could be achieved. Use of folic acid was recommended but not mandatory.

After 16 weeks of treatment, 41.9% of all MTX treated patients achieved a PASI75 response. In general, MTX was well tolerated throughout the study. Until week 26, 8 of 211 (3.8%) of the MTX-treated patients discontinued the study due to an adverse event; 1.4% of the MTX-treated patients discontinued due to hepatotoxicity related adverse events (Barker 2011).

For expected side effects please refer to the SPC for Metoject® in appendix J.

7.2 Rationale

Until today, despite its common use no recommendations for a standardized dosing regimen of MTX in psoriasis exists. The data of the studies described above indicate, that neither the safety nor the efficacy profile benefits from a slow uptitration of MTX. A dose increase from 15 to 20 mg MTX per week after 8 weeks of treatment leads to an improved efficacy in a considerable part of slow responding patients. However, a further increase to 25 mg MTX per week only marginally influences the overall responder rate (Saurat 2008). A splitting of the weekly MTX dose into three portions according to the schedule of Weinstein and Frost (Weinstein 1971) does not improve the tolerability of MTX. However, administration of 5 mg folic acid per week demonstrably reduces the hepatotoxicity of MTX. The subcutaneous administration of MTX further increases the tolerability and efficacy compared to oral administration.

The present study is initiated to further increase the knowledge about the optimal dosing regimen and to thus optimize the efficacy and safety of MTX treatment for patients with moderate to severe psoriasis.

In view of the described risk-benefit profile of MTX, an initial dose of at least 15 mg per week administered subcutaneously followed by 5 mg folic acid p.o. 24 hours after MTX application seems appropriate. Since 20 mg MTX per week has been proven to be beneficial in a considerable part of patients, who did not respond sufficiently to 15 mg MTX per week, we intend to start with a dose of 17.5 mg MTX per week, administered subcutaneously. At such a starting dose, we expect to find the highest MTX efficacy possible, but with appropriate safety margins. If in a patient, a PASI50 response is not achieved in week 8, the dose will be increased to 22.5 mg MTX per week. The choice of this dose is supported by the comparatively clinical effect seen at doses up to 20 mg MTX per week and the rather poor increase of efficacy rates following titration up to 25 mg MTX per week (Saurat 2008). Thus, in low responders an increased efficacy may still be obtained in as many slow responding patients as possible, but without risking unnecessary side effects by using high dosages that are known to be ineffective in slow responders. All dosages used in this study lay within the approved dosing range of MTX.

The study will be conducted in a double-blind, placebo controlled manner. Placebo was chosen as control since only this comparator allows a reliable interpretation of safety and efficacy data. Furthermore, placebo-controlled MTX-trials are rare until today.

In addition long term treatment data (52 weeks) will be recorded. These data are still rare. In recent studies using MTX as a comparator the MTX arm was limited to a maximum of 16 weeks (briakinumab (Reich 2011), adalimumab (Saurat 2011) and infliximab (Barker 2011)).

7.3 Potential Risks and Benefits

The starting dose of 17.5 mg MTX per week, which is slightly higher compared to the commonly used dosing regimen (15 mg), may increase the risk for side effects. A recently published study in patients with rheumatoid arthritis did not show apparent differences regarding safety aspects when comparing starting doses of 15 mg or 25 mg MTX per week respectively. However, in this study the statistical differences could not be assessed due to the limited number of patients included (Hobl 2012). The risk for short-term haematological events appears to be associated with certain genetic variations (Caliz 2012). In this study we do not assess any genetic markers. To minimize the risk for severe short term haematological issues we perform a blood test 5 days after the first injection of MTX. The second dose will only be administered by the patient if the blood results do not reveal any abnormal values or a clinically relevant unfavourable trend compared to baseline. This safety criterion is exclusively set up for this study following internal discussions with international MTX experts e.g. Alan Menter (Dallas, USA). Not only the absolute lab values are important at the defined time point, but also the change of each value compared to baseline. For example: patient has a normal number of leukocytes (9.500 / μ l) at baseline and the leukocyte count drops to 5.000/ μ l within one week after the first administration of MTX. 5.000/ μ l are still within the normal range, but there was a drop rate of almost 50% indicating a relevant myelosuppressive effect of MTX in this patient. If the patient would be dosed for the second time at week two, this trend may be continued and could result in a severe leukopenia.

As there are no general recommendations or guidelines available yet, we have defined the thresholds used in this study: For leukocytes, lymphocytes, erythrocytes or platelets a relative decrease of 30% or more at day 5 after the first administration of MTX compared to baseline is regarded significant. Such patients will be excluded from the treatment with MTX and will be treated with other appropriate medication. We expect that less than 5% of the patients will show a relevant decrease of the haematological values according to the criteria mentioned above within the first week.

The initial dose of 17.5 mg MTX per week should provide an optimized clinical response regarding time to onset and absolute response rate after 16 weeks. Details regarding this dosing regimen are provided in section 11.6.

8 Study Objectives and Purpose

The PASI 75 rate has been assessed as a clinically meaningful improvement by the CHMP and in the German S3 guideline. A PASI reduction of $\geq 50\%$ is currently not considered to be sufficient to demonstrate efficacy by the CHMP (CHMP 2004, Nast 2006). Best evidence of efficacy is demonstrated by a PASI reduction of $\geq 90\%$, but in patients with severe disease at baseline a PASI improvement of $\geq 75\%$ can be considered as response if prospectively defined (CHMP 2004). In the German S3 guideline, the efficacy of the different treatment options was assessed on the basis of the PASI 75 (Nast 2006). The PASI 75 has been used as a primary efficacy outcome in the recent placebo-controlled trials that tested biological agents. This parameter has further been used to compare the efficacy of treatments in recent meta-analyses (Schmitt 2008, Brown 2009).

8.1 Primary Objective

The primary objective is to evaluate the efficacy of subcutaneous application of MTX in patients with moderate to severe psoriasis compared to placebo as determined by the number of patients reaching the primary endpoint PASI 75 after a 16 week treatment phase in the two study arms.

8.2 Secondary Objective(s)

The following endpoints, which evaluate the efficacy, tolerability and safety are assessed:

- PASI75 after 52 weeks treatment
- PASI50 and 90 after 16 and 52 weeks treatment
- PASI75 after 32 weeks treatment in placebo arm (cross-over)
- NAPSI, BSA, PGA, , PsA and questionnaires such as PSAT metex[®], EQ-5D and DLQI after 16 and 52 weeks treatment
- Safety and tolerability assessed by AE/SAE, laboratory values and local tolerability at the injection site
- Changes of levels of molecular biologic analysis (UBC and B2M as housekeeping gens; TNF- α , IL-17, IL-4, IFN-gamma) and immunohistochemistry analysis (CD3, CD1a, Ki67) at baseline and after 16 weeks (at 3 sites for approx. 30 patients); for explorative scientific purpose only

The data up to week 16 will be analyzed regarding the difference between verum and placebo treatment. The data from week 16 to week 52 will be analyzed regarding long term treatment effects in a descriptive manner only.

9 Study Design

This trial will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH-GCP guideline “Note for Good Clinical Practice” (CPMP/ICH/135/95) based on the principles of the Declaration of Helsinki. The independent ethics committee and the competent authority must review and approve the study before any patients are enrolled.

9.1 Description of the Study Design

This is a prospective, randomized, placebo-controlled, multi-centre, international Phase III double blind study of an optimized treatment schedule with Methotrexate.

* If PASI50 is not reached after 8 weeks, up-titration to 22.5 mg MTX / 0.45 mL Plac / week will be done.

** If PASI75 is not reached at week 24, up-titration to 22.5 mg MTX / week will be done. If patients were already dosed with 22.5 mg MTX/week and PASI50 is not reached, patients will be excluded from treatment.

*** Patients will receive 17.5 mg MTX / week. Patients, who will reach PASI75 under placebo-treatment after 16 weeks, will be dosed neither with placebo nor with MTX until relapse. After relapse the patients will be dosed with a starting dose of 17.5 mg MTX / week.

150 patients are planned, randomized 3:1 (verum:placebo)

In the UK, the Netherlands and France not more than a maximum of 20 patients per site should be enrolled. Enrolment will cease if the target number of patients is reached.

9.2 Study Endpoints

Primary Endpoint

- PASI75 after 16 weeks

Secondary Endpoints

- PASI75 after 52 weeks treatment
- PASI50 and 90 after 16 and 52 weeks treatment
- PASI75 after 32 weeks treatment in placebo arm (cross-over)
- NAPSI, BSA, PGA, PsA and questionnaires such as PSAT metex[®], EQ-5D and DLQI after 16 and 52 weeks treatment
- Safety and tolerability assessed by AE/SAE, laboratory values and local tolerability at the injection site from V1- V10
- Changes of levels of molecular biologic analysis (UBC and B2M as housekeeping gens; TNF- α , IL-17, IL-4, IFN-gamma) and immunohistochemistry analysis (CD3, CD1a, Ki67) at baseline and after 16 weeks (at 3 sites for approx. 30 patients); for explorative scientific purpose only

The data up to week 16 will be analyzed regarding the difference between verum and placebo treatment. The data from week 16 to week 52 will be analysed regarding long term treatment effects in a descriptive manner only.

9.3 Randomisation

A randomisation list will be generated by an independent third party of the Clinical Research Organization (CRO) who is not involved in other processes of the study. The randomisation numbers will be generated to insure that treatment assignment is unbiased and concealed from patients and investigator staff. Eligible patients will be randomised to treatment arm 1 (verum/verum) or treatment arm 2 (placebo/verum). The ratio between treatment arm 1 and treatment arm 2 will be 3:1. A randomization list will be produced using the randomization software randlist 1.2 as random generator. The randomization numbers will be assigned at visit T0 by the eCRF in an ascending order to the subjects eligible for treatment after all inclusion and exclusion criteria has been checked and the investigator has confirmed the randomisation of the patient. No number should be omitted or skipped.

Randomization numbers will be a 8-letter/digit number. The first digit is letter R, the following 4 digits include the combined site number (combination of 2 digits for the country number and 2 digits for the site number), and the last 3 digits include the patient number.

Patient numbers will be assigned in an ascending order starting with 51 to ensure clear distinction from patient identification numbers.

Example: R0101051 includes includes the combined site number 0101 (France, site 01) and the patient random number 051 (refer to appendix I).

Once assigned to a patient, the randomisation number will neither be replaced nor reused.

9.4 Blinding

Patients of arm 1 and 2 will remain blind to the identity of the treatment from the time of randomisation until an interim database lock for the data up to and including week 16 of their treatment. The interim data cleaning and database lock as described in the data management plan will be performed after the assessments scheduled for week 16 were performed. The unblinding process is performed in the eCRF (ClinCase) if all parameters as defined in the data management plan for the interim analysis have been completed. The unblinding procedure is specified in detail in the ClinCase User Guide.

The trial will be performed in a double-blind manner at least up to week 16 (see above). All trial drugs will be supplied in identical packages. From week 16 the commercial product will be handed out to the patients with an additional label “for clinical study use only”.

The trial blind up to week 16 should not be broken except in a medical emergency (where knowledge of the trial drug received would affect the treatment of the emergency) or regulatory requirement (e.g., SAE).

If the blind is broken, the date, time and reason must be recorded in the patient’s eCRF, and any associated AE report.

If time permits, the Investigator should notify the sponsor’s designee Dr. Nibler & Partner and the Sponsor.

If an Investigator, site personnel performing assessments, or patient, is unblinded, the patient must be withdrawn from the trial and procedures accompanying withdrawal are to be performed. In cases where there are ethical reasons for the patient to remain in the trial, the Investigator must obtain specific approval from the Sponsor for the patient to continue in the trial.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded before submission to the Regulatory Authorities by the Sponsor’s dedicated staff.

9.5 Emergency Unblinding Procedure

Emergency unblinding should only be performed when necessary in order to treat the patient.

The site receives sealed emergency envelopes for each patient. The envelope contains the information about which treatment is assigned to the respectively patient. The envelope should only be opened by the investigator in case of emergency when it is essential for effective treatment of the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat the patient. SCIderm is to be informed immediately about any unblinding procedure.

The documentation of the unblinding must contain the name of the study personnel performing the unblinding, the date of unblinding and the reasons that led to unblinding and has to be reported on the blind break form filed in the investigators site file. SCIderm will inform the sponsor about any unblinding procedure immediately. AEs or SAEs related to the unblinding have to be appropriately reported.

The investigators are advised not to reveal the study treatment assignment to the site monitor or sponsor personnel.

Study medication must be discontinued after emergency unblinding. Study medication must also be discontinued for any patient whose treatment code has been broken inadvertently or for any non-emergency reason.

9.6 Withdrawal of Patients

In accordance with the informed consent and the Declaration of Helsinki, any patient can refuse to participate or withdraw from the study without giving reasons at any time without any penalty or loss of benefits to which the patient is otherwise entitled. When appropriate, patients may be placed on other conventional therapy when clinically indicated.

If the patient withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data except for the premature Follow-up Visit.

Patients must be withdrawn from the treatment immediately if any of the following occur:

Clinical significant abnormal laboratory results that preclude continuation of study medication, as determined by the investigator and/or medical monitor, including any of the following:

- Elevation of liver enzymes (ALT/AST, GGT) > 3 ULN
- leukocytes < 3000/ μ L and neutrophile granulocytes < 1000/ μ L,
- Thrombopenia <75.000/ μ L thrombocytes,
- Anemia Hb < 8.0 g/dL (females) or <10.0 g/dL (males)
- Impaired renal function:

Patients with Creatinine $\geq$ 2.0 mg/dL and CCL < 20 ml/min are withdrawn immediately

Patients with 20 ml/min < CCL < 50 ml/min will stop treatment immediately; a control measurement after one week will be performed. If the value is 20% below the last value the patient will be withdrawn from the study and assigned to a specialist for further clarification. If the value is still below 50 ml/min, however not 20 % decreased a

further control after 1 week has to be performed. If the value is still below 50 ml/min the patient should be withdrawn from the study and assigned to a specialist for further clarification.

