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Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Methotrexate

Proprietary Product Name: TREXJECT and
TREXJECT IN

Sponsor: Link Medical Products Pty Ltd T/A Link
Pharmaceuticals

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About the Extract from the Clinical Evaluation Report

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List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence interval
C _{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CrCL	Creatinine Clearance
CRP	C-Reactive Protein
CS	Corticosteroids
CsA	Cyclosporine A
CV	Coefficient of Variation
DAS28	Disease Activity Score – 28 joint count
DMARD	Disease Modifying Anti-Rheumatic Drug
ESR	Erythrocyte Sedimentation Ratio
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
IFX	Infliximab
IM	Intramuscular
ISR	Injection Site Reaction

Abbreviation	Meaning
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
LBS	Literature Based Submission
LEF	Leflunomide
LOCF	Last Observation Carried Forward
LLQ	Lower Limit of Quantification
MCID	Minimal Clinically Important Difference
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamic
PhGA	Physician Global Assessment
PK	Pharmacokinetic
PSOR	Psoriasis
PsA	Psoriatic Arthritis
PtGA	Patient Global Assessment
SAE	Serious adverse event
SC	Subcutaneous
SOC	System Organ Class
SSZ	Sulfasalazine
T _{max}	Time to maximum plasma concentration
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal

1. Introduction

This is a hybrid submission containing a mixture of sponsor initiated studies and published literature to register a new dose form (that is parenteral injection) of methotrexate (MTX) for the treatment indications of rheumatoid arthritis (RA) and psoriasis (PSOR).

Note throughout this report the trade name Metoject is used. The trade name Trexject and Trexject IN were subsequently approved for use in Australia for this product (not Metoject)

Methotrexate is currently registered as an oral preparation for RA and PSOR, and as an injectable product for PSOR and several malignancy indications such as breast and bladder cancer, squamous cell carcinoma of the head and neck, gestational trophoblastic disease, acute leukaemia, Non-Hodgkin's lymphoma, mycosis fungoides and osteosarcoma. MTX (by oral or parenteral administration) is also recommended in treatment guidelines for chronically active or frequently relapsing inflammatory bowel disease, but this patient group is not a registered treatment indication in Australia (Therapeutic Guidelines – Gastrointestinal, version 5, 2011).

In support of the clinical efficacy and safety of low dose weekly MTX by parenteral administration in adult patients with RA, the submission contains 2 pivotal controlled studies, one of which is published in the literature (MTX was administered by intramuscular [IM] injection) and the other trial was conducted by the sponsor (Study MC-MTX.6/RH; MTX was given by subcutaneous [SC] injection). The supporting data for parenteral MTX use in RA includes a total of 36 publications in the literature based submission, as well as 2 additional in house studies (MC-MTX.5/RH and MC-MTX.10/RH). The supporting trials are limited by small sample sizes, lack of blinding (open label design) and/or no appropriate comparator group.

In support of the clinical efficacy and safety of low dose pulsed MTX in adult patients with PSOR, the submission contains 10 published randomised controlled studies, 2 small case series and a systemic review evaluating the dose and route of administration of MTX in patients with PSOR. The PSOR submission is literature based and no new trial evidence has been provided by the sponsor. The literature search methodology contributing to this submission is discussed in the Clinical Summary.

Justification and supporting data for the biopharmaceutical section of this application consists of 2 in house studies (MC-MTX.7/PH and MC-MTX.9/PH), as well as 36 publications relating to the comparative bioavailability of MTX (including trials conducted in patients with RA and PSOR).

Methotrexate is a folic acid antagonist, which primarily acts by competitively inhibiting the enzyme dihydrofolate reductase. As a result, DNA synthesis and cell replication are inhibited by blocking the conversion of folic acid to folinic acid. MTX has anti-proliferative, immunosuppressive and anti-inflammatory effects. Oral formulations of MTX are classified as an immunosuppressant drug with the ATC code L04AX03. Systemic formulations of MTX are classified as anti-neoplastic agents with the ATC code L01BA01.

MTX is currently approved in Australia for the treatment of RA by the oral route of administration only, at a starting dose of 7.5 mg/week and up to a maximum dose of 20 mg/week. Parenteral administration of MTX is not currently approved in Australia for the treatment of RA. For the indication of PSOR, low dose MTX (starting at 10 to 25 mg/week, and up to a maximum of 50 mg/week) is registered when administered orally, or by intramuscular (IM) or intravenous (IV) injection. The subcutaneous (SC) route of administration is not currently approved. The treatment indication wording proposed by the sponsor for RA and PSOR is identical to that for currently approved MTX formulations.

The proposed indications in this submission are:

Psoriasis therapy (see WARNING box)

Metoject may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitively established, as by biopsy and/or after dermatologic consultation.

Rheumatoid arthritis therapy (see WARNING box)

Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.

Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold or penicillamine has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

1.1. Dosage forms and strengths

Currently registered oral formulations of MTX are presented as 2.5 mg and 10 mg tablets. Parenteral formulations currently registered for supply are vials containing 5 mg/2 mL, 50 mg/2 mL, 500 mg/5 mL, 500 mg/20 mL, 1000 mg/10 mL and 5000 mg/50 mL (containing sodium chloride).

With this application, the sponsor proposes registration of the following dosage forms and strengths: MTX (as sodium) solution for injection, 50 mg/mL in pre-filled syringes, in the following colour coded presentations; 7.5 mg/0.15 mL, 10 mg/0.2 mL, 12.5 mg/0.25 mL, 15 mg/0.3 mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL, 25 mg/0.5 mL, 27.5 mg/0.55 mL and 30 mg/0.6 mL. The pre-filled glass syringes are supplied with an embedded injection needle protected by a styrene-butadiene rubber needle shield.

1.2. Dosage and administration

The sponsor proposes the following dosage regimens for Metoject:

Rheumatoid Arthritis therapy:

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 not be exceeded. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Psoriasis therapy:

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. 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. Dosage should not ordinarily exceed 20 mg/week due to significant

increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 to 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

The dosage and administration recommendations proposed for Metoject differ from the currently approved MTX products in a few ways:

- Add the SC route of administration as alternative to IM, oral and IV injection
- Specify a starting dose of 7.5 mg/week in PSOR (versus initial dose of 10 mg/week currently)
- Specify a maximum weekly dose of 25 to 30 mg (versus 50 mg/week currently) and
- Advise that response is generally seen within 6 to 8 weeks of drug commencement.

2. Clinical rationale

Rheumatoid arthritis (RA) is a chronic autoimmune disorder, which affects approximately 1% of the Australian population. The burden of the disease is significant. After 5 years, one-half of patients with RA have developed important changes in health status. Low dose MTX is recommended as the first-line, disease modifying treatment for patients with RA according to international guidelines (Smolen et al, 2014). MTX has been shown to be efficacious, with an acceptable toxicity profile, and is cost effective (Swierkot and Szechinski, 2006).

Psoriasis is a common, inflammatory and proliferative skin disease with a genetic determinant. Although PSOR may occur at any age, 2 age peaks of onset are identified: second decade of life (early onset) and fifth decade (late onset). Chronic stable plaque PSOR (PSOR vulgaris) is the most common form of the disease, accounting for 85 to 90% of all cases. While the majority of patients have mild PSOR, studies have found that 25% of patients reported their disease as moderate, and 10% as severe. Psoriasis can be disabling, affecting the physical, social and psychological wellbeing of patients. Plaque PSOR manifests as thickened, well demarcated, erythematous patches of skin covered with silvery scales. The lesions often arise in predisposed areas such as the extensor aspects of the knees and elbows, but can be generalised. Other sites affected by PSOR include the nails, scalp, palms, soles and intertriginous areas. The skin lesions frequently cause symptoms of pruritus and discomfort. Topical agents such as salicylic acid, corticosteroids (CS) and vitamin D analogues are often used as a first line therapy, particularly if the PSOR is localised. Phototherapy with UVB or psoralen + UVA is often used as a first line treatment for widespread PSOR or as a second line treatment if topical therapy is insufficient. Systemic treatment with oral retinoids, MTX and cyclosporine (CsA) are indicated in severe forms of PSOR. All of the systemic treatments have demonstrated efficacy but their long-term use is limited by potential risks and toxicities. Biologic therapies such as anti-TNF drugs and ustekinumab have been demonstrated to be highly effective in the treatment of moderate to severe PSOR but their use is limited by the risk of significant Adverse Events (AEs) such as serious infection and malignancy potential. Despite the variety of treatment options available in PSOR, patients are often dissatisfied (> 70% prevalence) with current therapy options due to lack of sustained efficacy, adverse events and/or treatment inconvenience. Hence, there is an unmet need for additional therapies for patients with moderate to severe PSOR, which is refractory to topical treatment.