- Patients who show a decrease of leukocytes, lymphocytes, erythrocytes or platelets counts of 30% 5 days after the first administration of IMP compared to values from the previous safety laboratory (baseline compared to visit 2 for all patients and visit 5 compared to visit 6a for the patients of arm 2 only)
- Patients of arm 1 who show no PASI 50 after 24 weeks of treatment
- In case of any clinical impression of MTX-induced pneumonitis the MTX treatment will be discontinued and patients will be withdrawn from the study. Furthermore the patients have to be assigned to a pulmonologist for further clarification.
- In case of occurrence of ulcerative stomatitis
- Diarrhoea of grade 2 (5-7 loose stool a day or diarrhoea lasting more than one week) and higher will lead to interruption of the treatment (maximal 2 consecutive dosages). If the symptoms will be still present the patient will be withdrawn from the study and assigned to a specialist for further clarification.
- In case of a significant increased PIIINP-value a control measurement will be performed. If the PIIINP-value is still increased the MTX-treatment will be interrupted (max. 2 consecutive dosages). If PIIINP values are still increased the patient will be withdrawn from the study and assigned to a medical specialist for clarification (e.g. a liver biopsy could be recommended)

Moreover, female patients have to be withdrawn from the study in case of pregnancy.

Patients should also be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the trial for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, become lost to follow up for any other reason, or if any of the following occurs: discovery of failure of randomization or blinding; discovery of patient ineligibility; errors in treatment compliance; missed/unscheduled/off-schedule/incomplete/incorrect assessments.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for the patient's premature withdrawal from the trial and record this information on the eCRF.

Patients who prematurely withdraw from the study will be scheduled for an end-of-study visit as soon as possible. An end-of-study page will be completed in the eCRF, giving the date and primary reason for stopping treatment.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who prematurely withdraw from the study for any reason at any time are excluded from the continuation of the study and will be treated if indicated as for any event still ongoing at the end of a clinical study according to standard practice under supervision by an experienced dermatologist or will be referred to a dermatologic practice for further treatment according to standard practice. In the case of premature discontinuation due to an AE, the investigator should ensure that the patient receives a suitable therapy appropriate to patient's condition.

9.7 Discontinuation of Entire Study

If the Investigator, the Sponsor, or the Safety Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties. The trial may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the trial leading to unacceptable high withdrawal rate
- Failure to enrol patients at an acceptable rate,

The trial can be terminated prematurely by the Sponsor at an individual centre due to:

- Safety concerns based on reported data
- Unsatisfactory enrolment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

10 Selection of Patients

10.1 Inclusion/Exclusion Criteria

The investigator must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrolment in the study. Patients will be enrolled if all inclusion and none of the exclusion criteria are met. All patients screened to participate in the study will be documented and the reason for study exclusion will be documented to avoid enrolment bias.

10.1.1 Inclusion Criteria

To be eligible for the study, patients must meet all of the following criteria:

1. Are 18 years of age or older at time of informed consent; may be men or women.
2. Are MTX naïve
3. Moderate to severe plaques psoriasis (according rule of ten (PASI ≥ 10 or BSA ≥ 10 or DLQI ≥ 10) for at least 6 months with or without psoriatic arthritis (however, highly active psoriatic arthritis is excluded, defined by > 5 swollen tender joints or soles and CRP >2 x UNL) .
4. Women of childbearing potential and all men must be using a highly effective method of contraception (pearl index < 1%) as defined below and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 6 months after receiving the last injection of IMP. Highly effective method is defined as: Use of oral, injected or implanted hormonal methods, intrauterine device (IUD) or intrauterine system (IUS), barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
5. Able to adhere to the study visit schedule and other protocol requirements.
6. Capable of giving informed consent. The informed consent must be obtained prior to any study related procedures.
7. Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.
8. Must agree not to receive a live virus or live bacterial vaccination 4 weeks prior to the first IMP s.c. administration, during the trial and up to 3 months after the last injection.
9. Chest X-ray investigation within the last 6 months prior to first s.c. administration of IMP and show no clinically relevant abnormalities

10.1.2 Exclusion Criteria

Patients meeting any of the following criteria may not be enrolled in the study:

1. Currently have non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
2. Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, (hydroxy-) chloroquine, or lithium).
3. Are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study.
4. Have screening laboratory test results for the following parameters outside the stated ranges (please refer also to :

- a. Hemoglobin < 10 g/dL
- b. White blood cells < $3.0 \times 10^9/L$
- c. Neutrophils < $1.5 \times 10^9/L$
- d. Platelets < $100 \times 10^9/L$
- e. Creatinine clearance (calculated according to Cockcroft-Gault) < 50 mL/min
- f. AST, ALT, and γ -GT levels must be > 2 times the upper limit of normal range
- g. Bilirubin > 5mg/dl (85,5 μ mol/l)
- h. Hypalbuminemia < 3,5 g/dl
5. Have used any other IMP within the previous 4 weeks or 5 times the half-life of an investigational agent prior to the first s.c. administration of the IMP of this study, whichever is longer.
6. Not able or willing to wash out any prohibited medications as listed below.

Medication / Therapy	Washout requirements (all times with regard to first s.c. administration of the IMP)
Any biologics	5 times of half-life
Phototherapy or any systemic medications that could affect the psoriasis (including but not limited to oral or injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, sulfasalazine, hydroxyurea, or fumaric acid derivatives)	Within 4 weeks
Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene)	Within 2 weeks
Any systemic immunosuppressants (e.g. azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus)	Within 4 weeks
lithium, antimalarial agents	To be stopped directly prior to first s.c. administration of IMP
Intramuscular gold	Within 4 weeks

Patients who take prohibited medications that cannot be washed out within 4 weeks or at least 5 times of the half-life of the investigational agent prior to first s.c. administration of IMP should not be asked to participate in the trial.

7. Have a history of chronic or recurrent infectious disease or had a serious infection or have been hospitalized or received i.v. antibiotics for the treatment of an infection within 2 months prior to screening.
8. History of radiotherapy or planned concomitant radiotherapy
9. Ulcers of the oral cavity (e.g. ulcerative stomatitis) and/or known gastrointestinal ulcer disease
10. A known B12/cobalamin deficiency
11. Known diagnosed ascites or pleural effusions

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12. Have a history of latent or active TB (prior to screening).
 13. Have current signs or symptoms of severe, progressive, or uncontrolled renal (specifically with calculated creatinine clearance < 20), hepatic (especially with bilirubin > 5mg/dl (85,5 mol/l), hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.
 14. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent).
 15. Have shown a previous immediate hypersensitivity response, including anaphylaxis, to the folic acid
 16. Are unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
 17. Are known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
 18. Staff or relatives/partner of any clinical research site

11 Study Medication

11.1 Investigational and Control Drugs

The investigational product metex[®]/Metoject[®], 50 mg/ml Injektionslösung and placebo will be manufactured by medac GmbH. medac will also responsible for the packaging, release and supply of the investigational product and placebo to each centre on request after randomization of the patient. This process will be described in a separate document.

The description of trial drug is provided in table 1 and the listing of ingredients in table 2.

Table 1: Description of trial drug

Name of investigational product:	metex [®] /Metoject [®] 50 mg/ml	Matching Placebo for metex [®] /Metoject [®] 50 mg/ml
Chemical name:	methotrexate	NaCl (0.9 %)
Pharmaceutical form:	Solution for injection	Solution for injection
Appearance:	Clear solution of yellowish-brown colour	Clear solution without colour.*
Strength:	A prefilled syringe with 17.5 mg and 22.5 mg methotrexate, respectively (0.35 ml / 0.45 ml of 50 mg/mL)	A prefilled syringe with 0.35 mL and 0.45 mL NaCL (0.9 %) solution, respectively
Stability:	Acceptable physical and chemical stability over study time	Acceptable physical and chemical stability over time
Storage:	Do not store >25°C; prefilled syringes have to be stored in the respective covering box to protect them from light	Do not store >25°C ; prefilled syringes have to be stored in the respective covering box to protect them against light
Batch number(s):	Will be provided with the clinical trial report.	Will be provided with the clinical trial report.
Expiry date(s):	Will be provided with the clinical trial report.	Will be provided with the clinical trial report.

**To ensure the blinding, the syringes pre-filled with MTX as well as the syringes pre-filled with placebo will be covered with a yellow foil, which prohibits distinguishing between the two arms.*

Table 2: List of ingredients of trial drug

Name of investigational product:	metex [®] /Metoject [®] 50 mg/mL (syringe with 0,35 mL contains 17,5 mg Methotrexat)	Matching Placebo for metex [®] /Metoject [®] , 50 mg/mL (syringe with 0,35 mL 0,9 % Sodium Chloride solution)	metex [®] /Metoject [®] 50 mg/mL (syringe with 0,45 mL contains 22,5 mg Methotrexat)	Matching Placebo for metex [®] /Metoject [®] 50 mg/mL (syringe with 0,45 mL contains 0,9 %ige Sodium Chloride solution)
<u>Active Ingredients:</u> methotrexate	17.5 mg	none	22.5 mg	none
<u>Other Ingredients:</u> Sodium Chloride	X	X	X	X
Sodium Hydroxide	X	X	X	X
Water	X	X	X	X

11.2 Route of Administration, Dosage, Dosage Regimen and Treatment Period

Pharmaceutical form	Syringe containing solution for s.c. injection
Concentration	50 mg/mL
Dosage (total weekly dose)	17.5 mg (0.35 mL) or 22.5 mg (0.45 mL) respectively
Dose regimen	
Route	Subcutaneous
Frequency	Once weekly
Duration of treatment	51 weeks
Time of day for dosing	Not specified
Location of treated area	Abdomen

Refer to chapter 11.6 for further instructions concerning prescribing, dose adjustments and taking the study medication.

11.3 Packaging and Labelling

Medication labels will comply with all (local) legal requirements (e.g. DE: AMG § 10 section 10, GCP-guideline § 5; Annex 13 of the EU Guideline to Good Manufacturing Practice (GMP)).

They will include storage conditions for the drug, but no information about the patient except for the randomisation number, by which the patient is identified.

In this double-blind study the identity of the treatments will be concealed by the use of study medications that are almost identical in packaging, labelling and schedule of administration up to week 16. However, the strength mentioned on the label will be either 17.5 mg MTX/0,35 mL NaCL (0.9 %) solution or 22.5 mg MTX/ 0.45 mL NaCL (0.9 %) solution. The IMP and the respective comparator are indistinguishable in appearance, consistency and odour.

From week 16 onwards the study will be unblinded. Placebo treated patients having achieved a PASI75 response will not be medically treated until a relapse of their psoriasis occurs. In case of a relapse of the disease, the patients will be treated with 17.5 mg MTX per week.

All other patients will receive the commercial product after week 16 with an additional label "for clinical study use only" for Germany.

For the other European countries the label will comply with the requirements given in Annex 13 of the EU Guideline to Good Manufacturing Practice (GMP) also in the unblinded part of the study. The labels will be in the local language (i.e. French, Dutch and English).

11.4 Storage of Study Medication

The study medication should not be stored at a temperature of $>25^{\circ}\text{C}$. The study medication should be stored in a safe and secure place.

11.5 Study Medication Supply and re-supply, accountability procedures

The study sites will be supplied by medac or its designee with sufficient study medication. Study medication must be received by a designated person at the investigation site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel has access.

All study drug sent to the investigator will be accounted for and in no case used in any unauthorised situation. They are to be dispensed only in accordance with the protocol.

Upon receipt, all study drug should be stored according to the instructions specified on the drug labels and/or accompanied documents. Trained study personnel at each site will be responsible for dispensing of new and returning of used and unused study drug to / from the patient at each visit during the treatment / maintenance period/phase.

The investigator must maintain an accurate record of the shipment and dispensing/returning of study medication, using a designated drug accountability form. All medication will be counted before dispensing and after returning. Monitoring of drug accountability will be performed by the clinical research associate (CRA) during site visits and at the completion of the study before database lock. At the conclusion of the study and if appropriate during the course of the study, the CRA will collect or the investigator will return all used and unused study medication, packaging, drug labels, and a copy of the completed drug accountability form to medac or its designee provided in the investigator folder at each site.

11.6 Instructions for Prescribing, Dose Adjustments/Interruptions and Taking the Study Medication

The study medication will be applied as s.c. injections in the abdomen with prefilled syringes preferably in the evening. The first dosing at visit 1 will be performed by the investigator. At this visit the patient will be instructed in detail how to self-administer the study medication.

The second dose will only be given if the investigator decides that the safety laboratory check, (visit 2 for all patients and visit 6a for the patients of the placebo/verum arm only) performed 5 days after the first administration allows a continued treatment. If a patient shows a decrease of leukocytes, lymphocytes, erythrocytes or platelets counts of 30% at day 5 after the first administration of methotrexate compared to baseline, then he will withdrawn from treatment (refer also to withdrawal criteria in chapter 9.6).

Furthermore an instruction sheet will be handed out to the patient.

From week 0 to week 16:

The starting dose and regular maintenance dose will be 17.5 mg MTX (verum)/0.35 mL NaCl (0.9 %) solution (placebo) administered once weekly (every 7 days).

However, if PASI50 is not reached after 8 weeks (**week 8**) the dosing will be increased to 22.5 mg MTX / week or 0.45 mL placebo. The Primary endpoint will be achieved after 16 weeks.

From week 16 to week 52:

Verum/verum-arm:

The patients will stay on their dose in the verum/verum-arm. However, if **at week 24** the patients receive 17.5 mg MTX but PASI75 is still not reached, the dosing will be increased to 22.5 mg MTX. If patients were already dosed with 22.5 mg MTX/week **at week 24** and PASI50 is not reached, patients will be excluded from treatment.

Placebo/verum-arm:

The patients will receive from week 16 to week 52 MTX according to the dose schedule of the verum-verum-arm (starting dose 17.5 mg with the possibility of up-titration after 8 weeks (**week 24**)). However, patients who will reach PASI75 under placebo-treatment after 16 weeks, will be dosed neither with placebo nor with MTX until relapse. After relapse the patients will be dosed with a starting dose of 17.5 mg MTX as described above.

Withdrawal due to safety reasons:

For safety reasons patients will be withdrawn from the treatment in case of the criteria given in chapter 9.6.

Dose interruptions

Dose interruptions will be allowed for safety reasons e.g. in the case of abnormal laboratory values. Dose interruptions of more than 2 consecutive administrations have to be discussed with the coordinating investigator or his designee.

Dose interruptions will be required in case of:

Diarrhoea of grade 2 (5-7 loose stool a day or diarrhoea lasting more than one week) and higher will lead to interruption of the treatment (maximal 2 consecutive dosages). If the symptoms will be still present the patient will be withdrawn from the study and assigned to a specialist for further clarification.

In case of a significant increased PIIINP-value a control measurement will be performed. If the PIIINP-value is still increased the MTX-treatment will be interrupted (max. 2 consecutive dosages). If PIIINP values are still increased the patient will be withdrawn from the study and assigned to a medical specialist for clarification (e.g. a liver biopsy could be recommended).