A folate analogue, MTX's mode of action in treating autoimmune disease is not entirely clear, although increasing adenosine levels and reducing pro-inflammatory cytokines seem to play an important role. The recommended dose of MTX for RA and PSOR can range from 7.5 to 25 to 30 mg/week, depending on guidelines. The sponsor has proposed an initial MTX dose of 7.5 mg once weekly, but a systematic literature review of MTX monotherapy in RA has recommended initial treatment with 10 to 15 mg orally, as well as dose increases to 20 to 30 mg/week if

needed and tolerated (Visser et al, 2009). Parenteral administration of MTX has been suggested to be more effective with fewer gastrointestinal adverse effects in patients with suboptimal response or intolerance to oral MTX (Mouterde et al, 2011).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 2 in house comparative bioavailability studies (MC-MTX.7/PH and MC-MTX.9/PH) as well as 36 clinical pharmacology studies in the literature providing pharmacokinetic data.
- No population pharmacokinetic analyses.
- 1 pivotal efficacy/safety studies (MC-MTX.6/RH) in adult patients with RA supported by published cohort of RA subjects (Rau et al, 1991 onwards).
- No dose finding studies.
- 2 additional in house efficacy/safety studies (MC-MTX.10/RH and MC-MTX.5/RH) in adult subjects with RA.
- Literature based submission containing 36 articles for the RA indication and 13 publications for the PSOR indication.
- No pooled analyses, meta-analyses or Integrated Summaries of Efficacy or Safety.
- Application letter, Application form, draft Australian PI and CMI, European Summary of Product Characteristics, Pre-submission meeting notes and processes, and methodology of the literature based submission including details and output of the database search.
- Clinical Overview and Clinical Summary for both of the proposed treatment indications (RA and PSOR; presented separately).

3.2. Paediatric data

The submission did include paediatric data in juvenile idiopathic arthritis (JIA) supporting the requested treatment indication of RA, but the sponsor is not proposing registration in any paediatric treatment indication in Australia.

3.3. Good clinical practice

All of the studies conducted by the sponsor in the Metoject clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The literature based submission contained a total of 36 pharmacology studies (18 relating to bioavailability and 18 pharmacokinetic studies). All but 1 of the PK studies in the target populations were conducted in either adult subjects with RA or children/adolescents with JIA.

The sponsor has also submitted 2 in house comparative bioequivalence studies (MC-MTX.7/PH and MC-MTX.9/PH). None of the pharmacokinetic (PK) studies had significant methodological deficiencies that excluded their results from consideration, but many of the published trials had very small subject numbers to make clinically meaningful interpretation of their results.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans.

4.3. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summary. The active substance in the Metoject product is soluble MTX disodium salt at a concentration of 50 mg/mL, which is prepared by chemical synthesis. The pH of the drug product is 7.5 to 9.0. Stability tests support a product shelf life of 24 months.

4.4. Pharmacokinetics in healthy subjects

4.4.1. Absorption

4.4.1.1. Sites and mechanisms of absorption

Low dose MTX (< 25 mg/m²) is generally well absorbed from the gastrointestinal tract after oral ingestion with an estimated oral bioavailability of 70 to 80%. However, at higher oral doses there is considerable intra and inter individual variability in absorption. Oral MTX is absorbed from the proximal jejunum via active transport by the proton coupled folate transporter. The transport system is polymorphic in nature and contributes to significant inter patient differences in absorption. The active transport system is also capacity limited and may diminish with increased oral doses of MTX. This may explain why bioavailability decreases with increasing oral doses of MTX.

4.4.2. Bioavailability

The sponsor has conducted two comparative bioavailability studies with prefilled MTX syringes. Study MC-MTX.7/PH used the 10 mg/mL injection solution to directly compare the same doses of MTX given by IM and SC injection. Study MC-MTX.9/PH compared the bioavailability of the 10 mg/mL injection solution with the commercially proposed 50 mg/mL preparation when given by the IM or SC route of administration.

4.4.2.1. Study MC-MTX.7/PH

Study MC-MTX.7/PH was an open label, single dose, 2 period crossover Phase I study comparing IM and SC doses of MTX 15 mg (using the 10 mg/mL injection solution) in 16 healthy male Caucasian subjects aged between 18 and 45 years of age with a Body Mass Index (BMI) between 18 to 29 kg/m². The primary objective of the study was to evaluate the PK characteristics, and the rate and extent of absorption of MTX 15 mg given by IM versus SC administration. The study was conducted at single study centre in Germany between February and May 2003.

The primary PK parameters evaluated were AUC, C_{max} and AUC_{0-t} for MTX. For statistical analysis, the results of these parameters were log transformed and compared by ANOVA with 90% CIs for the geometric mean ratios of test (SC)/reference (IM) product. The secondary PK parameters assessed were T_{max}, T_½ and C_{max}/AUC for MTX; as well as all of the above PK parameters for the metabolite, 7-OH MTX. Secondary PK parameters were handled by descriptive statistics. Serial blood samples were collected up to 24 hours post dose and plasma was assayed by a validated HPLC with fluorescence detection method. The Lower Limit of Quantification (LLQ) was 5.26 µg/L for MTX and 5.08 µg/L for 7-OH MTX.

On study Day 1 of each treatment period, a single dose of MTX (15 mg; either by SC or IM injection; by random assignment) was administered as close as possible to 8 am after an overnight fast of at least 10 hours. The IM injection was given into the gluteal muscle, and the SC injection was given into the anterior abdominal wall. Patients received a total MTX dose of 30 mg during the trial, given in 2 treatment periods. Treatment periods were separated by a washout period of 14 days, which was sufficient for plasma levels to fall below the detection limit. All subjects received 15 mg of oral folinic acid 24 and 48 hours after each MTX dose as a rescue therapy. All study treatments were administered under supervised conditions. Patients were excluded from enrolment if they had a prior or current history of alcohol or substance abuse.

A total of 47 subjects were screened, 28 of whom failed screening and 19 subjects were included into the treatment phase of the trial. Most screen failures were due to abnormal baseline laboratory results, in particular, total white cell count $< 6.0 \times 10^9/L$ and neutrophil count $< 3.5 \times 10^9/L$. Three of the 19 subjects terminated prematurely, 2 of whom developed abnormal safety laboratory results (serum transaminases $> 2x$ ULN). Of the 16 subjects who were included in the PK analysis population, the mean age was 34.3 years (range: 23 to 45 years), the mean body weight was 81.3 kg (range: 63 to 106 kg) and the mean BMI was 25.5 kg/m² (range: 21 to 29 kg/m²).

Table 1 provides a summary of the primary PK results of Study MC-MTX.7/PH. The data showed that the SC and IM routes of administration for MTX were bioequivalent in terms of the extent of drug exposure (based on AUC) but with higher peak plasma levels achieved from the IM injection (0.5 versus 1 hour). In addition, the mean C_{max} for SC administration is approximately 60% of that seen following IM injection of MTX.

Table 1: Primary pharmacokinetic parameter results for Study MC-MTX.7/PH

Parameter	MTX s.c. (test)	MTX i.m. (reference)	Geometric mean ratio s.c./i.m. (%)	90% CI (%)
T_{max} h	1 (1.7)	0.5 (1.7)		
AUC_{0-t} (µg*h/L)	1020.79 (1.23)	1043.33 (1.18)	97.84	91.07 – 105.11
AUC_{0-∞} (µg*h/L)	1058.89 (1.22)	1088.86 (1.18)	97.25	91.00 – 103.92
C_{max} (µg/L)	221.76 (1.39)	381.28 (1.37)	58.16	47.61 – 71.06
<i>AUC = area under the plasma concentration time curve; C_{max} = maximum plasma concentration</i>				

The secondary PK results for 7-OH MTX showed a similar pattern to the primary PK observations. The mean AUC for 7-OH MTX achieved following SC and IM administration were similar, and the geometric mean C_{max} was also similar (44.84 µg/L for SC and 52.85 µg/L for IM administration).

4.4.2.2. Study MC-MTX.9/PH

Study MC-MTX.9/PH was an open label, single dose, randomised crossover Phase I study with 2 treatments (b1 and b2; or b3 and b4) conducted in 2 phases and involving 24 healthy male Caucasian subjects aged between 18 and 45 years of age with a BMI between 18 to 29 kg/m². The primary objective of the study was to evaluate the relative bioavailability of MTX 15 mg given by IM and SC administration as 2 formulation presentations (50 mg/ml and 10 mg/mL). Treatments b1 (50 mg/mL) and b2 (10 mg/mL) refer to SC administration (n = 12 subjects), while treatments b3 (50 mg/mL) and b4 (10 mg/mL) were given IM injection (n = 12 subjects). The study was conducted at single study centre in Germany between August and November 2006.

The study consisted of an ambulant screening day (within 21 days before the first drug administration), 2 study periods of 4 days each (study Days -1 to 3) and an ambulant safety

follow-up period of 5 days. Subjects were confined to a testing centre on study Day -1 (12 to 14 hours before drug administration) until discharge on study Day 3 (that is until safety laboratory tests became available). The investigational medicine was given on study Day 1 of each period. There was a wash-out between study periods of at least 2 weeks. The IM injection was given into the gluteal muscle, and the SC injection was given into the anterior abdominal wall. Patients received a total MTX dose of 30 mg during the trial, given in 2 treatment periods. All subjects received 15 mg of oral folinic acid 24 and 48 hours after each MTX dose as a rescue therapy.

The primary PK endpoint was the AUC ratio for MTX. For statistical analysis, the results of these parameters were log transformed and compared by ANOVA with 90% CIs for the geometric mean ratios of test/reference (that is 50 mg/mL versus 10 mg/mL solution). The secondary PK parameters assessed were T_{max} , $T_{1/2}$ and C_{max}/AUC (absorption index) for MTX; as well as all of the above PK parameters for the metabolite, 7-OH MTX. Secondary PK parameters were handled by descriptive statistics. Blood samples for PK analysis were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours post dose. Plasma was assayed by a validated HPLC with fluorescence detection method. The LLQ was 5.031 µg/L for MTX and 5.032 µg/L for 7-OH MTX. The assay precision was < 6% for MTX and < 7% for 7-OH MTX.

To be eligible for inclusion in the study, subjects had to be healthy male Caucasian subjects aged between 18 and 45 years of age with a BMI between 18 to 29 kg/m². The exclusion criteria were extensive and included total white cell count < 5.0 x 10⁹/L or neutrophil count < 3.5 x 10⁹/L, CRP reading > ULN, creatinine clearance < 80 mL/min, abnormal liver function tests, positive serology for HBV, HCV or HIV, alcohol or substance abuse, moderate smoker (> 10 cigarettes per day), mouth ulcers or past peptic ulcers, malignancy, vegetarians, history of asthma, urticaria or severe allergy, recent infection or fever (within 7 days), consumption of xanthine containing food or beverages and blood donation within the last 30 days.

A planned sample size of 24 subjects (2 groups of 12 subjects) was considered to be sufficient for examining the study objectives. This number of subjects is the minimum required for the regulatory guideline relating to investigation of bioavailability and bioequivalence. Altogether, 62 subjects were screened for inclusion, and 25 healthy Caucasian men were enrolled into the treatment phase. Of the 37 cases of screen failure, 24 had abnormal baseline laboratory results, 5 withdrew consent and 3 had positive drug screens. One of the subjects discontinued prematurely because of an AE before receiving any study medicine, but was replaced by another subject. One of the 25 subjects who received study medication was lost to follow-up before the study conclusion and his results were excluded from the PK analysis. A total of 18 blood samples were collected outside the recommended protocol schedule window and these were recorded as protocol deviations. Of the 24 subjects who were included in the PK analysis population, the mean age was 31.5 years (range: 19 to 43 years), the mean body weight was 78.0 kg (range: 59 to 104 kg) and the mean BMI was 24.7 kg/m² (range: 21 to 29 kg/m²).

Table 2 provides a summary of the primary PK results of Study MC-MTX.9/PH. The study showed that the 50 mg/mL and 10 mg/mL formulations were bioequivalent in terms of the extent of MTX exposure (based on comparative AUC results). Thus, the primary PK endpoint of the trial was observed.

Table 2: Pharmacokinetic results for MTX in Study MC-MTX.9/PH

Pharmacokinetic parameter methotrexate	ANOVA CV [%]		Point estimate Test/Ref.	90% Confidence interval
AUC	11.69	b ₁ / b ₂	97.56	89.90 - 105.88
		b ₃ / b ₄	91.85	84.63 - 99.68
AUC _{0-t}	11.60	b ₁ / b ₂	98.07	90.42 - 106.37
		b ₃ / b ₄	91.90	84.73 - 99.68
C _{max}	34.24	b ₁ / b ₂	114.93	90.96 - 145.22
		b ₃ / b ₄	120.67	95.51 - 152.48

b₁ = 50 mg/mL MTX; 15 mg s.c.

b₂ = 10 mg/mL MTX; 15 mg s.c.

b₃ = 50 mg/mL MTX; 15 mg i.m.

b₄ = 10 mg/mL MTX; 15 mg i.m.

Table 2 also demonstrates that the peak plasma levels of MTX were slightly higher with the 50 mg/mL injection compared to the 10 mg/mL injection, whether given by SC (b₁ versus b₂) or IM administration (b₂ versus b₄), but in both pair wise treatment comparisons the 90% CIs were overlapping and crossed 100 indicating no significant difference in C_{max} by formulation strength.

Investigation of the inter-subject differences from the ANOVA comparing the 50 mg/mL and 10 mg/mL products showed a moderate coefficient variation (CV %) of 34.24% for C_{max}. The inter-subject differences in AUC for SC versus IM administration were low at 11.6 to 11.69%.

As summarised in Table 3, the comparative AUC and C_{max} results for the active metabolite 7-OH MTX are also similar when the formulations (50 mg/mL and 10 mg/mL) are given by the same route of administration. The ANOVA results for 7-OH MTX confirmed similarity in the rate and extent of absorption for SC and IM administration, with the 90% CIs for all PK variables falling within 80 to 125% bioequivalence limits. In addition, the ANOVA derived CVs were low at ≤ 16.55.

Table 3: Pharmacokinetic results for 7-OH MTX in Study MC-MTX.9/PH

Pharmacokinetic parameter 7-Hydroxymethotrexate	ANOVA CV [%]		Point estimate Test/Ref.	90% Confidence interval
AUC	16.55	b ₁ / b ₂	94.77	84.43 - 106.38
		b ₃ / b ₄	98.46	87.72 - 110.51
AUC _{0-t}	15.25	b ₁ / b ₂	95.51	85.86 - 106.24
		b ₃ / b ₄	99.97	89.87 - 111.21
C _{max}	13.75	b ₁ / b ₂	94.27	85.63 - 103.78
		b ₃ / b ₄	98.68	89.64 - 108.64

b₁ = 50 mg/mL MTX; 15 mg s.c.

b₂ = 10 mg/mL MTX; 15 mg s.c.

b₃ = 50 mg/mL MTX; 15 mg i.m.

b₄ = 10 mg/mL MTX; 15 mg i.m.

The study also did a cross group comparison examining the effect of route of administration. The C_{max} point estimate (with 90% CI) for b₁ (50 mg/mL SC) versus b₃ (50 mg/mL IM) was 69.2 (90% CI 53, 90) and the C_{max} point estimate (with 90% CI) for b₂ (10 mg/mL SC) versus b₄ (10 mg/mL IM) was 72.64 (90% CI 58, 90); refer to Table 4. Overall, these PK results indicate

that SC injection of MTX is associated with lower C_{max} values than IM administration, but slightly higher AUC results for MTX. The clinical significance of these PK differences is unknown. A limitation of the cross study comparison is that it does not permit extraction of variability due to subject differences or period effects. The differences between the IM and SC routes for the two injection concentrations in the cross study-arm comparisons are similar, suggesting there are population differences contributing to this finding which could not be assessed by the t-test comparison (as the studies used different populations). However, both study arms were conducted at the same time, in the same facility and samples were assayed using the same bioanalytical method.

Table 4: Pharmacokinetic results in Study MC-MTX.9/PH for SC versus IM administration of MTX

MTX	s.c. 50 v i.m. 50			s.c. 10 v i.m. 10		
AUC	b1 / b3	124.1	112 - 137	b2 / b4	116.98	104 - 131
AUC _{0-t}	b1 / b3	123.9	112 - 137	b2 / b4	116.14	104 - 130
C_{max}	b1 / b3	69.2	53 - 90	b2 / b4	72.64	58 - 90
7-OH MTX						
AUC	b1 / b3		93 - 172	b2 / b4		103 - 168
AUC _{0-t}	b1 / b3		88 - 152	b2 / b4		98 - 150
C_{max}	b1 / b3		83 - 139	b2 / b4		92 - 138

b1 = 50 mg/mL MTX; 15 mg s.c.

b2 = 10 mg/mL MTX; 15 mg s.c.

b3 = 50 mg/mL MTX; 15 mg i.m.

b4 = 10 mg/mL MTX; 15 mg i.m.

4.4.2.3. Bioequivalence of different dosage forms and strengths

Study MC-MTX.9/PH (already reviewed) was an open label, single dose, Phase I crossover study which examined the relative bioavailability of MTX 15 mg given by IM and SC administration as 2 formulation presentations (50 mg/ml and 10 mg/mL). No significant PK differences relating to MTX concentration were identified in this analysis.

4.4.2.4. Bioequivalence to relevant registered products

The sponsor has not conducted a direct comparison between Metoject and any of the Australian registered oral MTX medicines. For the SC and IM routes of administration, the sponsor has provided comparative biopharmaceutical data indicating that the osmolality, pH and concentration of injectable MTX formulations available in Australia (DBL and Kabi MTX) and the USA are highly similar to that of the sponsor product. Osmolality may influence diffusion by disturbing interstitial fluid flow, pH by affecting drug ionisation and concentration by its effect on passive diffusion. Minor variations in excipients between Metoject and existing Australian reference formulations are noted, but these differences should not have PK or clinical impacts. The evaluator concurs with the sponsor that the proposed formulation of Metoject to be made commercially available in Australia shows no clinically relevant biopharmaceutical characteristics from those already registered in Australia.

4.4.2.5. Influence of food

The oral bioavailability of low dose oral MTX (7.5 to 25 mg) is estimated to be 70 to 80%. Under fasting conditions, the C_{max} of low dose MTX ranges from 0.3 to 1.6 $\mu\text{mol/L}$ and occurs at T_{max} of 0.75 to 2 hours. MTX is absorbed more rapidly and reaches higher serum concentrations after IM or SC administration compared to oral dosing. For low dose MTX therapy, mean absolute bioavailability is similar for oral tablets and SC administration compared to IM dosing, suggesting that these administration routes are interchangeable.