Patients with 20 ml/min < CCL < 50 ml/min will stop treatment immediately; a control measurement after one week will be performed. If the value is 20% below the last value the patient will be withdrawn from the study and assigned to a specialist for further clarification. If the value is still below 50 ml/min, however not 20 % decreased a further control after 1 week has to be performed. If the value is still below 50 ml/min the patient should be withdrawn from the study and assigned to a specialist for further clarification.

11.7 Prior and Concomitant Treatment

Prior Treatment

All prior medication which was prescribed to the patient up to 3 month prior to randomisation should be recorded in the eCRF.

Not able or willing to wash out any prohibited medications as listed below.

Medication / Therapy	Washout requirements (all times with regard to first s.c. administration of the IMP)
Any biologics	5 times of half-life
Phototherapy or any systemic medications that could affect the psoriasis (including but not limited to oral or injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, sulfasalazine, hydroxyurea, or fumaric acid derivatives	Within 4 weeks
Any topical medications that could affect the psoriasis (e.g. corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene	Within 2 weeks
Any systemic immunosuppressants (e.g. azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus	Within 4 weeks
lithium, antimalarial agents	To be stopped directly prior to first s.c. administration of IMP
Intramuscular gold	Within 4 weeks

Concomitant Treatment and other restrictions

- **No** immunosuppressive or other systemic or topical anti-psoriatic therapy will be allowed.
- Medication that may increase MTX toxicity (drugs affecting renal clearance, with high plasma binding, with adverse reactions to the bone marrow, causing folate deficiency, proton-pump

inhibitors and theophylline) may be prescribed (with the exception of co-trimoxazole) only with permission of the investigator.

Please see table below for medications that may increase MTX toxicity:

Non-steroidal anti-inflammatory drugs (in case of reduced creatinin clearance)	Antibiotica	Other
Salicylates	Co-Trimoxazole (absolute contraindicated)	Barbiturates
Naproxen	Sulfonamides	Colchicine
Ibuprofen	Penicillins	Dipyridamole
Indomethacin	Tetracyclin	Phenytoin
	Ciprofloxacin	Probenecid
		Furosemide
		Thiazide-diuretics

According to German S1 Guideline

- During the first 24 hours after MTX/placebo dosage medications/supplements containing folate additionally are prohibited.
- Consumption of alcohol should be avoided, or strongly reduced.
- Consumption of beverages containing caffeine should be kept low.
- For topical usage only bland emollients will be allowed.
-
- **24 hours after each MTX/placebo dosage 5 mg folic acid will be administrated as part of the therapy**

11.8 Procedures for Monitoring Compliance

The investigator should promote compliance by instructing the patient to apply the study drug exactly as prescribed and by emphasising that compliance is necessary for the patient's safety and clinical efficacy and the validity of the study. The first application of the study medication will be performed under the supervision of the investigator or designee. The patient will be instructed verbally and in written form how to apply the medication and to contact the investigator if he is unable for any reason to apply the study drug as prescribed. Compliance with the treatment assignments will be controlled by the investigator and the study site personnel at every visit. Patients will be questioned regarding irregularities in terms of application since the last visit (e.g. missing doses, overdoses, failures in the application technique, frequency of application). Any kinds of

irregularities are documented in the eCRF. The eCRFs are monitored by a site monitor for compliance with the protocol as described in a separate monitoring manual.

12 Study Schedule

12.1 Study Flow Chart

Please refer to flow chart in synopsis. The flow chart lists all of the assessments and indicates with an 'X' the visits at which they will be performed.

12.2 Study Visit Description

12.2.1 Visit 0 – (Screening/Day -28 - -1)

The investigator informs the patient about the study and obtains the informed consent form for the patient. The form must be dated and signed by both the patient and the investigator. A signed copy will be provided to the patient (for details refer to chapter 18.2).

After informed consent form is signed a patient identification number (randomization number) will be assigned to the patient.

The Screening Visit 0 will take place up to 28 days before Visit 1.

During the screening visit, the Investigator will:

- Obtain written informed consent,
- Assess PASI, BSA and PGA.
- Assess patients eligibility according to the inclusion and exclusion criteria,
- Ask the patient for current treatment
- Document demographic data,
- Record medical history (incl. plaque psoriasis history); check of chest X-ray investigation (has to be performed within the last 6 month prior to first administration of study medication)
- Document vital signs including body weight and height
- Perform a physical examination
- Recording of (S)AEs that occurred after signing the informed consent. All "AEs" prior to the 1st Injection will be recorded as signs and symptoms as part of the medical history
- Record previous and concomitant medications within the last 3 month prior to first dosing.
- Collect blood sample for safety lab (incl. bilirubin, serum albumin, serology (Hep. A, B, C) and PIIINP. A serum pregnancy test will be carried out for females only.)

12.2.2 Visit 1 – (Baseline/Day 0)

Visit 1 will take place on Day 0. At Visit 1, the Investigator will:

- Document vital signs including body weight
- Carry out urine pregnancy test in female patients
- Check safety lab results from Visit 0
- Collect blood sample for baseline safety lab check (incl. bilirubin, serum albumin) if more than 8 days between screening (V0) and baseline (V1)
- Assess PASI, BSA, PGA, PsA, reduced NAPSI,
- Hand out and collect DLQI, EQ-5D, and PSAT metex[®]
- Perform a physical examination
- Assess vital signs
- Assess inclusion and exclusion criteria to confirm that the patient is still eligible
- Randomize the patient (timing is described in the eCRF, First the inclusion- and exclusion criteria need to be checked, then the rest of the visit will be performed)
- Document any (S)AEs
- Document all changes in concomitant medications
- Administrate the study medication and give instructions for self-administration to the patient
- Distribute emergency card
- Perform a skin biopsy (optional for a subset of approx. 30 patients from German sites only, after signing extra informed consent for this sub-study)

12.2.3 Visit V2 (Day 5) and Phone Call on Day 7

Visit 2 will take place on day 5. The investigator will:

- Document vital signs
- Perform a physical examination
- Collect blood sample for safety lab
- Document any (S)AEs.
- Document all changes in concomitant medications.
- Distribute study medication for the next self-administrations at home
- Distribute medication card and administration instructions

On day 7 after receiving and evaluating the laboratory results, the patient will be informed by a phone call concerning the laboratory results. If the results are without findings that would lead to dose interruptions or withdrawal from treatment, the patient will be instructed to self-administrate at home. In case of findings (see above) a date for a laboratory control visit will be scheduled. No dosing will be performed prior to normalization of laboratory values.

12.2.4 Visit 3 and Visit 4 (week 4 (day 28 ± 2) and week 8 (day 56 ± 2))

For visit 3 and visit 4 the required examinations are equal except for DLQI and EQ-5D which will be handed out to the patients only at visit 3. The investigator will:

- Document vital signs
- Perform a physical examination
- Collect a blood sample for safety lab
- Assess PASI, BSA, PGA, reduced NAPSI
- Hand out and collect DLQI and EQ-5D at visit 3 only
- Document any new (S)AEs
- Document all changes in concomitant medications
- Collect used and unused study medication and distribute new study medication
- Collect and review medication card, add dosing instructions and provide it to the patient

12.2.5 Visit 5 (week 16 (day 110 - 2))

At visit 5 the primary endpoint will be evaluated. The investigator will::

- Collect a blood sample for safety lab incl. PIIINP
- Document vital signs including weight
- Perform a physical examination
- Assess vital signs
- Perform a skin biopsy (optional for a subset of approx. 30 patients for German sites only, refer to visit 1)
- Assess PASI, BSA, PGA, reduced NAPSI, PsA
- Hand out and collect PSAT metex[®], DLQI, and EQ-5D
- Document any (S)AEs.
- Document all changes in concomitant medications.
- Collect used and unused study medication
- Collect and review medication card,

12.2.6 Visit 6 (week 16 (day 112))

At visit 6 the unblinding phase will start. The investigator will:

- Check of the safety lab results from visit 5
- Document any (S)AEs.

-
- Document all changes in concomitant medications.
 - Check that all data from visit 5 including the results of the safety lab evaluation were transferred to the eCRF. All automatically produced queries have to be resolved.

The unblinding will be performed via the eCRF only if above mentioned requirements are met. Thereafter the investigator will hand out the commercial product and inform the patients to which study arm they were assigned.

- The patients that received placebo up to week 16 will now receive the first time metex®/Metoject® with a start dose of 17.5 mg. The patients that received metex®/Metoject® already up to week 16 will stay on their dose (17.5 or 22.5 mg, see chapter 11.6). The injection will be performed at the study center.
- Distribute study medication for the next self-administrations at home
- Distribute medication card and administration instructions

12.2.7 Visit 6a and 6b (week 17, day 117 and week 20, day 140 ± 2) and Phone Call on Day 119 (week 18)

Visit 6a and 6b affects only patients of arm 2. The investigator will:

- Document vital signs including weight
- Perform a physical examination
- Assess vital signs
- Collect a blood sample for safety lab
- Assess PASI, BSA and PGA (only relevant for visit 6b)
- Hand out and collect DLQI and EQ-5D (only relevant for visit 6b)
- Document any (S)AEs
- Document all changes in concomitant medications.

On day 119 after receiving and evaluating the laboratory results, the patient of arm 2 will be informed by a phone call concerning the laboratory results. If the results are without findings that would lead to dose interruptions or withdrawal from treatment, the patient will be instructed to self-administrate at home. In case of clinically significant findings (see above) the patient will be informed accordingly and a date for a laboratory control visit will be scheduled. No dosing will be performed prior to normalization of laboratory values.

12.2.8 Visit 7 and Visit 8 (week 24, day 168 ± 2 and week 32 day 224 ± 2)

For visit 7 and visit 8 the required examinations are equal except for the hand out of DLQI and EQ-5D questionnaires which will be done on visit 8 only. The investigator will:

- Document vital signs

- Perform a physical examination
- Assess vital signs
- Collect blood sample for safety lab
- Assess PASI, BSA reduced NAPSI and PGA
- Hand out and collect DLQI and EQ-5D (only relevant for visit 8)
- Document any (S)AEs.
- Document all changes in concomitant medications.
- Collect used and unused study medication and distribute new study medication
- Collect and review medication card, add dosing instructions and provide it to the patient

12.2.9 Visit 9 (week 44, day 308 ± 7)

Visit 9 will take place on day 308, week 44. The investigator will:

- Document vital signs
- Perform a physical examination
- Collect blood sample for safety lab
- Document any (S)AEs
- Document all changes in concomitant medications.
- Collect used and unused study medication and distribute new study medication
- Collect and review medication card, add dosing instructions and provide it to the patient

12.2.10 Visit 10 (week 52, day 364 ± 7)/Early Termination Visit

Visit 10 will take place on day 364, week 52. The last dosing will be in week 51. The same investigations will be performed in case of a prematurely drop out of a patient approx. one week after last dosing (early termination visit). The investigator will:

- Document vital signs including weight
- Perform a physical examination
- Assess vital signs
- Collect blood sample for safety lab
- Assess PASI, BSA, reduced NAPSI, PsA and PGA
- Hand out and collect DLQI, PSAT metex[®], and EQ-5D
- Document any (S)AEs.
- Document all changes in concomitant medications.
- Collect used and unused study medication
- Collect and review medication card

12.2.11 Unscheduled Visits

Due to clinically significant elevated or decreased laboratory values or other significant reasons additional visits can be required.

13 Assessments

Every effort should be made to ensure that the investigator who performs the assessments for a patient at screening/randomisation should also perform these assessments for all subsequent visits.

13.1 Demographics and baseline characteristics

Patient demography consists of:

- Age at screening
- Height
- Weight
- Race
- Sex

Furthermore, the status of employment (e.g. student, full-time employee, part-time employee, pensioner, etc.) and the kind of health insurance (private or compulsory) will be recorded

13.2 Efficacy Assessments

13.2.1 *Psoriasis Area and Severity Index (PASI)*

The PASI scoring system will be used and the score will be calculated based on the evaluation of the single elements of erythema (redness), infiltration and scaling as well as the involved skin area on head/neck, arms, body and legs – using the standard formulas for such calculation. The PASI evaluation will be performed by an Investigator with relevant experience in dermatology, psoriasis as well as the use of the PASI scoring system (see scoring form in Appendix A):

All participating Investigators will be trained in the study specific procedures especially in the foreseen questionnaires and scores by an experienced dermatologist to achieve consistency in the assessments. The training session will be scheduled during the Initiation Meeting or he will receive training by other means, e.g., a kit for self-training. The training of Investigators will be documented in a training log.

13.2.2 *Physician's Global Assessment (PGA)*

In this study, the PGA (Bewley 2011) will be used as a parameter for the evaluation of the efficacy of the study interventions. The PGA describes the severity of psoriasis using 7 categories (for details please refer to appendix B).

13.2.3 *Body Surface Area Index (BSA)*

In this study, the BSA (Finlay 2005) will be used to estimate the area of skin affected with psoriasis (for details please refer to appendix C). Affected BSA has been frequently used to assess disease severity. One percent of BSA is approximately equal to the patient's open hand (from wrist to tips of fingers) with fingers tucked together and the thumb tucked to the side, as stated in the Koo-Menter Psoriasis Instrument (Feldmann 2005).

13.2.4 *Reduced Nail Psoriasis Severity Index (reduced NAPSI)*

The NAPSI will be used for evaluation of response to treatment of psoriatic nails in this study. It is a numeric, reproducible, objective, simple tool. This Evaluation of the severity of nail bed psoriasis and nail matrix psoriasis with this scale is based on the assessment of area of involvement in the nail unit. In this study the NAPSI will only be applied for the best and worst finger. As the assessment of nail psoriasis is not the main objective in this study, this reduced form should be sufficient (for details please refer to appendix D).

13.2.5 *Psoriatic Arthritis Index (PsA)*

Characteristic features of psoriatic arthritis (PsA) include: swelling, erythema, warmth, and inflammation of the affected joint. PsA can present with asymmetrical joint distribution, involving more joints over time and progressing as an oligoarticular/polyarticular disease. Almost any joint can be involved including peripheral (e.g., the DIPs) and/ or axial joints (e.g., spine and sacroiliac joints). PsA can also manifest with involvement of periarticular structures such as tenosynovitis (inflammation of the tendon sheath), dactylitis or "sausage digit" (inflammation of entire digit), and enthesitis (insertion of the tendon) (Qureshi 2005).