4.4.3. Distribution and plasma protein binding

The apparent volume of distribution for MTX is 0.87 to 1.43 L/kg, which corresponds to distribution into the intracellular space. Uptake into cells is also via active transport using the reduced folate transporter. Within cells, MTX is converted to active polyglutamate moieties, which are retained for long periods (for example for weeks in the kidneys and for several months in the liver). Approximately 50% of MTX is bound to plasma proteins.

4.4.4. Metabolism

Metabolism of MTX in humans is small. Hepatic metabolism to 7-OH-MTX is via aldehyde oxidase and xanthine oxidases which are polymorphic and of low extraction ratio. The 7-OH-MTX metabolite has approximately 10% biological activity of the MTX. Metabolism by intestinal bacteria accounts for less than 5% of MTX metabolism. Biliary excretion is responsible for 10 to 20% of MTX clearance, and may be more important in subjects with renal insufficiency. A small amount of MTX is also excreted in the stool, which indicates enterohepatic recirculation.

4.4.5. Excretion

Of the drug absorbed, about 80% is excreted unchanged in the urine within 48 hours, mostly within the first 12 hours after administration. Renal excretion of MTX occurs through a combination of glomerular filtration and active tubular secretion. Active tubular secretion contributes to the inter patient variability of MTX kinetics. Because of the slow elimination of MTX from the intracellular space, the drug disappears from plasma in a triphasic manner. The β phase half-life of MTX is between 6 and 15 hours. The median terminal half-life is 55 hours.

4.5. Pharmacokinetics in the target population

4.5.1. Studies comparing oral with parenteral administration

Four studies in adult patients with RA have compared oral MTX 7.5 to 30 mg/week with equivalent doses administered by either IM or SC injection. Hoekstra et al (2004) demonstrated 15 adult patients with RA that the mean bioavailability after oral MTX 30 mg/week was 0.64 (range 0.21 to 0.96) compared to the SC administration of the same dose. There was a statistically significant difference in the bioavailability of oral versus SC administration of MTX in this study. The authors also stated that the bioavailability of a high oral dose of MTX in adult patients with RA is highly variable, and on average two-thirds that of the SC administration and therefore may improve the clinical efficacy of MTX given at a dose \geq 25 mg weekly. Hoekstra et al (2006) used cross study results (in 7 of 10 of the same patients reported in 2004) to show that there was an improvement in oral bioavailability relative to the SC dose by splitting the 30 mg/week oral dose over 8 hours. Seideman et al (1993) reported 9 RA patients involved in a crossover study who received IM, IV and oral doses of 15 mg MTX. While AUC was not reported for the IV dose, the IM and oral doses met bioequivalence criteria (90% CI 92 to 121% for the AUC ratio). Hamilton et al (1997) compared the relative bioavailability of orally administered MTX with IM administration in 21 patients with RA. The 24 hour AUC was significantly lower with oral versus IM therapy at a mean MTX dose of 17 mg/week ($p = 0.027$), but this was not seen at the lower 7.5 mg weekly dose of MTX. This trial confirmed data from other study groups in that the bioavailability of oral MTX decreases with increasing doses. In a study published by Auvinet et al (1992) involving 8 adult patients with RA, a 10 mg/week oral dose was found to be 60% bioavailable relative to the same SC dose, which is consistent with the findings of Hamilton and Hoekstra. Another study by Herman et al (1989) reported oral bioavailability of a 10 mg dose as 70% compared with the same dose given by IM injection in a study involving 41 RA patients. Overall, the published data indicates that a lower AUC is seen with oral therapy versus parenteral administration for doses of MTX as low as 10 mg, consistently when the dose is \geq 15 mg.

4.5.2. Studies comparing different parenteral routes of administration

In addition to the sponsor-initiated studies, the submission contained 4 small patient number trials (n = 32 in total) in adult patients with RA comparing the different parenteral routes of administration of low dose MTX. All of the studies demonstrated that IV versus IM versus SC administration was bioequivalent (according to 90% CIs for relative AUC) in the dose range of 7.5 to 40 mg. Two of the studies (Brooks et al, 1990; Jundt et al, 1993) also reported peak plasma MTX levels, which showed that C_{max} was higher after IM versus SC injection by a mean of 24% (90% CI 1 to 56%).

4.6. Pharmacokinetics in other special populations

4.6.1. Pharmacokinetics in subjects with impaired hepatic function

The submission contained a single study by Jones et al (1986) which showed that the presence of hepatic fibrosis in 7 patients with PSOR versus 12 control subjects with PSOR and no hepatic damage did not significantly affect the PK of MTX after oral or IM dosing (10 to 25 mg/week). The mean C_{max} and AUC results for MTX (sequentially collected up to 144 hours post-dose) were similar in all 4 treatment groups (oral or IM administration, in patients with or without hepatic fibrosis).

4.6.2. Pharmacokinetics in subjects with impaired renal function

Another study by Bressolle et al (1998) examined the effect of varying degrees of renal impairment on the clearance of MTX in 77 adult patients with RA receiving IM MTX 7.5 to 15 mg/week. The trial conducted regression analysis of the results and demonstrated that MTX clearance and half-life are linearly related to creatinine clearance (CrCL). In the group of 7 patients with CrCL < 45 mL/min, the mean MTX clearance was 3.82 L/h (versus 6.91 L/h in the 30 subjects with CrCL > 80 mL/min) and mean half-life was significantly prolonged (22.7 hours versus 10.8 hours).

4.6.3. Pharmacokinetics according to age

The submission contained a publication by Bressolle et al (1997) which showed that although there is a slow decline in MTX clearance with increased age in adult patients with RA, no MTX dose adjustment based on age is required when renal function is preserved. The study compared 2 age related cohorts of patients with RA given IM MTX 7.5 to 15 mg/week. The younger age patient cohort had a mean age of 37 years (range: 21 to 45 years; n = 24 subjects) and the older age group had a mean age of 70 years (range: 65 to 85 years; n = 38 subjects). In this study, mean MTX clearance was higher in the younger patients (7.57 L/h/m² versus 5.73 L/h/m²) and mean half-life was shorter (9.4 hours versus 14.3 hours). However, mean apparent volume of distribution was similar at 1.6 versus 1.9 L/kg.

4.7. Pharmacokinetic interactions

4.7.1. Pharmacokinetic interactions demonstrated in human studies

Various studies have examined the effect of concomitant NSAID administration on MTX absorption and elimination. Although all of the trials are limited by small subject numbers, no significant clinically relevant effect on low dose MTX kinetics (oral and IM administration; 10 to 25 mg/week) has been observed with concurrent NSAID. Skeith et al (1990) demonstrated no effect with ibuprofen and flurbiprofen on MTX PK in 6 adult patients with RA. A study examining concomitant naproxen in 12 patients (aged 30 to 78 years) with RA and normal renal function showed no significant difference in MTX renal clearance or plasma protein binding with or without naproxen (Stewart et al, 1990). However, another study by Stewart et al (1991) demonstrated that high dose oral aspirin (3,900 mg/day) in conjunction with IV MTX 10 mg lowered the clearance of MTX and increased its AUC.

A couple of studies have examined the effect of concurrent hydroxychloroquine or chloroquine on low dose MTX (oral or IV; 15 mg) in a small number of adult and adolescent patients with inflammatory arthritis and demonstrated that co-administration with anti-malarial drugs results in lower C_{max} , longer T_{max} and higher AUC for MTX. The clinical relevance of this observation is unclear.

4.8. Evaluator's overall conclusions on pharmacokinetics

In this submission, the PK properties of low dose parenteral MTX when used in patients with RA and PSOR was assessed from data published in the literature, which included 18 PK studies in total (17 in RA or JIA patients, and 1 small pilot Study in subjects with PSOR). The submission also contained 18 bioequivalence studies and 2 sponsor initiated trials evaluating comparative bioavailability. Many of the PK characteristics of low dose MTX are already known in both healthy volunteer subjects, as well as patients with RA, and to a lesser extent, PSOR.

The sponsor has presented data showing that the 10 mg/mL injection when given SC is bioequivalent to the IM injection in terms of the amount of drug distributed from the injection site (as measured by AUC) in healthy volunteers receiving MTX 15 mg. The sponsor has also demonstrated that the 50 mg/mL injection is bioequivalent to the 10 mg/mL injection formulation for the amount of drug distributed from the injection site, when both products were given by the same route of injection. Cross study comparison of the 50 mg/mL product when given SC versus IM found a similar AUC but a slightly lower C_{max} from the SC dose. The published supporting studies also report these observations. This PK result is unlikely to be of clinical relevance given the proposed maximum dose of 25 mg/week for the 50 mg/mL product is being requested. Analyses comparing parenteral dosing with oral administration over a dose range 7.5 to 40 mg/week showed that the AUC with oral dosing is on average lower than that with IM dosing.

The PK of low dose, orally administered MTX is known to be highly variable, particularly when the weekly dose is ≥ 15 mg. The presence of moderate to severe renal impairment significantly reduces the clearance of MTX, which is an observation regardless of the route of drug administration. Age does not appear to have significant effect on the PK of low dose MTX. Low dose MTX demonstrates significant inter-individual variability, the majority of which cannot be readily explained.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

This submission did not contain any new pharmacodynamic (PD) data.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated. The following information is derived from the sponsor's summaries as well as the currently approved PI.

5.2.1. Mechanism of action

MTX is a folic acid antagonist which primarily acts by competitive inhibition of the enzyme, dihydrofolate reductase, and thereby inhibits the synthesis of DNA and cellular reproduction. Tissues with high rates of cellular turnover (for example skin, intestinal mucosa and bone marrow) are susceptible to this effect of MTX. In PSOR, the rate of production of epithelial cells in the skin is increased compared to normal skin, and this provides the basis for the use of MTX

in controlling PSOR. The mode of action of MTX in RA is not entirely clear, although increasing adenosine levels and reducing pro-inflammatory cytokines seem to play a more predominant role than inhibition of cellular proliferation.

5.2.2. Pharmacodynamic effects

No new information has been provided in this submission.

5.3. Evaluator's overall conclusions on pharmacodynamics

The PD properties of MTX when used in adult patients with active RA and PSOR have been previously described in the literature. No new PD data was presented in this submission and the sponsor is not proposing any changes to the PD section of the PI that are different from alternative formulations of low dose MTX approved in Australia.

6. Dosage selection for the pivotal studies

The dose and administration frequency of MTX used in the pivotal Study MC-MTX.6/RH (15 to 20 mg/ week) is consistent with RA treatment guidelines. However, the commercially proposed 50 mg/mL formulation of Metoject has only been studied in Studies MC-MTX.9/PH (bioequivalence trial) and MC-MTX.10/RH (patient satisfaction study). The pivotal study in this submission (Study MC-MTX.6/RH) investigated the 10 mg/mL formulation of MTX. The literature based submission in both RA and PSOR have presented trials that have utilised the same doses and regimens of MTX that are generally in current clinical practice, but no specific dose finding studies have been performed in either treatment indication. The doses of previous and concurrent treatments (for example NSAID and corticosteroids [oral or topical]) used in the reported studies are also appropriate and consistent with contemporary clinical practice.

7. Clinical efficacy

7.1. Indication 1

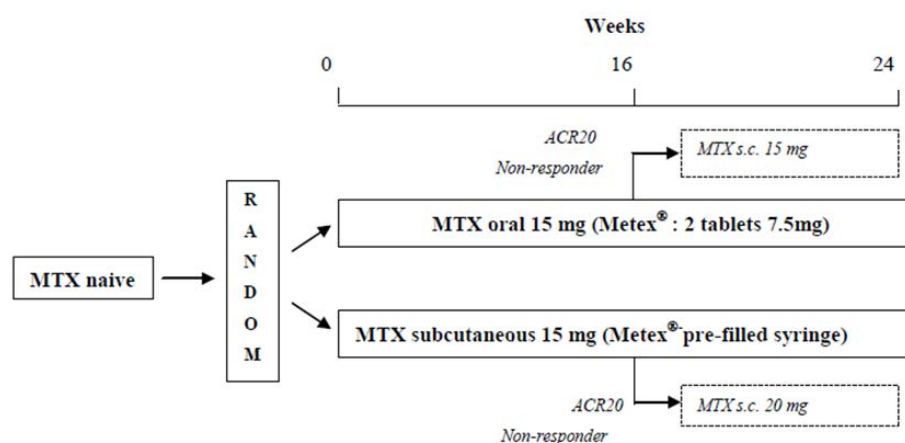
Indication 1: Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAID and one or more disease modifying drugs.

7.1.1. Pivotal efficacy studies

7.1.1.1. Study MC-MTX.6/RH

Study design, objectives, locations and dates

Study MC-MTX.6/RH was a Phase IV randomized, double blind, parallel group trial that evaluated the efficacy and safety of SC administered MTX compared to oral MTX in adult subjects with active RA who were MTX naive. The study had an active treatment period of 24 weeks with a fixed weekly MTX dose of 15mg; however, study medication could be changed at Week 16 if ACR20 response had not been attained. In the non-responder patients, those treated with oral MTX could be switched to SC MTX 15 mg/week after Week 16, and those receiving initial treatment with SC MTX could have the weekly dose up-titrated from 15 mg to 20 mg after Week 16. Figure 1 displays the study design.

Figure 1: Design schema for Study MC-MTX.6/RH

The primary efficacy objective of the study was to compare the efficacy of MTX given by SC injection versus oral administration (both given at a fixed weekly dose of 15 mg) on the signs and symptoms of active RA. At baseline, patients were randomly allocated in a 1:1 ratio to either treatment with oral MTX (2 x 7.5 mg tablets taken concurrently once per week) or SC injections of MTX (given once weekly). The baseline visit was performed on Day 1, and then during the 24 week, double blind treatment period assessments were scheduled to occur at Weeks 1, 2 and 3; every 2 weeks up until Week 12; and thereafter every 4 weeks.

The study was conducted at 29 centres in Germany. The number of enrolled patients by site varied from 1 to 44. Six centres randomised more than 20 subjects with a total number of 200 patients (52.1% of all 384 subjects). Seven centres enrolled less than 6 patients each. Because of insufficient numbers, the study did not investigate the impact of study centre on efficacy or safety outcomes. In Study MC-MTX.6/RH, the first subject was enrolled on 20 November 2003, and the last subject procedure for this efficacy dataset occurred on 28 July 2005. There were 2 amendments to the original protocol (dated 14 August 2003), both of which were instituted before the commencement of patient recruitment. The amendments contained clarifications about the inclusion/exclusion criteria, and the timing of efficacy and safety assessments. None of the amendments resulted in major changes to the study design, which may have adversely affected the integrity of the study's outcomes or statistical analysis.

Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be aged between 18 and 75 years of age with a diagnosis of active RA, and be MTX naive. Active arthritis at baseline was defined as a DAS28 score of ≥ 4 . Patients were allowed to enrol and continue receiving stable NSAID treatment and/or low dose oral prednisone ≤ 10 mg/day if the treatment was stable for 2 weeks prior to randomisation.

The exclusion criteria were extensive and involved 4 domains. Patients meeting any 1 of the criterion were to be excluded from study.

- Current or past history; alcohol or substance abuse; severe diabetes mellitus with obesity; mouth ulcers or known ulcers of the gastrointestinal tract within the last 6 months; infection with Hepatitis B or C virus, HIV or tuberculosis; clinically relevant pulmonary or liver disease; psychiatric illness and malignancy.
- Abnormal baseline laboratory results; liver function tests $> 2 \times$ ULN, serum creatinine > 1.36 mg/dL, or impaired haematopoiesis (platelet count $< 120 \times 10^9/L$; total white blood cell count $< 3.5 \times 10^9/L$).
- Recent or concurrent treatments; use of conventional DMARD therapy within 2 weeks prior to baseline (4 weeks for leflunomide), drugs causing folate deficiency (for example

sulfonamides and trimethoprim-sulfamethoxazole), live virus vaccinations and oral prednisone > 10 mg/day.

- Prior treatment; any exposure to a biological drug.

Study treatments

Following randomisation, patients in the oral MTX arm received 2 tablets of MTX 7.5mg and one dummy pre-filled syringe. Patients of the SC MTX group received one pre-filled syringe containing 15 mg of MTX and two dummy tablets. Patients who fulfilled the entry criteria had to successfully learn the SC injection technique with syringes pre-filled with sodium chloride solution before participating in the study. If patients (or their spouses/carers) were already able to administer SC medication, then drug administration training was not necessary. Parenteral MTX was supplied as pre-filled syringes containing the 10 mg/mL presentation.

To maximise the tolerability of MTX, all patients received 5mg folic acid once per week, taken approximately 24 hours after the MTX dose. MTX therapy could be interrupted for up to 2 doses during the study if: serum transaminases and/or alkaline phosphatase increased > x 3 ULN, serum creatinine increased to > 2 mg/dL, leucocytes decreased to < 3 x 10⁹/L, neutrophils < 2 x 10⁹/L, platelets < 100 x 10⁹/L, as well as patient reporting painful stomatitis or experiencing serious infection. If these problems continued to persist after 1 to 2 weeks, or after MTX therapy had been reinstated, treatment with MTX had to be terminated.

Efficacy variables and outcomes

The main efficacy variables were:

- American College of Rheumatology (ACR) response criteria
- Disability Index of the HAQ (Health Assessment Questionnaire) and
- European League Against Rheumatism (EULAR) response criteria.

The primary efficacy outcome was the proportion of subjects in each of the treatment groups who obtained ACR20 response at 24 weeks.

There were 6 secondary efficacy outcomes:

- Median time to initial ACR20 response
- Rate of ACR50 and ACR70 response at Week 24
- Change in individual ACR component parameters over 24 weeks
- Median DAS28 score in each arm over time
- Proportion of patients in each treatment group fulfilling EULAR response criterion over time
- Rate of ACR20, ACR50 and ACR70 response at 24 weeks in the subgroup of patients not achieving ACR20 response at Week 16 who switched therapy.

In general, the key efficacy endpoints in Study MC-MTX.6/RH use validated metrics that have served as the basis of previous published studies, prior regulatory approvals, and are consistent with published guidelines.

The ACR response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA. A patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 66) and tender (maximum of 68) joint counts, as well as a 20% improvement in any 3 of the 5 core set measures which include Patient's Global Assessment (PtGA), Physician's Global Assessment (PhGA) of disease activity, Patient's Assessment of Pain score (on 10 cm VAS), Disability (Index of the HAQ), and acute phase reactants (ESR or CRP). The analyses of ACR50 and ACR70

included the same criteria as ACR20, but with the use of a higher percentage improvement (50% or 70%) instead of 20%.