If the patient suffers from a psoriatic arthritis besides the plaques psoriasis, the patient will be asked at different time points (see flow chart) concerning the current status (for details refer to appendix E). Therefore, with this questionnaire the progress of the psoriatic arthritis under treatment of MTX could be shown.

13.2.6 *Dermatology Life Quality Index (DLQI)*

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of a disease on the patient's daily life (Finlay, 1994). It is a 10-item questionnaire and can be used to assess 6 different aspects: symptoms and feelings, leisure, daily activities, work or school performance, personal relationship and treatment. The questionnaire was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. The DLQI could also be expressed as a percentage of the maximum possible score of 30.

See appendix F.

13.2.7 EQ-5D Questionnaire

The EQ-5D (Rabin R 2001) is a descriptive questionnaire on health-related quality of life (QOL). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status (for details please refer to appendix G).

13.2.8 Patient's satisfaction with metex[®] pre-filled syringe (PSAT metex[®])

There is a need to assess the patients' experience with self-injection, and to gauge their success in giving self-injection regimen.

This Patient's satisfaction with metex[®] pre-filled syringe was exclusively developed for this study. However, this questionnaire was not validated the descriptive analysis should give a first image concerning perceived advantages of self-injection and the potential barriers to self-injection, including psychological barriers and physical barriers, as well as satisfaction with self-injection and willingness to continue the treatment by self-injection. Furthermore the following aspects will be considered with this index:

- Benefit
- Satisfaction

See appendix H.

13.3 Safety Assessments

13.3.1 Adverse Events (AE)

Adverse events are to be monitored throughout the course of the study from 1st injection of IMP (each sign/symptom that occurs between signing informed consent and 1st injection of IMP will be recorded as part of the medical history). The investigator will assess and record any AEs in detail including the date of onset, severity, relationship of the AE to study drug, action(s) taken, event stop date and outcome. All adverse events are to be reported on the adverse event page of the eCRF with complete information as required (see chapter 15.2). If adverse events occur, the main concern will be the safety of the study patients. At time of the informed consent signature, each patient must be given the name and phone number of investigation site personnel for reporting adverse events and medical emergencies.

13.3.2 Laboratory

A central laboratory will be used for analysis of all specimens for the German sites. For the sites in the Netherlands, the UK and France the respective local laboratory will be used. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. The investigators of the sites in the Netherlands, the UK and France will be provided with separate laboratory manuals.

The amount of blood which is needed for analyzing will be approx. 9 mL / visit. approx. 100mL blood will be drawn for the whole study within an overall study duration of 54 weeks (incl. 14 days for screening). The small amount of blood which will be drawn per visit is completely nonhazardous from a medical point of view. An anemia due to blood drawings can be excluded for this study.

Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

The following laboratory testing will be performed:

Haematology:

A sufficient amount EDTA blood sample will be taken at each visit for the determination of:

Haemoglobin, hematocrit, white blood cells count with differential, red blood cells count, platelets count.

Blood Chemistry:

Additional sufficient blood samples will be taken to determine:

gamma-glutamyltransferase (GGT), sGOT (serum glutamic-oxaloacetic transaminase - AST), sGPT (serum glutamic-pyruvic transaminase - ALT), alkaline phosphatase (AP), Serum-creatinine, calculated creatinine clearance, CRP, PIIINP (at screening/baseline, V5, V8 and V10), bilirubin (total) (at screening/baseline only), serum albumin (at screening/baseline only), pregnancy test (for females at screening).

Urinalysis:

Specific gravity, pH, protein, glucose, ketones, bilirubin, leukocytes, blood (hemoglobin and erythrocytes), nitrite, pregnancy test per dip stick at the sites (for females at baseline)

In case of findings within the Urine status a microscopic examination of the urine sediment should be performed including the following parameters: Red blood cells, white blood cells, epithelial cells, microorganisms, casts.

In case of out of range laboratory values the investigator has to judge the clinical significance. Clinical significant abnormal laboratory values must be repeated until they return to normal or are otherwise explained by the investigator. Clinically significant laboratory values are to be reported as AEs on the adverse event page of the eCRF.

13.3.3 Vital Signs

Evaluation of vital signs will be performed after 10 minutes supine rest. Blood pressure (systolic/diastolic) will be measured with a mercury manometer or an automated device (same type of device for all measurements).

Normal blood pressure will be defined as a systolic pressure of 90 - 120 mmHg and diastolic pressure of 50 – 90 mmHg. Notable blood pressure will be hypertension (systolic pressure > 140 mmHg and/or diastolic pressure > 90 mmHg) or hypotension (systolic

pressure < 90 mmHg and/or diastolic pressure < 50 mmHg). A blood pressure indicative of prehypertension (systolic pressure 120 - 140 mmHg and/or diastolic pressure 80 - 90 mmHg) will not be regarded as notable according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Pulse rate and blood pressure should be measured on the same arm on each occasion with the subject sitting. These data will be recorded in the eCRF. A normal pulse rate will be defined as a rate of 60 – 100 beats per minute. Notable pulse rates are a rate above 100 bpm (tachycardia) and under 60 bpm (brachycardia).

Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

13.3.4 *Physical Examination*

A physical examination will be performed at the study visit as outlined in the flow chart. It will include the examination of general appearance and a symptom oriented physical examination. Moreover, for this study it is required to examine the oral and pharyngeal mucosa at each visit.

Whether action needs to be taken to address notable values will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the protocol.

If indicated based on the symptoms or medical history, additional exams will be performed at the discretion of the investigator.

Significant findings that are present prior to 1st injection of IMP must be included in the medical history on the eCRF. Significant findings made after 1st injection of IMP that meet the definition of an adverse event effect must be recorded on the adverse event page of the eCRF.

Local tolerance and tolerability

Local tolerance and tolerability at the injection site will be assessed at each study visit (starting with visit 1 after first injection) by the investigator regarding the following clinical criteria.

Erythema (redness): diameter (mm) and severity from none to severe (0 = none, 1 = mild, 2 = moderate 3 = severe)

Swelling/Induration: diameter (mm) and severity from none to severe (0 = none, 1 = mild, 2 = moderate 3 = severe)

Hematoma: yes/ no and if present diameter (mm)

Local pain - assessed by the study subject on a visual analogue scale (1-10)

Refer to appendix K

Pruritus – assessed by the study subject on a visual analogue scale (1-10)

Refer to appendix L

13.4 Sub-study skin biopsy

This study includes an optional skin biopsy investigation which requires a separate signature in a separate informed consent for skin bopsies. Approximately 30 patients from 2-3 German centers are foreseen to take part in this study. This sub-study has explorative purpose only. The statistical analysis will only be descriptive. It is required as part of this protocol that the investigator presents this option to all patients in the respective selected centers. If the patient consents to participate in this part of the study, at Visit 1 (week 0, baseline) and Visit 5 (week 16) skin biopsies will be taken from lesional (respectively formerly affected skin) skin by two connecting 3 mm punches that will be closed afterwards with one suture.

These samples will be used for analyzing the following parameters / marker:

- Molecular biologic analyses: Quant. RT-PCR, Kryo-samples: UBC and B2M as housekeeping gens; TNF-alpha, IL-17, IL-4, IFN-gamma
- Immunohistochemistry analyses: Paraffin-samples: CD3, CD1a, Ki67

The investigations are exploratory and are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational drug. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new biomarkers.

Exploratory research studies are planned as a part of this study with the objectives of identifying inherited factors which may (1) be related to psoriasis, (2) predict response to treatment with methotrexate, or (3) predict predisposition to side effects. The intent is to develop a better understanding of psoriasis and how patients respond to methotrexate.

Sampling method

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date and exact time must be entered on the sample collection eCRF page. The biopsies will only be performed by respectively experienced investigators / dermatologists.

Packaging of samples

Once the sample has been taken, it will be immediately placed in a receptor tube already marked for identification. Storage and shipping procedures will be described in a separate document.

14 Adverse Event Reporting

14.1 Definition

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events occurring in subjects in the course of a clinical study during treatment-free periods or on treatment with placebo or a comparative medicine are also to be considered AEs.

Adverse Reaction (AR):

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship, assessed as "related" or "possible" by either the reporting investigator or the company.

Unexpected Adverse Reaction:

An AR, the nature or severity of which is not consistent with the applicable product information [see summary of product characteristics (metex® 50 mg/ml Injektionslösung for German sites and the country specific SmPCs (Metoject 50 mg/ml solution for injection) for the UK, the Netherlands and France)].

Serious Adverse Event/ Serious Adverse Reaction (SAE/SAR):

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation*,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect or
- is medically important**

* NOTE: "*In-patient hospitalisation*" is defined as 24 hours in hospital or an overnight stay.

** NOTE: "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such

medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

Suspected unexpected serious adverse reaction (SUSAR):

A SAR, the nature or severity of which is not consistent with the applicable product information [see investigator’s brochure for [drug name] and / or summary of product characteristics for [drug name].

Significant Adverse Events:

Other significant AEs are defined as e.g. other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of investigational medicinal product, dose reduction, or significant additional concomitant therapy.

14.2 Documentation of Adverse Events

At each visit, the investigator should ask the study subject in a non-leading manner about the state of his/her health in order to elicit information on AEs which may have occurred since the last visit. Any clinically relevant observations made during the visit itself also constitute AEs.

The investigator has to document all AEs in the patient’s chart and in the eCRF. For documentation of Adverse Events in the report listings MedDRA should be used. Follow-up information must be entered as soon as available. The causality assessment must be assigned by the investigator.

Corrections to most AE details may be made, but must be dated and signed according to ICH guidelines. (Exceptions: Changes in severity and/or seriousness). If a suspected diagnosis has been ruled out, the investigator may change the AE term, but should add a comment stating the original suspected diagnosis as well as reasons for change.

Any change of an AE in severity or seriousness must result in a new entry. The outcome of the original entry must be entered as “worsening” and is given an end date reflecting the date of the worsening. The onset date of the new entry is also the date of worsening. The onset date of a SAE is the time as of which the event fulfils a criterion for seriousness.

Laboratory values out of normal range which have been collected according to the protocol have to be reported on the eCRF form “Laboratory Values” only, unless a value is clinically significant and/or fulfils a criterion for seriousness. These values have to be documented on the CRF “AE form” and in addition on the SAE report.

Laboratoy values out of normal range which have been collected in addition to the protocol have to be reported on the eCRF “AE form” if clinically relevant as assessed by the investigator.

For all AEs the following information has to be entered on the eCRF:

- Description);

-
- Severity
 - Date of onset;
 - Outcome;
 - Date ended, if resolved;
 - Causality to the investigational drug;
 - Seriousness;
 - Action taken regarding the investigational drug.

Unblinding of single cases by the investigator or sponsor will only be performed if relevant for the safety of the study subject.

Assessment of Causality

The investigator assesses the suspected causal relationship between the investigational drug and the AE. In case of SAEs the drug-relatedness must be assessed separately by the investigator and by the sponsor's designee Dr. Nibler & Partner.

The relationship of an AE to the investigational product is defined as follows:

- Related:** There is a reasonable causal relationship between the study drug and the clinical event. The event occurs with a plausible time relationship to drug administration and cannot be explained by concurrent disease, other drugs, chemicals, or procedures. The event responds to withdrawal of the study drug (dechallenge). This response should be clinically plausible. The event recurs with rechallenge, when clinically feasible.
- Possible:** There is a reasonable causal relationship between the study drug and the clinical event. The event occurs with a reasonable time sequence to drug administration but could also be explained by concurrent disease, other drugs, chemicals, or procedures. Information on drug withdrawal is lacking or unclear.
- Unlikely:** The temporal relationship to study drug administration and / or causality assessment between the study drug and the event makes a relationship improbable. The concurrent disease, other drugs, chemicals, or procedures provide plausible explanations.
- Not Related:** There is no temporal relationship to study drug administration (too early, too late,) and there is sufficient information of a causal relationship between another drug, concurrent disease, or circumstance and the event (aetiology unrelated to study drug); or IMP not administered for any reason.

Adverse Events assessed as "Related" or "Possible" by either the reporting investigator or by the sponsor's designee Dr. Nibler & Partner, will be classified as AR. Adverse Events assessed as "unlikely" or "not related" will not be classified as AR. At the start of an AE a proper assessment of causality might be difficult e.g. due to outstanding examinations. Additional information / results might require a change of the causality assessment. In this case, the investigator changes the entry in the CRF. If the causality assessment of a SAE is to be changed, the investigator completes a SAE- "Follow up"-Report with the changed assessment and sends it to the sponsor's designee Dr. Nibler & Partner.

14.3 Reporting of Serious Adverse Events

SAEs must be reported on the SAE form in addition to the AE documentation in the eCRF by the clinical study site to the sponsor or sponsor's designee:

Primary Contact (24/7): Dr. Nibler & Partner

Fax: +49-700-3784723389
Fax: +49 -700-DRUGSAFETY
E-mail: SAE@drugsafety.de
Phone: +49-89-56823726

Secondary Contact

Dr. Reinhard Nibler	Dr. Susanne Lüdeling
Phone: +49-171-3860445	Phone: +49-171-4469891
Fax: +49-89- 57967495	Fax: +49-89-57967495
E-mail: rn@dr-nibler.de	E-mail: sl@dr-nibler.de

For expedited reporting of SAEs, the sponsor's designee Dr. Nibler & Partner must be informed immediately. Only for information received by fax or e-mail, Dr. Nibler & Partner can guarantee the assessment and reporting of the given case within the legally required time frame.

During the safety surveillance period all SAEs need to be reported immediately but within 24h upon first notification of a SAE by the investigator. The SAE form (copies included in the ISF of the investigator) has to be sent by fax or e-mail, whether or not complete information is available at this time. In case of incomplete information, the investigator must provide follow-up information at the latest within 5 days, using the same SAE template form as for the initial reporting. Any further necessary follow-up information and clarification on the event will be requested by the sponsors' responsible designee Dr. Nibler & Partner to ensure complete and appropriate reporting to authorities within the required timeframe in accordance with applicable national and international regulations.

SAEs which, according to present knowledge, might be caused by the IMP require immediate, thorough medical assessment by the investigator. The decision regarding termination of the entire study will be taken on the basis of this assessment and in accordance with the legal requirements and in conjunction with the sponsor or delegate.

All SAEs must be followed-up until the event is completely resolved or cannot be resolved any further according to conventional medical practice which will also be documented in the source documentation.

The investigational site will send copies of any relevant data like hospital notes, ECG results, laboratory test, discharge summary, autopsy reports etc. to Dr. Nibler & Partner as soon as they become available. SAE reports will be checked against the source documentation by the site monitor during the next monitoring visit.