The Disability Index of the Health Assessment Questionnaire (HAQ-DI) is a validated method for measuring disability in inflammatory arthritis (range: 0 to 3 with higher score indicating more functional impairment). It assesses physical function by measuring the patient's ability to perform the following 8 activities (using 20 questions): dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity. The measure uses a scale ranging from zero (best) to three (worst). A change in the HAQ-DI of -0.22 units is considered to be the minimal clinically important difference (MCID) in treatment studies of patients with RA.

The 28 joint Disease Activity Score (DAS28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP, and the patient's assessment of general health using a 10 cm visual analogue scale. The final score is derived by a complex mathematical calculation of the individual elements. The DAS28 score is a continuous scale ranging from 0 to 9.4, and most scores range from 2 to 7. According to EULAR guidelines, DAS28 > 5.1 indicates high disease activity, < 3.2 indicates low disease activity, and clinical remission is indicated by a DAS28 score of < 2.6. A change of 1.2 (that is, 2 times the measurement error) of the DAS28 score in an individual patient is considered a significant change. The EULAR response criteria classify patients as good, moderate or non-responders. To be classified as a good EULAR responder a patient must reach low disease activity (DAS28 score of ≤ 3.2). Moderate EULAR response is the attainment of a DAS28 score between 3.2 and 5.1.

Randomisation and blinding methods

Permuted block randomisation with a block length of 6 subjects and stratified according to study centre was undertaken with a balanced allocation of patients into the 2 treatment groups.

Unbiased evaluation was ensured by blinding. Neither the patients nor investigators had knowledge of the patient's treatment assignment. Placebo tablets were identical in appearance to the MTX tablets. As the optical identity of the dummy pre-filled syringes (0.9% sodium chloride; clear solution covered by a transparent yellow label) and the MTX pre-filled syringes (yellow solution) could not be achieved for technical reasons, investigators were not allowed to see the pre-filled syringes during the course of the study in order to maintain blinding.

Analysis populations

Efficacy assessments were conducted using the Full Analysis Set (FAS), which comprises all randomized patients who received at least 1 dose of study treatment and have at least 1 documented efficacy evaluation at least 2 weeks after randomisation. The patients within the FAS were analysed according to the intention to treat principle, based on their initial group of randomisation.

Sample size

Sample size was determined by assuming a 15% difference in the ACR20 response at 24 weeks (55% in the oral MTX treatment group versus 70% in the SC arm) in the FAS. The 2-tailed significance level was set at 5%, and the statistical power was fixed at 80%. Based on these assumptions, 180 patients were to be enrolled in each treatment group. Assuming 5% of all patients would not fulfil the criteria of the FAS, a total of 380 patients were planned to be randomised.

Statistical methods

The primary efficacy endpoint was to examine for the superiority of SC MTX versus oral MTX based on the rate of patients who fulfilled the ACR20% improvement criterion after 24 weeks treatment. For patients withdrawing from the study the last value recorded for the endpoint

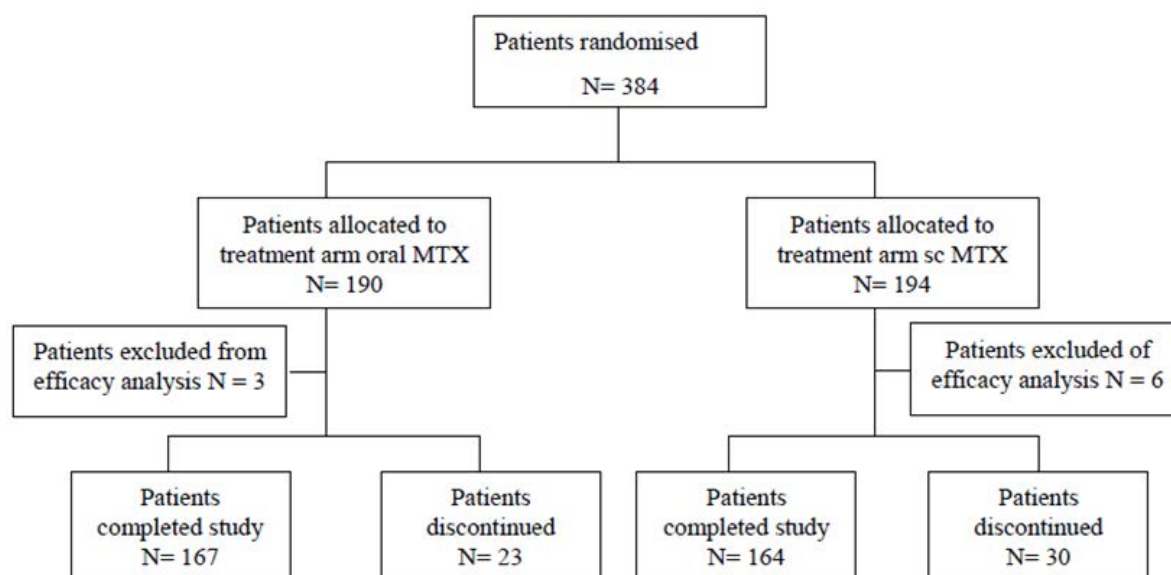
was carried forward for endpoint analysis (Last Observation Carried Forward, LOCF). The 16 Week values for all patients who did not achieve an ACR20 response after 16 weeks, or who were changed to a higher SC dose of MTX were likewise carried forward.

The Cochran-Mantel-Haenszel (CMH) test was applied for the analysis of the primary efficacy endpoint. A chi-square test was used to compare percentages in a two by two contingency table, replaced by Fisher's exact test if the expected frequency in at least one cell of the associated table was < 5%. Comparison of ordinal variables between treatment arms were performed using asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with small number of categories. Time to event analyses were performed using Kaplan-Meier methods. For all efficacy endpoints, the associated 95% confidence intervals (CIs) based on standard errors according to the Greenwood formula were calculated. No adjustment of significance levels for multiple testing was undertaken. Consequently, all other significance tests presented (other than the primary efficacy outcome) were interpreted as supportive only.

Participant flow

The disposition of patients in Study MC-MTX.6/RH is displayed in Figure 2. A total of 384 patients were enrolled into Study MC-MTX.6/RH: 194 in the SC MTX group and 190 in the oral treatment arm. Nine patients (6 in the SC group and 3 in the oral arm) were excluded from the efficacy analysis. One patient in the SC group did not receive any study medication and the other 8 excluded subjects took MTX at least once but discontinued from the trial very early (< 2 weeks) and didn't have a valid post-baseline efficacy assessment to be included in the FAS. As such, 188 patients in the SC MTX group and 187 subjects in the oral treatment arm were included in the efficacy analysis. Over 24 weeks of treatment follow-up, 1 patient in each treatment group was lost to follow-up. The overall rate of discontinuation from the study was higher in the SC group (15.5%; 30 out of 194) compared to the oral arm (12.1%; 23 out of 190), but this was not statistically significant ($p = 0.4960$). Adverse events were the most common reason for study cessation (18 subjects in the SC group and 10 in the oral arm) followed by withdrawal of consent (6 in the SC group and 3 in the oral arm) and insufficient response (2 in the SC group and 4 in the oral arm).

Figure 2: Subject disposition in Study MC-MTX.6/RH



Major protocol violations/deviations

Approximately one third of patients in each treatment group (34.6% [65 out of 188] in the SC group and 35.8% [67 out of 187] in the oral arm) had an efficacy assessment performed outside the scheduled visit window. In addition, the protocol violation category of "excluded

concomitant treatment” was recorded in 20.7% patients of the SC group and in 16% of patients in the oral arm. These protocol deviations were mostly due to a change in the dose of NSAID (11.2% of patients in the SC group and 11.8% of subjects in the oral arm) or corticosteroids (8.6% of patients in both groups) just before or during the study. Only modifications of the corticosteroid dosage with an absolute difference to baseline ≥ 2.5 mg within 7 days before an efficacy examination were considered a protocol deviation. Changes in the dose of NSAID were defined as protocol deviations if they occurred within 24 hours before an efficacy examination and if change of dosage $> \times 2$ dosage at baseline, or $\leq \times 0.5$ dosage at baseline. In total, 7 patients (3.7%) in the SC group and 6 patients (3.2%) in the oral arm received a weekly dose of MTX outside the range of 12.75 mg and 17.25 mg.

Baseline data

There were no significant differences between the treatment groups for demographic and baseline clinical characteristics; refer to Table 5. The median age of subjects enrolled in this trial was 59 years (range: 20 to 75 years) and the majority (76.8%; 288 out of 375) of subjects were female. The median body weight of the enrolled subjects was 74.0 kg (range: 45.0 to 147.0 kg). The median duration of RA prior to study entry was 2.5 months in the SC group and 2.1 months in the oral arm, indicating that the majority of recruited subjects had very early disease. More than half of all enrolled patients (55.0%; 206 out of 375) had a disease duration of < 3 months at baseline. Because the trial mainly recruited patients with a recent diagnosis of RA, the majority of subjects (75%; 141 subjects in each arm) had not received any previous DMARD therapy for RA. In those who had used prior DMARD therapy, the most common previous treatments were sulfasalazine (14% overall), hydroxychloroquine (8% overall) and leflunomide (6% in the SC group and 2% in the oral arm). Most subjects had received low dose corticosteroids within 2 weeks of the study commencement (70.7% [133 out of 188] in the SC group and 66.8% [125 out of 187] in the oral arm) and concomitant NSAID (62.2% [117 out of 188] in the SC group and 64.2% [120 out of 187] in the oral arm). Consistent with expectations, almost two thirds of all enrolled subjects (63%) were positive for rheumatoid factor.

Table 5: Baseline characteristics of subjects in Study MC-MTX.6/RH

	SC MTX (n = 188)	Oral MTX (n = 187)
Demographic characteristics		
Sex, % female	79	74
Age, median (range) years	58 (20–75)	59 (22–75)
Body weight, median (range) kg	73 (45–126)	75 (47–147)
Time since RA diagnosis, median (range) months	2.5 (0–535)	2.1 (0–293)
% taking concomitant steroids	71	67
% taking concomitant NSAIDs	62	64
No. of previous DMARDs taken, median (range)	0 (0–4)	0 (0–3)
% receiving no previous DMARDs	75	75
% receiving only 1 previous DMARD	18	20
% RF positive	66	59
Clinical characteristics		
Tender joint count (68 assessed), median (range)	23 (4–68)	24 (3–68)
Swollen joint count (66 assessed), median (range)	14 (1–58)	16 (2–58)
DAS28, median (range)	6.1 (3.9–8.8)	6.3 (4.0–8.7)
HAQ score, median (range)	1.25 (0–2.88)	1.38 (0–2.88)
CRP, median (range) mg/liter	8.6 (0–126)	11.6 (0–260)
ESR, median (range) mm/hour	24 (1–120)	28 (2–103)
Patient's assessment of disease activity, median (range)	58 (6–92)	62 (2–100)
Patient's assessment of pain, median (range)	63 (0–98)	66 (2–100)
Physician's assessment of disease activity, median (range)	57 (19–97)	60 (12–95)

* Rheumatoid arthritis (RA) patients were randomized to receive subcutaneous (SC) or oral methotrexate (MTX) therapy. A 0–100-mm visual analog scale was used for the patient's assessment of disease activity and pain and for the physician's assessment of disease activity. NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire (disability index); CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

In terms of RA disease activity at baseline, the median numbers of tender and swollen joints were similar for the 2 treatment groups at 23 to 24 and 14 to 16, respectively. The median HAQ-DI score was slightly lower in the SC group at 1.25 compared with 1.38 in the oral arm. The median DAS28 score was high in both groups at 6.1 to 6.3, which indicates high levels of disease activity at baseline. The median PtGA and PhGA were similar in the 2 treatment groups at 58 to 62 mm and 57 to 60 mm, respectively. The median baseline CRP readings were lower in the SC treatment groups at 8.6 mg/L compared with 11.6 mg/L in the oral MTX arm.

The risk of MTX hepatotoxicity is increased by the intake of alcohol. The regular consumption of alcohol was recorded in 35.6% (67 out of 188) of subjects in the SC treatment group and 31.6% (59 out of 187) of patients in the oral administration arm. The incidence of relevant co-morbid conditions was similar in the treatment groups. A past history of hypertension was recorded in just over one third of all subjects, and one third of all patients had endocrine disorders (mainly, thyroid disease and/or diabetes mellitus).

Results for the primary efficacy outcome

At 24 weeks, a statistically higher percentage of patients treated in the SC MTX group (78.2%; 147 out of 188) achieved ACR20 response compared to the original oral administration arm (70.1% [131 out of 187]; $p = 0.0412$ by CMH test).

In order to examine the influence of potential prognostic factors like DAS28 categories (moderate disease activity [that is DAS28 score of 4 to 5.1] versus high disease activity [DAS28 score > 5.1]), joint counts (high disease activity [that is at least 12 tender and 10 swollen joints] versus moderate disease activity) or disease duration at baseline on ACR20 response, additional stratified analyses of the primary endpoint was performed. The only subgroup analysis of ACR20 response at 24 weeks to show a differential treatment related effect was for patients with a diagnosis of 1 year or more prior to study enrolment. In this subgroup, a

greater proportion of patients treated with SC MTX achieved ACR20 response (88.5%; 46 out of 52) compared to those given oral MTX treatment (63.0% [29 out of 46]; $p = 0.0112$).

Results for other efficacy outcomes

Median time to initial ACR20 response

Study MC-MTX.6/RH did not identify any difference in the time to the onset of effect with MTX by administration route. In both treatment groups, the median time to initial ACR20 response was 6 weeks (evaluated using Kaplan-Meier methods).

Rate of ACR50 and ACR70 response at week 24

The proportion of patients achieving ACR70 response at 24 weeks was also higher in the SC group (41.0%; 77 out of 188) compared to the oral MTX treatment group (33.2% [62 out of 187]; $p = 0.0343$). However, the rate of ACR50 response at 24 weeks was not statistically different between the 2 treatment groups (62.2% [117 out of 188] in the SC group versus 59.4% [111 out of 187] in the oral arm; $p = 0.4286$). A stratified analysis of the percentage of patients with ACR50 response by visit did not reveal any statistically significant treatment related difference at any time point during the 24 week evaluation period.

Change in individual ACR component parameters over 24 weeks

Apart from the median PtGA and HAQ scores for which no difference between the treatment groups could be identified, all individual parameters of the ACR response criteria were lower in the SC treatment group compared with the oral MTX arm at Week 24. Analysis of the mean relative change of the individual parameters comprising the ACR response criteria in subjects obtaining ACR20 response at Week 24 showed that for patients in the SC group (versus the oral arm) that this outcome was mainly driven by greater reductions in the swollen and tenders joint counts. At 24 weeks, the median tender joint count was decreased by 80% in the SC group (median of 3.5 joints) versus 73.5% in the oral arm (median of 6.0 joints; $p = 0.048$), and the median swollen joint count was decreased by 87.1% in the SC group (median of 2.0 joints) versus 77.8% in the oral arm (median of 3.0 joints; $p = 0.009$). Median plasma CRP readings were also statistically lower in the SC group at 24 weeks (3.1 mg/L) versus the oral arm (3.6 mg/L; $p = 0.018$). However, median ESR levels at 24 weeks were similar between the two treatment groups at 13.5 to 14.0 mm/hour ($p = 0.216$).

Median DAS28 score in each arm over time

The median DAS28 score was statistically higher in the oral group compared with the SC arm at Weeks 16 and 24. At Week 16, median values of the DAS28 score was 3.4 for the SC arm versus 3.8 in the oral arm ($p = 0.008$); and at Week 24, the median DAS28 score was 3.3 in the SC group and 3.7 in the oral arm ($p = 0.049$). At all earlier evaluation time points (Weeks 4, 6, 8, 10 and 12), no statistically significant difference between the 2 treatment groups for the median DAS28 score in the FAS was observed.

Proportion of patients fulfilling EULAR response criterion over time

Consistent with the median DAS28 results, a higher percentage of patients in the SC treatment group fulfilled the EULAR criteria for a good response (47.3%; 89 out of 188) compared to the oral arm (40.1%; 75 out of 187) at Week 24 ($p = 0.11$). At Week 16, the results between the 2 treatment groups also are statistically different with 45.2% (85 out of 188) of patients in the SC arm recording a good EULAR response compared to 32.6% in the oral arm (61 out of 187; $p = 0.012$). However, at all earlier evaluation time points (Weeks 4, 6, 8, 10 and 12), no statistically significant difference between the 2 treatment groups for the rate of good EULAR response was observed.

ACR Response at 24 weeks in the subgroup of patients not achieving ACR20 response at week 16

Thirty patients in the oral treatment group did not show an ACR20 response at Week 16 and their MTX therapy was changed from 15 mg/week oral to 15 mg/week SC. Nine patients (30%)

satisfied the ACR20 response criterion 8 weeks after changing the route of administration, including 2 patients who achieved ACR50 response. These results suggest that switching MTX from oral to SC administration increases clinical response in RA.

A total of 22 patients in the original SC group were ACR20 non responders at Week 16. Their weekly dose of SC MTX was increased from 15 mg to 20 mg, and 20 patients of these subjects were evaluated at Week 24. Increasing the MTX dose appeared to improve the rate of response with 5 of the 20 patients reaching ACR20 response at 24 weeks, including 2 patients with an ACR50 response and 1 subject was an ACR70 responder after 8 weeks of increased SC MTX.

7.1.1.2. Study by Rau et al (various publications dating from 1991 onwards)

The sponsor has nominated this published cohort as pivotal in the submission as it is a randomised, double blind, parallel group trial comparing IM MTX 15 mg/week with IM gold sodium thiomalate 50 mg/week in the treatment of 174 adult patients (87 subjects in each treatment arm) with early active erosive RA. The patient cohort appears to have been studied at the same 2 German centres over 6 years with a recruitment period between 1986 and 1990. The patient cohort appears to have featured in at least 8 publications with several different lead authors (but overlapping author names with each publication). The recruited population has similar but slightly different overall numbers in each study arm with slightly different reported concomitant medications (such as intra-articular or oral CS in some publications). The publications relate to Rau et al (1991, 1992, 1997, 1998 and 2002), Menninger et al (1997), Sander et al (1999) and Herborn et al (1992).