Further detailed instructions for reporting SAEs in the study is described in the Safety Management Plan which will be provided by Dr. Nibler & Partner before start of study enrolment.

SAE information reported by the study site will be processed and evaluated by Dr. Nibler & Partner. SAE assessments as suspected unexpected serious adverse reaction (SUSAR) or as a serious adverse reaction (SAR) will be done by Dr. Nibler & Partner.

Authorities as well as IECs will be informed according to their policies and respective national and / or international regulations.

Dr. Nibler & Partner will submit all expedited safety reports to the national competent authorities as required. Adequate information will also be made available to the Principal Investigators.

The investigators / clinical study sites will submit SAE reports including expedited safety reports to their responsible EC, as required.

Supporting and Follow up Information on Serious Adverse Events

Supporting information as requested on the SAE Report Form or by the sponsor (e.g. hospital reports, autopsy reports) as well as follow up information must be delivered immediately if available. Information must be documented on an additional SAE Report Form and the box "Follow up" must be ticked. The completed form must be sent to the recipients of the initial information.

- Hospitalisation for diagnostic or regular therapy as provided in the clinical study protocol does not need to be handled/ documented as a SAE.
- An overnight stay in the hospital that is only due to transportation, organisation, or accommodation problems and without medical background does not need to be handled/ documented as a SAE.
- Hospitalisation which is due to a planned study visit (diagnostic or regular therapy) and for no other reason and without prolongation does not need to be handled/ documented as a SAE.
- Hospitalisation, that was planned before inclusion of the patient in the study for elective operations or treatments does not need to be handled/ documented as a SAE.
- Progression of the basic disease or death due to the basic disease without causality with investigational drug does not need to be handled/ documented as a SAE.

Upon identification of an unexpected, serious adverse reaction the sponsor's designee Dr. Nibler & Partner will proceed to break the code or un-blinding of the corresponding patient so that the treatment allocation is made known. Code breaking will be only performed if the national or local requirements for expedited reporting demand the submission of un-blinded adverse reactions. Treatment allocation will be exclusively communicated to the competent authorities for regulatory purposes and will not be communicated to any other party under any circumstance.

Blinded therapies

In case of an emergency situation the investigator is allowed to unblind the therapy of the concerned patient. Time and reason for unblinding has to be documented.

Unblinding in not-emergency cases by the sponsor's designee Dr. Nibler & Partner, has to be approved by the sponsor and the Coordinating Investigator.

Notification of Health Authorities, Ethics Committees, and Investigators

The sponsor's designee Dr. Nibler & Partner notifies SUSARs to the concerned authorities, ethics committees, and investigators according to Directive 2001/20/EC and to current local laws and guidances. As a general rule, fatal and life-threatening SUSARs must be reported by the sponsor's designee Dr. Nibler & Partner within 7 days; hospitalisation, disability, birth defect or medically important cases must be reported within 15 days

In addition, the sponsor's designee Dr. Nibler & Partner provides the concerned authorities and the Ethics Committee(s) with a periodic safety report on the investigational drug under development (development safety update report according to ICH guideline E2F).

Pregnancy

Pregnancy discovered during a clinical study must lead immediately to exclusion (if at screening) or withdrawal of the subject.

If the subject has already received study medication, the pregnancy should be documented as a SAE. The SAE Report Form and the AE page in the CRF should be filled out – entering the event as medically important. The case must be reported within 24 h of knowledge to the monitor/other persons mentioned in the protocol and/or CRF as recipients of SAE reports. The investigator must follow-up on pregnancies discovered after study medication intake until the end of pregnancy to document the outcome. The event fulfils the criterion for a SAE if a congenital anomaly results.

Overdose

Overdose which occurs during a clinical study is to be treated and documented as a SAE. The information contained therein should include: centre identification, reporter identification, patient identification, study medication, dose, action taken, and any comments.

Safety issues not falling within the definition of SUSAR — other measures

Events may occur during a clinical trial which do not fall within the definition of SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. Examples are:

- new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:
- a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study (such as carcinogenicity),
- a temporary halt of a trial for safety reasons if the trial is conducted with the same IMPs in another country by the same sponsor,
- in the case of advanced therapy IMPs relevant safety information regarding the procurement or the donor.

These events/observations are not to be reported as SUSARs, but they might require other action, such as:

- urgent safety measures and their notification
- substantial amendment, or
- early termination of the trial

Moreover, it is recommended that the sponsor informs the national competent authority and the Ethics Committee(s) of safety issues which might materially alter the current benefit-risk assessment of an IMP while not falling within the actions listed above.

15 Statistics

The Statistical Analysis Plan (SAP) is written as a separate document to be completed after finalizing the protocol developed during the conduct of the study. The SAP will be finalised prior to the interim database lock of the first patient (data up to week 16).

Any changes to the statistical analyses planned in the protocol will be justified and documented in the SAP if they were decided before interim database lock of the first patient. Any changes made to the SAP after the interim database lock of the first patient will be documented in the final study report.

Summary statistics for continuous variables will include number (N), mean, standard deviation, median, minimum, maximum, lower and upper quartiles.

Summary statistics for discrete variables will include frequencies and percentages.

In general, data summaries will be presented by treatment arm.

If not otherwise specified, p-values will be presented as two-sided p-values and the level of significance is set to 5% (two-sided). Additionally, corresponding 95% confidence intervals will be provided.

15.1 Protocol deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as “minor” or “major” in cooperation between the Sponsor Representatives, SCIderm GmbH and the Principal Investigator (optional). This will be performed during the data review meeting prior to final data base lock at the end of the study.

15.2 Analysis Populations

Full analysis set

The full analysis (FAS) set comprises all patients who receive the investigational treatment at least once. Patients will be analysed according to the treatment they were assigned to at randomisation.

For the primary analysis of the primary efficacy parameter patients terminating their participation in the trial before week 16 the last observation will be carried forward (patients withdrawn before the first post-randomization efficacy assessment will be classified as non-responders). Under the assumption that adverse reactions to methotrexate may lead to premature withdrawal this approach is conservative.

Per Protocol set

The per protocol (PP) set comprises all patients who receive the investigational treatment at least once, whose primary endpoint (PASI at week 16) is available and who complete the study with no major protocol deviations.

The efficacy analyses (primary and secondary endpoints) will be done for both the FAS and PP set if there is more than 10% difference in the population sets. The primary analysis of the primary efficacy parameter based on the FAS will be regarded as confirmatory analysis. All other analyses will be considered as exploratory.

Safety set

The safety set comprises all patients who receive the investigational treatment at least once. Patients will be analysed according to the treatment they were actually received.

All safety analyses will be done for the safety set.

15.3 Demographics and Baseline Characteristics

Demographics

Demographic data and baseline characteristics will be summarized by descriptive statistics or frequency tables, as appropriate. Tables will be provided for all analysis populations.

Medical History

Medical history will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by MedDRA system organ classes (SOC) and preferred terms (PT).

15.4 Treatments

Concomitant medication

Frequency tables will summarise the number of patients receiving concomitant medication by ATC class.

15.5 Analysis of Primary Objective

The primary objective of this study is to evaluate the efficacy of methotrexate in patients with moderate to severe Psoriasis compared to Placebo as assessed by the primary endpoint PASI 75 during a 16 week treatment phase.

The efficacy analysis of the primary objective will be done for both the FAS and the PP set.

15.5.1 Primary Variable

The primary outcome measure for treatment efficacy will be the percentage of patients who exhibit a $\geq 75\%$ reduction of the PASI (PASI 75 responder rate) after 16 weeks of randomized treatment.

15.5.2 Statistical Methods of Analysis

Differences in PASI 75 responder rates at week 16 between treatment arms will be analysed using a two-sided Pearson Chi-square test at a significance level of 5%. Additionally, 95% confidence intervals for differences in rates between treatment arms will be provided.

15.6 Analysis of Secondary Objectives

The secondary objective is to evaluate safety and tolerability as assessed by:

- PASI 75 after 52 weeks treatment
- PASI 50 and 90 after 16 and 52 weeks treatment
- PASI 75 after 32 weeks treatment in placebo arm (cross-over)
- NAPSI, BSA, PGA, PsA and questionnaires such as PSAT metex[®], DLQI and EQ-5D after 16 and 52 weeks
- Safety and tolerability assessed by AE/SAE, laboratory values and local tolerability at the sites of administration from V1-V10

Changes of levels of molecular biologic analysis (UBC and B2M as housekeeping gens; TNF- α , IL-17, IL-4, IFN-gamma) and immunohistochemistry analysis (CD3, CD1a, Ki67) at baseline and after 16 weeks (at 3 sites for approx. 30 patients) The data up to week 16 will be analysed regarding the difference between verum and placebo treatment. The data after week 16 will be analysed regarding long term treatment effects in a descriptive manner only.

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15.6.1 Efficacy

The efficacy analysis will be done both for the FAS and PP set (if there is a difference in the FAS und PP set of 10% or more).

Each endpoint will be summarized by treatment arm and visit as a frequency table of the observed score. In addition, the scores will be summarized descriptively as continuous variables again by treatment arm and visit. Further specification will be given in the SAP.

For the data up to week 16 differences in response rates of PASI 50 and 90 will be analysed using a two-sided Pearson Chi-square test at a significance level of 5%. Additionally, 95% confidence intervals for differences in rates between treatment arms will be provided.

The PASI response at week 16 will also be categorised as follows:

1=PASI <50%

2= 50%≤ PASI <75%

3= 75%≤ PASI <90%

4= 90%≤ PASI

The treatment arms will be compared using the two-sided exact Mann-Whitney- Wilcoxon test at a significance level of 5%.

15.6.2 Safety

All safety evaluations will be performed on safety set.

Adverse Events

The AEs will be summarized separately for the both parts of the study (V1-V5 and V6-V10).

AEs will be tabulated in frequency tables by SOC and PT based on the MedDRA dictionary. Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study drug and AEs leading to discontinuation. For a given AE, a subject will be counted once even if he or she has experienced multiple episodes of that particular AE. Additionally, a summary table by SOC, PT and severity will be provided. For this several AEs of one subject within in a PT with different severities will be collapsed to one event with the highest occurred severity.

Molecular Biologic and Immunohistochemistry Analysis

Parameters of molecular biologic and immunohistochemistry analysis will be summarized with descriptive statistics separately for both treatment arms. The change from baseline for week 16 will be calculated and summarized with descriptive statistics separately for both treatment arms.

Other

Data of other safety assessments (physical examination, safety lab and vital signs) will be summarised by treatment arm and visit by descriptive statistics or frequency tables, as appropriate.

15.7 Handling of Missing Values

For the primary analysis of the primary efficacy parameter based on the FA set a last observation carry-forward (LOCF) analysis will be performed. In LOCF analysis the last observation will be carried forward to the last time point for missing assessments of the primary endpoint. The LOCF analysis treats the carried forward data as observed data at the last time point.

The remaining study variables will not be imputed.

15.8 Sample Size Calculation

The sample size estimation is based on the primary outcome measures for treatment efficacy, the PASI 75 responder rate at treatment week 16. From literature data derived

from adult patients a placebo responder rate of 10% is assumed for the primary outcome measure, and a responder rate of 35% in patients treated with methotrexate is considered a meaningful treatment effect (Reich K 2011; Barker J 2011; Saurat JH 2008).

The calculation of the sample size is based on Pearson Chi-square test, a type I error rate of $\alpha=0.05$ (two-sided), a power of 80% and PASI 75 responder rates of 35% and 10% for methotrexate and placebo, respectively. Based on these assumptions the resulting sample size is given by in total 120 patients. Due to the 3:1 randomization 90 evaluable patients will be required in the verum/verum-arm and 30 evaluable patients in the placebo/verum-arm group. For this high starting dose the empirical data regarding the response rates are limited. The total number of patients will be elevated by 25% percent to 150.

16 Data Handling and Record Keeping

16.1 Data Collection

The CRF data for this study are being collected by an Electronic Data Capture (EDC) tool called ClinCase which is provided by the technology vendor Quadrantek Data Solutions Ltd., London, UK.

The EDC system and the study specific eCRFs are in compliance with FDA 21 CFR Part 11. The documentation related to the validation of the EDC tool is available through the vendor, Quadrantek Data Solutions Ltd., while the validation of study-specific eCRFs will be conducted by SCIderm and will be maintained by in the Trial Master File (TMF) at SCIderm.

The investigator will document patient data in his own patient files. These patient files will serve as the source data for the study. eCRF data stipulated by this protocol will be recorded by study personnel in the EDC tool. SAEs will be reported on paper forms.

DLQI, EQ-5D, and the PSAT metex[®] are completed on paper forms by the patient during study visit. The questionnaires completed by patient will serve as the source data for the study. The data of all questionnaires will be entered into the eCRF by study personnel.

The handling of the laboratory data will be described in the Data Management Plan.

The data of skin biopsy will not be filed in the eCRF.

If eCRF corrections are necessary, they will be made by the investigator or authorized study personnel. All change information, including the date and name of person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration has to be provided. The principal investigator will review the eCRFs for completeness and accuracy and provide his electronic signature and date to the eCRF as evidence thereof. This review and sign-off may be delegated to a sub-investigator.

Access to the EDC system will be provided by SCIderm GmbH for the duration of the study through a password-protected method of internet access. Such access will be removed for all investigational staff at the end of the site's participation in the study.

16.2 Source Documentation

Data defined before study start as not requiring a separate written record are recorded directly in the eCRF and are considered source documentation.

For source data verification at least the following information must be included in the patient file:

- Visit dates
- Date of patient's written informed consent
- Demographic data
- Inclusion and exclusion criteria
- Indication that the patient is taking part in clinical study 165-001
- Gender, age, details on psoriasis (onset, nails involvement, psoriatic arthritis)

-
- Medical history
 - Previous and concomitant medications/treatments for dermatologic diseases
 - AEs/SAEs
 - PGA

The eCRF will be the source document for the below listed data:

- Vital signs incl. body weight (only at screening, baseline, week 16 and week 52) and height (only at screening)
- Physical examination
- Randomisation

Additional documents filed in the ISF will also be regarded as source documents, e.g.:

- DLQI-Questionnaires
- Work-sheets for the assessment of PASI, BSA, reduced NAPSI, PsA, EQ-5D, PSAT metex[®] and PGA, if applicable
- Patient's assessments
- Reports of central / local laboratory

16.3 Archiving

The investigator must make arrangements to store the essential study documents (as defined in Essential Documents for the Conduct of a Clinical Trial [ICH E6, Guideline for Good Clinical Practice]) including the investigator site file, until the sponsor or its designee informs the investigator that the documents are no longer to be retained.

The ICH-GCP Guidelines (Section 5.5.11) state that essential documents be retained 'until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product'.

In addition, the investigator is responsible for archiving all relevant source documents, patient's files and patient's identification codes for a minimum of 10 years (German MBO).

The sponsor or its designee stores the original CRFs and the above essential documents for at least 15 years (2003/63/EC 5.2c), except for source documents pertaining to the individual site, which are kept only by the investigator.

17 Quality Control and Quality Assurance

The study is conducted in compliance with the applicable international and local regulatory requirements as well as applicable ICH-GCP guidelines, the Declaration of Helsinki and in respect of the SCIderm GmbH and/or sponsor SOPs (Standard Operating Procedures) for study preparation, conduct, close out and monitoring. SCIderm GmbH has established a

quality management system to ensure full compliance with all applicable regulatory and scientific standards throughout all projects.

17.1 Expert Advisory Board

For preparation, supervision and support of conduct, assessment of study results as well as presentation and publication of these, an international Expert Advisory Board has been established by the sponsor.

Members of the Expert Advisory Board are the study sponsor and the following persons (in alphabetical order and without academic titles):

Hervé Bachelez (Paris, France)

Elke M. de Jong (Nijmegen, The Netherlands)

Richard Warren (Salford, UK)

Ulrich Mrowietz (Kiel, Germany)

Kristian Reich (Hamburg, Germany)

17.2 Personnel Training

Site monitors and other applicable personnel will be trained prior to the study initiation to familiarise them with the SOPs, the protocol and all study specific items.

The investigator must ensure that all site staff involved in the conduct of the study is familiar with the protocol and study-specific procedures and have appropriate knowledge of the study drugs. The transfer of duties and a listing of all sub-investigators must be recorded in the investigator site file.

17.3 Clinical Monitoring

The conduct of the study will be closely monitored to verify adherence to ICH-GCP guidelines, AMG and applicable SOPs. An experienced CRA will advise the investigator during the clinical investigation and will perform the monitoring activities at the site which may include an initiation visit, periodic monitoring visits during the study, and a close-out visit.

At the initiation visit, the CRA will amongst others review the investigator site file, the protocol and the CRF with the investigator and his/her staff. During the study visit it is the responsibility of the CRA to secure that the documents required are present in the study documentation according to ICH-GCP guideline.

Periodic monitoring visits will take place on a regular basis according to a schedule fixed by mutual agreement. During these visits the CRA will check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP and the progress of enrolment. **The recruitment of patients will be monitored by sending random and weekly study visit listings faxes from site to SCIderm.**

Furthermore the CRA has to ensure the correctness of storage of study drug and will check study drug dispensing and accountability on every visit.

The investigator will allow the CRA to have direct access to all study records, CRFs, corresponding medical records, study drug dispensing records and study drug area and any other documents considered source documentation to confirm their consistency with the CRF entries. All information on CRFs must be traceable to these source documents in the patient's file. Data defined before study start as not requiring a separate written record will be recorded directly in the CRF and are considered source documentation. Key study personnel must be available to assist the CRA during the visit(s).

SCIderm monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of AEs/SAEs, medical history according to the monitor manual and recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

The close-out visit will occur close to LPO at the site. The CRA will, in addition to the matters mentioned for the periodic monitoring visits, clarify follow-up on open AEs, collect all required documents, clarify any remaining questions and inform the investigator about the archive requirements of signed informed consent forms, patient identification lists and CRF copies. Key study personnel must be available to assist the CRA during the visit(s). The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

17.4 Audits/Inspections

Audits may be carried out by the sponsor or its designees or medac before, during or after the study. The investigator will permit and assist the sponsor, its designee or responsible government agencies (as required by law) to have direct access to all source data/documents.

17.5 Data Management

The study personnel at each site must be trained on the completion of the eCRF and will be given an eCRF completion guideline for reference. The eCRFs will be reviewed periodically for completeness and validity by SCIderm staff (or their representatives). In addition, edit checks will be run automatically to identify inconsistent data. In addition to the automatic edit checks inconsistent, ambiguous or missing data not detected automatically will be clarified by a manual query process in the EDC system.

After the data have been source-data-verified by the CRA, a review of medical data (e.g. medical history, prior and concomitant medication, adverse events) will be conducted by a clinical reviewer at SCIderm. A manual review of selected listings will also be performed throughout the study.

18 Ethics

18.1 Regulatory and Ethics Compliance

The study will be conducted in accordance with applicable laws and regulations including, but not limited to, the German Drug Law, the ICH-GCP guideline and the ethics principles that have their origins in the Declaration of Helsinki. The protocol and the proposed informed consent form have been reviewed and approved by a properly-constituted Independent ethics committee before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors, auditors, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor or its designee immediately that this request has been made.

18.2 Informed Consent

Informed consent of patient will be obtained in accordance with ICH-GCP guideline by the investigator prior to inclusion of the patient to the study. For approx. 30 patients from 2-3 German sites an additional Informed Consent will be obtained if the patients are willing to participate in the biopsy sub-study (see above).

The nature, objective and importance of the study and sub-studies, the possible benefits and disadvantages or risks and the (sub-)study procedures will be explained to each patient orally and in writing. The patients will be informed that their participation is voluntary and that they are free to withdraw from the (sub-)study at any time, and that choosing not to participate would not impact on the patient's care or future treatment.

The patients will be also informed that, by signing the informed consent forms, they explicitly permitted access to personal data relating to (sub-)study by authorised representatives of the sponsor and the regulatory authorities without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and/or regulations.

Each patient will be given sufficient time to read and discuss the ICFs with the investigator prior to giving his/her written consent. Before entry to the study and prior to the conduct of any (sub-)study-related procedures consent will be recorded by means of the patient's dated signature. The patient is then given a copy of the information sheets and his/her signed consent forms. The collection of AE information will start at the time of the main informed consent.

18.3 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor and, where required, regulatory

authorities and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor or its designee should be notified of this action and the site-specific IRB/IEC should be informed within 10 working days.

18.4 Confidentiality

All involved investigators have to confirm that they handle the information available in the handed over documents strictly in confidence.

The process of collecting patient information will comply with the standards for protection of privacy by applicable local/regional/national requirements for patient confidentiality. All records will be kept confidential and the patient's name will not be released at any time. Throughout this study all data will not be released to anyone other than the sponsor or representatives of the responsible government agencies, if requested. Caution will be exercised to guarantee patient's confidentiality.

19 Financing and Insurance

19.1 Financing

A separate agreement is signed between the CRO and each investigator/institution containing supplemental information including the financial aspects.

19.2 Insurance

From the start of the study until its termination each patient will be insured against any health impairment occurring as a result of participation in the study in accordance with the national law and regulations. A copy of the insurance conditions will be handed out to the patient with the informed consent.

20 Publication Policy

During this clinical study, no information or unpublished data given to/collected by an investigator/study staff may be transmitted to a third party, without the written approval of Prof. Dr. med. Kristian Reich, who is the sponsor of this investigator initiated study (IIT). I.e., no investigator/study staff shall publish or otherwise disclose in any form any research findings resulting from the study, or any of its parts, including the investigative products/programmes and/or its development, prior to obtaining the sponsor's written consent.

The members of the Expert Advisory Board will, together with the sponsor, decide on the publication policy and will be authors of the resulting publication(s).

After conclusion of the study, the investigator/study staff shall notify the sponsor of any planned publication/communication to a third party of findings related to this clinical study at least sixty (60) days prior to submission for publication/disclosure, to allow the sponsor to ensure against inadvertent disclosure of unprotected discoveries or confidential information. In addition, the investigator/study staff shall delay any planned publication/communication for up to ninety (90) days to permit the sponsor to prepare and file one or more patent applications relating to the patient matter of such a publication/communication. Should the sponsor decide to file a patent application, the investigator/study staff agrees to withhold disclosure of any part of the manuscript or materials which the sponsor stipulates to be prejudicial to the granting of such a patent for a period not exceeding eighteen (18) months. The sponsor shall not have the right to influence the scientific content of the publication/communication. The publication/disclosure shall acknowledge medac for its financial support for this clinical study.

The sponsor shall not use the investigator's name in any publication without the prior written permission of the investigator. The investigator shall not use the sponsor's name in any publication without the prior written permission of the sponsor.

The sponsor ensures that the findings of this clinical study are made public through publications in scientific journals and presentations on scientific congresses. The sponsor/investigator shall undertake to use his best efforts to ensure that each publication that he seeks to publish in connection with the project complies with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" (Apr. 2010) published by the International Committee of Medical Journal Editors, including the requirements for financial disclosures.

21 References

Arzneimittelgesetz (AMG), Gesetz über den Verkehr mit Arzneimitteln, Änderung des Artikel 1 des Gesetzes zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 17. Juli 2009 (BGBl I S. 1190) in Kraft am 23. Juli 2009-(§ 40 – 42 AMG)

Barker J, Hoffmann M, Wozel G, Ortonne JP, Zheng H, van Hoogstraten H, Reich K. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol* 2011; 165(5): 1109-17

Bewley A, Page B. Maximizing patient adherence for optimal outcomes in psoriasis. *Journal of the European Academy of Dermatology and Venereology* 2011;25:9-14.

Chládek J, Simková M, Vanecková J, Hroch M, Chládková J, Martínková J, Vávrová J, Beránek M. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. *Eur J Clin Pharmacol* 2008; 64(4): 347-55

Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) 14, 15

Dervieux T, Wessels JA, van der Straaten T, Penrod N, Moore JH, Guchelaar HJ, Kremer JM. Gene-gene interactions in folate and adenosine biosynthesis pathways affect methotrexate efficacy and tolerability in rheumatoid arthritis. *Pharmacogenet Genomics* 2009 Oct 24

Dervieux T, Zablocki R, Kremer J. Red blood cell methotrexate polyglutamates emerge as a function of dosage intensity and route of administration during pulse methotrexate therapy in rheumatoid arthritis. *J. Rheumatology* 2010; 49:2337-2345

Edmundson WF, Guy WB. Treatment of psoriasis with folic acid antagonists. *AMA Arch Derm* 1958; 78:200–3

Feldmann SR, Koo JY, Menter A, Bagel J. Decision points for the initiation of systemic treatment for psoriasis. *J Am Acad Dermatol* 2005; 53:101-107

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - A simple practical measure for routine clinical use. *Clinical and Experimental Derm* 1994; 19:210-16

Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005 May;152(5):861-7.

GCP-V: Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen, GCP-Verordnung vom 9. August 2004 (BGBl. I S. 2081), zuletzt geändert durch Artikel 4 der Verordnung vom 3. November 2006 (BGBl. I S. 2523), in Kraft am 3. November 2006]

Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med*. 2003; 349(7): 658-65

ICH GCP Topic E6 (1996) "Guideline for Good Clinical Practice" CPMP/ICH/135/95

Morgan SL, Baggott JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, Koopman WJ, Krumdieck CL, Alarcón GS. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. A double-blind, placebo-controlled trial. *Ann Intern Med* 1994; 121(11): 833-41.

Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, Sterry W, Streit V, Augustin M, Erdmann R, Klaus J, Koza J, Müller S, Orzechowski HD, Rosumeck S, Schmid-Ott G, Weberschock T, Rzany B. S3-guidelines for the treatment of psoriasis vulgaris Update 2011. *J Dtsch Dermatol Ges* 2011; 9 Suppl 2: S1-104

Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients'beliefs and attitudes towards the disease. *Br J Dermatol* 1996;135: 533–537.

Nyfors A, Brodthagen H. Methotrexate for psoriasis in weekly oral doses without any adjunctive therapy. *Dermatologica* 1970; 140: 345–355

Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, Barker J, Bos JD, Burmester GR, Chimenti S, Dubertret L, Eberlein B, Erdmann R, Ferguson J, Girolomoni G, Gisondi P, Giunta A, Griffiths C, Höningmann H, Hussain M, Jobling R, Karvonen SL, Kemeny L, Kopp I, Leonardi C, Maccarone M, Menter A, Mrowietz U, Naldi L, Nijsten T, Ortonne JP, Orzechowski HD, Rantanen T, Reich K, Reytan N, Richards H, Thio HB, van de Kerkhof P, Rzany B. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; 23 Suppl 2: 1-70. Erratum in: *J Eur Acad Dermatol Venereol* 2010; 24(1): 117-8

Qureshi AA, Husni ME, Mody E. Psoriatic arthritis and psoriasis: need for a multidisciplinary approach. *Semin Cutan Med Surg* 24(1):46-51 (2005 Mar).

Rabin R, de Charro F EQ-5D: a measure of health status from the EuroQol Group. *Ann. Med.* 2001 Jul;33(5):337-43.

Reich K, Langley RG, Papp KA, Ortonne JP, Unnebrink K, Kaul M, Valdes JM. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med* 2011; 365(17): 1586-96.

Rich P, Scher RK. Nail psoriasis severity index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol*. 2003; 49:206-212.

Richtlinie 2001/20/EG GCP-Richtlinie 2001/20 EG des Europäischen Parlaments und des Rates vom 4. April 2001 zur Angleichung der Rechts- und Verwaltungsvorschriften der Mitgliedsstaaten über die Anwendung der guten klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Humanarzneimitteln (Artikel 2 h)

Saurat JH, Langley RG, Reich K, Unnebrink K, Sasso EH, Kampman W. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. *Br J Dermatol* 2011; 165(2): 399-406

Smith KC. Systemic therapy of psoriasis using methotrexate. *Skin Therapy Lett* 2000; 6:1–2

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *Hypertension* (2003); 42:1206

Weinstein G, Frost P. Methotrexate in psoriasis: a new therapeutic schedule. *Arch Dermatol* 1971; 103:33-38

Appendix A – Psoriasis Area and Severity Index (PASI)

The PASI is a scoring method that will be used for the assessment and grading of the severity of the patient's psoriasis. The severity of the disease is calculated by scoring the signs of the disease (erythema, induration and scaling) for each of the following four body regions: head (h), trunk (t), upper extremities (u) and lower extremities (l). The scoring dimensions are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0	=	No involvement
1	=	1% to 9% involvement
2	=	10% to 29% involvement
3	=	30% to 49% involvement
4	=	50% to 69% involvement
5	=	70% to 89% involvement
6	=	90% to 100% involvement

To help with the area assessment, the following conventions should be noted:

- The neck is considered part of the head
- The axillae and groin are part of the trunk
- The buttocks are part of the lower extremities

The PASI formula is:

$$\text{PASI} = 0.1(E_h + I_h + S_h) A_h + 0.3(E_t + I_t + S_t) A_t + 0.2(E_u + I_u + S_u) A_u + 0.4(E_l + I_l + S_l) A_l$$
where E = erythema, I = induration, S = Scaling, and A = area.

Appendix B – Physicians' Global Assessment (PGA) Psoriasis

Score	Category	Description
0	Clear	No signs of psoriasis (postinflammatory hyperpigmentation may be present)
1	Almost clear	Intermediate between mild and clear
2	Mild	Slight plaque elevation, scaling, and/or erythema
3	Mild to moderate	Intermediate between moderate and mild
4	Moderate	Moderate plaque elevation, scaling, and/or erythema
5	Moderate to severe	Marked plaque elevation, scaling, and/or erythema
6	Severe	Very marked plaque elevation, scaling, and/or erythema

Appendix C – BSA

The BSA will be used to estimate the area of psoriatic skin. The palm method will be applied: the patient's palm, including the five digits is used as a reference (representing approximately 1% of the total body surface area) and is used to repeatedly cover the lesions on the body. The investigator totals the number of palms required and then estimates the percentage in each of the four body regions.

The four body regions are:

- Head (including scalp) and neck (10%)
- Upper extremities (20%)
- Trunk (30%)
- Lower extremities (40%)

Appendix D – reduced NAPS I

The NAPS I in this study will only be recorded for the best and worst finger. The target nail is graded for nail matrix psoriasis and nail bed psoriasis. The sum of these 2 scores is the total score for that nail.

Nail Matrix Psoriasis consists of any the following: pitting, leukonychia, red spots in the lunula and nail plate crumbling.

<p>Score for matrix psoriasis</p> <p>0 = none 1 = present in ¼ of nail 2 = present in 2/4 of nail 3 = present in ¾ of nail 4 = present in 4/4 of nail</p>
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Nail Bed Psoriasis is the presence of any of the following:

Onycholysis, splinter haemorrhages, 'oil drop' (salmon patch) discoloration and nail bed hyperkeratosis.

<p>Score for nail bed psoriasis</p> <p>0 = none 1 = present in ¼ of nail 2 = present in 2/4 of nail 3 = present in ¾ of nail 4 = present in 4/4 of nail</p>
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Total for nail _____ (0-8)

NAPS I score according to Rich 2003.

Appendix E – PsA

The following PsA data will be recorded in this study to assess the status and improvement of PsA under treatment of MTX/Placebo, if the patient suffers from PsA besides their plaques psoriasis. At Visit 0 the diagnosis of PsA should be confirmed with answering a YES/NO-Question.

With the next question the type of the PsA should be recorded by the investigator (multiple crosses would be possible) and finally the severity of the PsA will be assessed.

1. The Patient suffers form a PsA? ☐ Yes ☐ No
2. If Yes, which type of PsA?
 - ☐ Spinal involvement
 - ☐ Multiple small joints affected
 - ☐ Dactylitis
 - ☐ Enthesitis
 - ☐ Arthritis mutilans
3. Severity rating:
 - ☐ mild
 - ☐ moderate
 - ☐ severe
 - ☐ very severe

At Visit 5/week 16 and Visit 19/week 52 the change of PsA compared to baseline will be assessed according to the following improvement rating:

1. Improvement rating:
 - ☐ worsened
 - ☐ slightly improved
 - ☐ improved
 - ☐ highly improved

Appendix F - DLQI

Dermatology Life Quality Index DLQI

Prior to treatment at each visit the patients were asked about the impact of their disease and the respective treatment on their lives. The questionnaire (DLQI; Finlay, 1994) was calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life was impaired. The DLQI could also be expressed as a percentage of the maximum possible score of 30.

Scoring

The scoring of each question was as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

Meaning of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

Detailed analysis of the DLQI

The DLQI can be analysed under six headings as follows:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Appendix G – EQ-5D

EQ-5D is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. (<http://www.euroqol.org/eq-5d/what-is-eq-5d.html>; 02 August 2011)

Appendix H – PSAT metex[®]

An example sheet of the PSAT metex[®] is given below. Any further use or copying of this questionnaire must be authorized by a separate licensing agreement with SCIderm GmbH.

Patient's satisfaction with metex[®] pre-filled syringe

The aim of this questionnaire is to find out how satisfied you are with **your self-injections of metex[®] pre-filled syringes**. When you fill in the questionnaire, please consider **the LAST 4 WEEKS OF TREATMENT with your current treatment**.

Please read through each statement carefully and put a cross in the box that best applies to you. If a statement does not apply to you, please tick the box that says "Does not apply to me".

Please select only one answer category for each statement and answer all questions.

		Strongly disagree	Disagree	Agree	Strongly agree	Does not apply to me
		0	1	2	3	99
I - Benefit to patients						
01	The treatment led to a rapid improvement in my skin symptoms.	☐	☐	☐	☐	☐
02	I can easily handle my condition with this treatment.	☐	☐	☐	☐	☐
03	With this treatment my skin no longer itches.	☐	☐	☐	☐	☐
04	My skin is no longer painful with this treatment	☐	☐	☐	☐	☐
05	The time expenditure for the daily therapy is acceptable.	☐	☐	☐	☐	☐
06	The treatment does not limit my general well-being.	☐	☐	☐	☐	☐
07	As a result of the treatment, I am not worried that my skin condition will get worse.	☐	☐	☐	☐	☐

		Strongly disagree	Disagree	Agree	Strongly agree	Does not apply to me
		0	1	2	3	99
08	I consider the improvement in the condition of my skin to be acceptable.	☐	☐	☐	☐	☐
09	The treatment has met my expectations.	☐	☐	☐	☐	☐
10	The side effects of the treatment were acceptable	☐	☐	☐	☐	☐
11	The positive aspects of the treatment outweigh the negative ones.	☐	☐	☐	☐	☐
II - Practicability						
12	I do not feel afraid before being treated with needles or syringes.	☐	☐	☐	☐	☐
13	I am certain that I perform the injection correctly.	☐	☐	☐	☐	☐
14	I am not concerned about the pain when the needle pierces the skin.	☐	☐	☐	☐	☐
15	I am concerned about reddening/swelling at the point of injection.	☐	☐	☐	☐	☐
16	The general handling of the syringe is not difficult for me.	☐	☐	☐	☐	☐
17	The injections can be performed easily when travelling.	☐	☐	☐	☐	☐
III - Satisfaction with the therapy						
18	I am satisfied with the speed at which the treatment takes effect.	☐	☐	☐	☐	☐
19	I am satisfied with the efficacy of the treatment.	☐	☐	☐	☐	☐
20	I am satisfied with the tolerability of the treatment.	☐	☐	☐	☐	☐
21	I am happy with the way the preparation can be handled, and its storage and application.	☐	☐	☐	☐	☐
22	I would recommend the treatment to other patients.	☐	☐	☐	☐	☐

		Strongly disagree	Disagree	Agree	Strongly agree	Does not apply to me
		0	1	2	3	99
23	I would repeat/continue with the treatment.	☐	☐	☐	☐	☐
24	I have confidence in the treatment.	☐	☐	☐	☐	☐

Please check that you have ticked only one box for each statement.

Many thanks for your assistance!

Appendix I – Patient / Random Number

The **patient identification number** is a **7-letter/digit number** and a combination of the **letter S** (1 digit), the combined site number (4 digits), consisting of the country number (2 digits) and the site number (2 digits) and the patient number (2 digits). Example: S010101 is the site number 0101 and the patient number 01. Once assigned to a patient, the patient identification number must neither be changed nor allocated to another patient.

Table 1: Composition of the patient identification number

Letter	Combined site number		Patient number
S	Country number		Site number
	France	01	Site numbers will be assigned in an ascending order: 01, 02, 03, 04,...
	Germany	02	
	Netherlands	03	
	United Kingdom	04	

Randomization numbers will be a **8-letter/digit number**. The first digit is **letter R**, the following 4 digits include the combined site number (combination of 2 digits for the country number and 2 digits for the site number), and the last 3 digits include the patient random number. Patient numbers of the randomization will start with 051 to ensure clear distinction from patient identification numbers.

Example: R0101051 includes the combined site number 0101 (France, site 01) and the patient number 051.

Table xx: Composition of the randomisation number

Letter	Combined site number		Patient number
R	Country number		Site number
	France	01	Site numbers will be assigned in an ascending order: 01, 02, 03, 04,...
	Germany	02	
	Netherlands	03	
	United Kingdom	04	

Appendix J – SPC Metoject®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metoject 50 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 50 mg methotrexate (as methotrexate disodium).

1 pre-filled syringe of 0.15 ml contains 7.5 mg methotrexate.
1 pre-filled syringe of 0.20 ml contains 10 mg methotrexate.
1 pre-filled syringe of 0.25 ml contains 12.5 mg methotrexate.
1 pre-filled syringe of 0.30 ml contains 15 mg methotrexate.
1 pre-filled syringe of 0.35 ml contains 17.5 mg methotrexate.
1 pre-filled syringe of 0.40 ml contains 20 mg methotrexate.
1 pre-filled syringe of 0.45 ml contains 22.5 mg methotrexate.
1 pre-filled syringe of 0.50 ml contains 25 mg methotrexate.
1 pre-filled syringe of 0.55 ml contains 27.5 mg methotrexate.
1 pre-filled syringe of 0.60 ml contains 30 mg methotrexate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, in pre-filled syringe.
Clear, yellow-brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metoject 50 mg/ml is indicated for the treatment of

- active rheumatoid arthritis in adult patients,
- polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate,
- severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.

4.2 Posology and method of administration

Metoject 50 mg/ml should only be prescribed by physicians, who are familiar with the various characteristics of the medicinal product and its mode of action. Metoject 50 mg/ml is injected once weekly.

The patient is to be explicitly informed about the unusual fact of administration once weekly. It is advisable to determine a fixed, appropriate weekday as day of injection.

spc (UK) Metoject 50 mg/ml solution for injection;
National version: 27.10.2010

1

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see section 5.2 and 4.4).

Dosage in adult patients with rheumatoid arthritis:

The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. However, doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 – 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis

The recommended dose is 10-15 mg/m² body surface area (BSA)/once weekly. In therapy-refractory cases the weekly dosage may be increased up to 20mg/m² body surface area/once weekly. However, an increased monitoring frequency is indicated if the dose is increased.

Due to limited data availability about intravenous use in children and adolescents, parenteral administration is limited to subcutaneous and intramuscular injection.

Patients with JIA should always be referred to a rheumatology specialist in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population. (see section 4.4)

Dosage in patients with psoriasis vulgaris and psoriatic arthritis:

It is recommended that a test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 – 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Patients with renal impairment:

Metoject 50 mg/ml should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)	Dose
> 50	100 %
20 – 50	50 %
< 20	Metoject 50 mg/ml must not be used

See section 4.3

The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate as toxicity will markedly increase.

Patients with hepatic impairment:

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is $> 5 \text{ mg/dl}$ ($85.5 \mu\text{mol/l}$), methotrexate is contraindicated.

For a full list of contraindications, see section 4.3.

Use in elderly patients:

Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patient with a third distribution space (pleural effusions, ascitis):

As the half-life of Methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required (see section 5.2 and 4.4).

Duration and method of administration:

The medicine is for single use only.

Metosject 50 mg/ml solution for injection can be given by intramuscular, intravenous or subcutaneous route (in children and adolescents only subcutaneous or intramuscular).

The overall duration of the treatment is decided by the physician.

Note:

If changing from oral to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid supplementation may be considered according to current treatment guidelines.

4.3 Contraindications

Metosject 50 mg/ml is contraindicated in the case of

- hypersensitivity to methotrexate or to any of the excipients,
- liver insufficiency (see section 4.2),
- alcohol abuse,
- severe renal insufficiency (creatinine clearance less than 20 ml/min. , see section 4.2 and section 4.4),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy, breast-feeding (see section 4.6),
- concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly informed that the therapy has to be applied once a week, not every day. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience

includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed by the physician of the risks involved and the recommended safety measures.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.2).

Recommended examinations and safety measures

Before beginning or reinstituting methotrexate therapy after a rest period:

Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (at least once a month during the first six months and every three months thereafter):

An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes
2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.
3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.
For psoriasis patients the need for a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged Methotrexate treatment or cumulative doses of 1.5 g or more.

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Renal function should be monitored by renal function tests and urinalysis (see sections 4.2 and 4.3).
As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects. Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.
5. Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate therapy. This lesion can occur at all dosages.
6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination results and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment (see section 5.2).

Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".
spc (UK) Metoject 50 mg/ml solution for injection; 5
National version: 27.10.2010

The absence of pregnancy should be confirmed before Metoject 50 mg/ml is administered. Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility. These effects appear to be reversible on discontinuing therapy. Effective contraception in men and women should be performed during treatment and for at least six months thereafter. The possible risks of effects on reproduction should be discussed with patients of childbearing potential and their partners should be advised appropriately (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products

The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time (see section 4.4). Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine). The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Combined treatment with methotrexate and retinoids like acitretin or etretinate increases the risk of hepatotoxicity.

Oral antibiotics

Oral antibiotics like tetracyclines, chloramphenicol, and non-absorbable broad-spectrum antibiotics can interfere with the enterohepatic circulation, by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Antibiotics

Antibiotics, like penicillines, glycopeptides, sulfonamides, ciprofloxacin and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Medicinal products with high plasma protein binding

Methotrexate is plasma protein bound and may be displaced by other protein bound drugs such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoin, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, which can lead to increased toxicity when used concurrently.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents

Probenecid, weak organic acids such as loop diuretics, and pyrazoles (phenylbutazone) can reduce the elimination of methotrexate and higher serum concentrations may be assumed inducing higher haematological toxicity. There is also a possibility of increased toxicity when low dose methotrexate and non steroidal anti-inflammatory medicinal products or salicylates are combined.

Medicinal products with adverse reactions on the bone marrow

In the case of medication with medicinal products, which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Medicinal products which cause folate deficiency

The concomitant administration of products which cause folate deficiency (e.g. sulphonamides, trimethoprim-sulphamethoxazole) can lead to increased methotrexate toxicity. Particular care is therefore advisable in the presence of existing folic acid deficiency.

Products containing folic acid or folinic acid

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

Other antirheumatic medicinal products

An increase in the toxic effects of methotrexate is, in general, not to be expected when Metoject 50 mg/ml is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprine, ciclosporin).

Sulphasalazine

Although the combination of methotrexate and sulphasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulphasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Mercaptopurine

Methotrexate increases the plasma levels of mercaptopurine. The combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Proton-pump inhibitors

A concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Theophylline

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Caffeine- or theophylline-containing beverages

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

4.6 Pregnancy and lactation

Metoject 50 mg/ml is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremity). If methotrexate is discontinued prior to conception, normal pregnancies have been reported. Women must not get pregnant during methotrexate therapy. In case of women getting pregnant during therapy medical counselling about the risk of adverse reactions for the child associated with methotrexate therapy should be sought. Therefore, patients of a sexually mature age (women and men) must use effective contraception during treatment with Metoject 50 mg/ml and at least 6 months thereafter (see section 4.4).

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. pregnancy test, prior to initiating therapy.

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

Lactation: Methotrexate is excreted in breast milk in such concentrations that there is a risk for the infant, and accordingly, breast-feeding should be discontinued prior to and throughout administration.

4.7 Effects on ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, Metoject 50 mg/ml has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

The most relevant undesirable effects are suppression of the haematopoietic system and gastrointestinal disorders.

The following headings are used to organise the undesirable effects in order of frequency:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Gastrointestinal disorders

Very common: Stomatitis, dyspepsia, nausea, loss of appetite.

Common: Oral ulcers, diarrhoea.

Uncommon: Pharyngitis, enteritis, vomiting.

Rare: Gastrointestinal ulcers.

Very rare: Haematemesis, haemorrhage, toxic megacolon.

Skin and subcutaneous tissue disorders

Common: Exanthema, erythema, pruritus.

Uncommon: Photosensitisation, loss of hair, increase in rheumatic nodules, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticaria.

Rare: Increased pigmentation, acne, ecchymosis.

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia.

General disorders and administration site conditions

Rare: Allergic reactions, anaphylactic shock, allergic vasculitis, fever, conjunctivitis, infection, sepsis, wound-healing impairment, hypogammaglobulinaemia.

Very rare: Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration.

Metabolism and nutrition disorders

Uncommon: Precipitation of diabetes mellitus.

Nervous system disorders

Common: Headache, tiredness, drowsiness.

Uncommon: Dizziness, confusion, depression.

Very rare: Impaired vision, pain, muscular asthenia or paraesthesia in the extremities, changes in sense of taste (metallic taste), convulsions, meningism, paralysis.

Eye disorders

Rare: Visual disturbances.

Very rare: Retinopathy.

Hepatobiliary disorders (see section 4.4)

Very common: Elevated transaminases.

Uncommon: Cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin.

Rare: Acute hepatitis.

Very rare: Hepatic failure.

Cardiac disorders

Rare: Pericarditis, pericardial effusion, pericardial tamponade.

Vascular disorders

Rare: Hypotension, thromboembolic events.

Respiratory, thoracic and mediastinal disorders

Common: Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever.

Rare: Pulmonary fibrosis, *Pneumocystis carinii* pneumonia, shortness of breath and bronchial asthma, pleural effusion.

Blood and lymphatic system disorders

Common: Leukopenia, anaemia, thrombopenia.

Uncommon: Pancytopenia.

Very rare: Agranulocytosis, severe courses of bone marrow depression.

Renal and urinary disorders

Uncommon: Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition.

Rare: Renal failure, oliguria, anuria, electrolyte disturbances.

Reproductive system and breast disorders

Uncommon: Inflammation and ulceration of the vagina.

Very rare: Loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge.

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, myalgia, osteoporosis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Very rare: There have been reports of individual cases of lymphoma which subsided in a number of cases once treatment with methotrexate had been discontinued. In a recent study, it could not be established that methotrexate therapy increases the incidence of lymphomas.

The appearance and degree of severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.

When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

4.9 Overdose

a) Symptoms of overdosage

Toxicity of methotrexate mainly affects the haematopoietic system.

b) Treatment measures in the case of overdosage

Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid analogues

ATC code: L01BA01

Antirheumatic medicinal product for the treatment of chronic, inflammatory rheumatic diseases and polyarthritic forms of juvenile idiopathic arthritis.

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis and chronic polyarthritis, is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

5.2 Pharmacokinetic properties

Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dosages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable interindividual and intraindividual deviations are possible (25 – 100 %). Maximum serum concentrations are achieved after 1 – 2 hours.

Bioavailability of subcutaneous, intravenous and intramuscular injection is comparable and nearly 100 %.

Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations in the form of polyglutamates are found in the liver, kidneys and spleen in particular, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts. The terminal half-life is on average 6 – 7 hours and

spc (UK) Metoject 50 mg/ml solution for injection;
National version: 27.10.2010

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demonstrates considerable variation (3 – 17 hours). The half-life can be prolonged to 4 times the normal length in patients who possess a third distribution space (pleural effusion, ascites).

Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus.

Approx. 5 – 20 % methotrexate and 1 – 5 % 7-hydroxymethotrexate are eliminated biliary. There is pronounced enterohepatic circulation.

In the case of renal insufficiency, elimination is delayed significantly. Impaired elimination with regard to hepatic insufficiency is not known.

5.3 Preclinical safety data

Animal studies show that methotrexate impairs fertility, is embryo- and foetotoxic and teratogenic. Methotrexate is mutagenic *in vivo* and *in vitro*. As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered not classifiable as to its carcinogenicity to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store below 25 °C. Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Nature of container:

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with attached injection needle. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger

or

Pre-filled syringes of colourless glass (type I) of 1 ml capacity with enclosed injection needle. Plunger stoppers of chlorobutyl rubber (type I) and polystyrene rods inserted on the stopper to form the syringe plunger.

Pack sizes:

Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of 1, 4, 6, 12 and 24 syringes with attached s.c. injection needle and alcohol pads.

and

Pre-filled syringes containing 0.15 ml, 0.20 ml, 0.25 ml, 0.30 ml, 0.35 ml, 0.40 ml, 0.45 ml, 0.50 ml, 0.55 ml or 0.60 ml solution are available in packs of 1, 4, 6, 12 and 24 syringes with enclosed s.c. injection needle and alcohol pads.

All pack sizes are available with graduation marks.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The manner of handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Metoject 50 mg/ml.

Methotrexate should not come into contact with the skin or mucosa. In the event of contamination, the affected area must be rinsed immediately with ample amount of water.

For single use only.

Any unused product or waste should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstraße 3
20354 Hamburg
Germany

8. MARKETING AUTHORISATION NUMBER

PL 11587/0046

9. DATE OF FIRST MARKETING AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2008

10. DATE OF REVISION OF THE TEXT

27/10/2010

Appendix K – Visual Analogue Scale for Pain

Injection site	
No pain	Worst imaginable pain

Appendix L – Visual Analogue Scale for Pruritus

Injection site	
No pruritus	Worst imaginable pruritus

Appendix M - Amendment History

Amendment XX.XX.XXXX		
Sections affected	Version XX-XX-20XX Original Content	Version XX-XX-20XX, amended XX-XX-20XX New Content
	Sample:	
2 CONTACTS	Page 5: CRO: SCIderm GmbH Stephansplatz 5 20354 Hamburg	Page 5: CRO: SCIderm GmbH Esplanade 6 20354 Hamburg
12.8 Prior and concomitant treatment	Page 31: None	Page 31: Added: Topical application of class II/III corticosteroids is allowed on all other psoriasis lesions.
12.8 Prior and concomitant treatment	Page 31: Topical application of emollients twice daily on the pre-defined test area is allowed.	Page 31: Removed
13.3.2. Visit 2	Page 34: The efficacy is assessed by PGA on a 5-point scale.	Page 34: The efficacy is assessed by PGA on a 6-point scale.

Resubmission of manuscript: THELANCET-D-16-04293R1

A 52-week double-blind placebo-controlled study of an intensified dosing schedule of subcutaneous methotrexate in patients with moderate-to-severe plaque-type psoriasis (METOP)

Point-by-point response to additional editorial comments

1. Please follow CONSORT for abstracts (for instance the method of randomisation and effect sizes have not been provided)

A1. The abstract has been completely revised to fulfil CONSORT requirements; the method of randomisation and the effect size of the primary endpoint analysis have been added. Please see abstract with tracked changes.

2. The abstract should be limited to the primary outcome and safety endpoints only

A2. The abstract has been revised to only contain the primary outcome and safety endpoints. However, with the information added to adhere to CONSORT rules, there are now 348 words. Please see abstract with tracked changes.

3. Please remove any additional analyses that were done in response to reviewers' comments

A3. The following analyses have been removed:

Results part:

Significantly different responses occurred early with 27.5% of patients in the MTX group achieving a PASI50 response at week 4 compared to 3.4% in the placebo group (p=0.0062; post-hoc analysis).

and

Post-hoc analyses showed trends for similar PASI75 response rates at week 16 among MTX-treated patients <100 kg (41.5%) compared to individuals ≥100 kg (38.5%) and higher responses at week 16 among patients naïve to previous conventional or biologic therapy (PASI75/90: 43.5%/21.0%) compared to those with prior systemic therapy (PASI75/90: 34.5%/10.3%).

Discussion part:

Evaluation of the effects of dose escalation was not part of the pre-specified analyses. The exploratory finding that 64% of patients with a PASI50 response at week 8 (48/53) achieved a PASI75 response at week 16 without dose escalation compared to 8% (3/38) of patients with no PASI50 response at week 8 who were dose escalated may be taken as preliminary evidence that a) early partial clinical response is a marker of later response to MTX and that b) the value of dose escalation in patients with no early partial response to 17.5 mg s.c. MTX is not supported by the findings of this study.

The method part has been adapted accordingly.

4. Please add the trial registration details (the initial clinicaltrials.eu number would be best, please)

A4. This information has been added to the abstract. "This study is registered with the European Medicines Agency, EudraCT number 2012-002716-10."

5. Please mention in the methods that topical use of bland emollients was allowed

A5. Has been added. Lines 108-9 “ Bland emollients were allowed during the study.”

Please also see answer to question 8.

6. Please present absolute numbers in addition to percentages wherever percentages are used throughout the manuscript

A6. The numbers have been added throughout the manuscript. All tracked.

7. Please report the EQ-5D results

A7. Please see lines 157-8 (outcomes section) and then 272-278 where the following has been added.

„The difference in the percentage of patients reporting “no problems” across the 5 dimensions assessed with the EQ-5D at week 16 compared to baseline indicated different effects of MTX compared to placebo. For example, 13.2% (12/91) more patients stated “no problems” with usual activities in the MTX arm compared to 13.8% less patients (4/29) in the placebo arm. Similarly, 6.6% (6/91) more individuals receiving MTX reported “no problems” with anxiety and depression at week 16 compared to baseline, but 17.2% less (5/29) among patients receiving placebo. A more detailed analysis is shown supplementary table S2.”

A table with EQ-5D results has been added to the supplement (Table S2)

8. Consort requirements, such as inclusion and exclusion criteria should be in the main paper, please

A8. The method part (lines 101-113) has been revised to now read:

“METOP was conducted as a double-blind, placebo-controlled randomised investigator-initiated trial. Eligible participants were aged 18 years or older, were naïve to MTX and had a diagnosis of plaque-type psoriasis for at least 6 months with currently moderate-to-severe disease based on the definition by Finlay.¹² Patients were required to have a normal chest x-ray within 6 months prior to study entry and were excluded if hepatic enzymes (ALT, AST, or γ GT) were elevated above 2x the upper limit of normal or total leukocyte counts were below $3.0 \times 10^9/L$ in screening laboratory tests. Previous treatment with biologics had to be discontinued at least 5 times their half-life, other systemic therapies and phototherapies used for the treatment of psoriasis at least 4 weeks and topical therapies at least 2 weeks before study entry. Bland emollients were allowed during the study. Patients with a previous diagnosis of psoriatic arthritis (PsA) could be enrolled; however, patients with currently active PsA as defined by 5 or more tender or swollen joints and peripheral C-reactive protein levels above 2x the upper limit of normal were excluded. The complete list of inclusion and exclusion criteria is available in supplementary table S1.

9. Please use exact p values unless $p < 0.0001$

A9. We have added exact p values.

10. Please expand the section on trial limitations

A10. We have taken care to use a very cautious wording throughout the manuscript. In addition, the following sentence is included in the first paragraph of the discussion part:

Limitations of the study primarily relate to the relatively small number of patients enrolled and the lack of an active comparator arm with oral MTX.

This has now been expanded (lines 338-340) to add “Additionally, the study population was mainly white so further study in non-white participants might be necessary to fully understand the efficacy and safety in a more genetically diverse population.”

11. Please comment on the imbalance between groups of PsA

A11. The following sentence is included in the first paragraph of the results part, lines 232-4:

Disease duration tended to be longer in patients started on MTX and a previous diagnosis of PsA was documented more frequently in this treatment arm.

12. Please mention the two studies by West in the Research in context panel

A12. The research in context panel has been adjusted in the section Evidence before this study to refer to both studies by West et al and now reads:

“Evidence before this study A recent meta-analysis on MTX⁷ reported a PASI 75 of 45.2% [95% confidence interval 34.1–60.0] from primary endpoints at either 12 or 16 weeks mainly based on three larger studies with oral MTX in psoriasis, of which two were not placebo-controlled. The safety meta-analysis found approximately 7% of patients had treatment limiting adverse events, but this part included a number of studies with MTX in indications other than psoriasis that differ in their susceptibility to safety events of interest. PubMed, MEDLINE and EMBASE databases and the Cochrane Library were searched for meta-analyses, randomized and non-randomized controlled clinical trials, case series, case reports and open studies involving MTX in psoriasis from inception to April 2016. One retrospective study (n=85) investigated the success of s.c MTX following failure of oral treatment.¹⁸ A larger retrospective analysis published after April 2016 included a subgroup of n=27 patients who switched from oral to s.c MTX.¹⁹ Both studies hint to the fact that patients who have failed oral therapy may benefit from switching to s.c treatment but neither included hard efficacy end points and carry the inherent bias that comes with the retrospective nature of the studies.”

13. Please limit the non-text items (tables and figures) to 5 (giving priority to CONSRT-specified items); others can be placed in a web appendix

A13. We have maintained one revised safety table (table 3) in the main manuscript and transferred a revised safety table (table S3) to the supplement.

14. Please do not exceed 4500 words for your revision

A14. We have condensed the safety part without losing relevant information and reduced analyses as requested (see A3) and do not exceed 4500 words.

CONSORT checklist

[Click here to download Necessary additional data: Warren et al. CONSORT-checklist.doc](#)