Inclusion/exclusion criteria

To be eligible for inclusion, patients were required to be between 18 and 70 years of age with a diagnosis of RA for at least 4 months duration as per the 1987 ACR diagnostic criteria. The subjects had to have active disease at baseline, which was defined as 3 of the following 4 criteria: ESR > 20 mm/h in men or > 30 mm/h in women, morning stiffness for > 1 hour, at least 6 swollen joints and at least 9 tender joints. Recruited subjects were required to have at least 1 erosion on plain X-ray of the hands and feet, but were excluded if they had established deformities such as subluxation or ulnar deviation. Prior treatment with either MTX or gold was an exclusion criteria, and any other DMARD therapy had to be ceased at least 3 months prior to entry. Patients were also excluded if they had a history of alcohol abuse or malignancy, active peptic ulcer disease or any other serious co-morbidity. There were also various laboratory exclusions at baseline including serum creatinine > 1.3 mg/100 mL, serum transaminases or bilirubin > x 2 ULN, platelet count < 150,000/mm³ and leucocyte count < 3500/mm³. Patients were allowed to continue prior NSAID therapy and prednisone < 10 mg/day. The doses of these concomitant medications were to remain stable for the first 6 months, but could be reduced or ceased thereafter.

Study treatments and statistical considerations

Patients were randomly allocated to their treatment which was double blinded. Both solutions have a similar light yellow appearance. During the first 2 weeks, patients only received half dose therapy; MTX 7.5 mg/week or gold 25 mg/week (to ensure tolerance). Thereafter, the doses were MTX 15 mg/week or gold 50 mg/week. None of the subjects received folate supplementation. Various appropriate statistical power calculations were presented in the publications. Efficacy analyses were performed on the intention to treat populations.

Patient characteristics and participant flow

Baseline demographic, clinical and laboratory features of both treatment groups are shown in Table 6 (sourced from the Rau et al 1997 publication). The treatment groups were comparable regarding baseline parameters. In total, 39.1% (34 out of 87) of patients in the IM gold treatment group and 16.1% (14 out of 87) in the IM MTX arm did not complete 12 months of

follow-up. Most discontinuations were due to side effects (32 patients in the gold group and 6 in the MTX arm).

Table 6: Baseline features of subjects in IM MTX versus IM Gold Study reported by Rau et al (1997)

	MTX (n = 87)	GSTM (n = 87)
Mean age (yr)	54.2 ± 8.6	56.8 ± 10.4
Female	52 (60%)	63 (72%)
Median disease duration (months)	11.5	11.2
Mean disease duration	25.9 ± 38.6	21.9 ± 31.9
Disease duration <12 months [range]	52 (60%) [4–12 months]	54 (62%) [4–12 months]
Disease duration <36 months [range]	71 (82%) [4–36 months]	73 (84%) [4–36 months]
On prednisone (<10 mg/day)	33 (38%)	29 (33%)
RF+	59 (68%)	47 (54%)
Morning stiffness*	3.36	3.41
Overall joint pain†	2.57	2.60
Tender joints (0–38)	18.5 ± 8.5 (1–36)	20.0 ± 7.9 (7–37)
Swollen joints (0–38)	15.3 ± 6.6 (6–32)	15.1 ± 7.2 (6–36)
Lansbury index of swollen joints (0–172)	65.9 ± 34.6 (7–143)	65.4 ± 35.8 (7–162)
Grip strength right hand (bar)	0.3 ± 0.2 (0–0.8)	0.3 ± 0.2 (0–1.3)
ADL score Hannover (normal = 100)	68.5 ± 18.9 (20–100)	70.3 ± 20.3 (0–100)
ESR (mm/h)	41.1 ± 24.5 (4–104)	40.6 ± 23.6 (2–111)
C-reactive protein (mg/100 ml)	4.1 ± 3.6 (0–17.6)	4.6 ± 4.4 (0–17.5)
Pre-treatment with DMARDs	8 (9%)	11 (13%)

The values are given as means ± s.d. and (range).

*Grading: morning stiffness was graded 1 = <15 min, 2 = 16–45 min, 3 = 46–90 min, 4 = 91–180 min, 5 = > 180 min.

†Grading: overall joint pain was graded 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable.

Efficacy results

As shown in Table 7 (sourced from Rau et al 1997 publication), significant improvements were seen in all clinical parameters of RA activity in both treatment groups, with no significant treatment related differences being observed. There was a reduction in the mean number of tender and swollen joints and the Lansbury articular index by approximately 40 to 50%, a reduction in the duration of morning stiffness of approximately 40%, increase in grip strength of approximately 60% and an improvement in the ADL score by 12 to 14%. The greatest improvement in the reduction of the number of tender and swollen joints and the Lansbury articular index was seen by 6 months in both groups and then stabilised between 6 and 12 months. The IM gold treatment group showed a numerically greater improvement than in the MTX arm for tender and swollen joint counts, but this was not statistically different between the two treatment groups at either 6 or 12 months. ESR and CRP improved by approximately 50% in both treatment groups. At 12 months, marked clinical improvement (≥ 50% change from baseline) occurred in 47% (34 out of 73) of MTX treated patients and 65% (34 out of 53) remaining gold subjects. This result includes 10 patients (14%) in the MTX group and 13 patients (25%) in the gold arm with clinical remission. The number of patients taking prednisone at baseline declined from 29% to 10% at 12 months in the MTX group and from 28% to 8% in the IM gold arm. In both groups, there was also a significant reduction in the mean daily dose of CS at 12 months compared to baseline.

Table 7: Mean response to treatment at 6 and 12 Months in Study reported by Rau et al 1997 (completing subject's data only included)

	MTX (n = 73)				GSTM (n = 53)			
	0	6	12	P	0	6	12	P
Tender joints (0–38)	18.4 ± 8.3	11.9 ± 10.4	11.4 ± 9.8	*	20.3 ± 8.4	12.4 ± 9.9	10.3 ± 10.8	*
Swollen joints (0–38)	14.9 ± 6.5	8.0 ± 6.7	7.6 ± 6.9	*	14.6 ± 7.2	7.5 ± 7.7	6.1 ± 7.5	*
Lansbury index of swollen joints (0–178)	64.6 ± 34.8	31.3 ± 25.4	29.0 ± 28.0	*	70.7 ± 36.4	29.6 ± 33.6	26.3 ± 37.6	*
Morning stiffness†	3.4	2.2	2.1	*	3.5	2.5	2.1	*
Overall joint pain‡	3.6	2.7	2.8	*	3.6	2.8	2.7	*
Grip strength right hand (bar)	0.3 ± 0.2	0.5 ± 0.2	0.5 ± 0.3	*	0.3 ± 0.2	0.4 ± 0.3	0.5 ± 0.2	*
ADL score %	69.1 ± 19.2	81.1 ± 25.7	78.4 ± 19.3	*	72.3 ± 20.6	79.8 ± 16.6	80.7 ± 20.7	*
ESR (mm/h)	41.5 ± 24.6	22.8 ± 19.8	21.1 ± 16.2	*	41.0 ± 25.7	26.0 ± 27.4	23.4 ± 29.8	*
CRP (mg/100 ml)	4.1 ± 3.6	2.2 ± 2.6	2.5 ± 3.2	*	4.3 ± 3.9	2.2 ± 3.0	2.1 ± 2.9	*
Haemoglobin (g/l)	13.5 ± 4.5	13.6 ± 2.1	13.6 ± 1.3	ns	12.9 ± 1.4	12.9 ± 1.5	13.1 ± 2.1	ns
IgG (mg/100 ml)	1307 ± 407	1163 ± 490	1276 ± 443	ns	1379 ± 440	1295 ± 358	1179 ± 274	*
IgA (mg/100 ml)	301 ± 130	266 ± 114	301 ± 135	ns	313 ± 115	357 ± 463	260 ± 136	ns
IgM (mg/100 ml)	186 ± 88	166 ± 74	188 ± 93	ns	188 ± 66	156 ± 49	141 ± 64	*
No. of patients on prednisone (dose/day)	21 (4.5 mg)				15 (2.9 mg)			4 (0.3 mg) *

*Statistically significant from baseline ($P < 0.05$); ns = statistically not significant from baseline ($P > 0.05$).

†Morning stiffness was graded 1 = <15 min, 2 = 16–45 min, 3 = 46–90 min, 4 = 91–180 min, 5 = >180 min.

‡Overall joint pain was graded 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable.

A subsequent publication by Rau et al (1998) with the same patient cohort reported on the radiographic outcomes after 6 and 12 months of therapy. X-rays were scored using the validated modified Sharp score, which evaluates 38 joints in total and grades each joint using a semi quantitative evaluation of destruction. Summary scores using this method range from 0 to 190, with a higher score indicating more radiographic damage. The mean baseline X-ray score was 5.8 in the MTX group and 4.6 in the IM gold arm. Between baseline and 6 months, the mean radiographic increased by 3.4 to 9.2 in the MTX group, and by 2.6 to 7.2 in the gold treatment arm. Between baseline and 12 months, the mean radiographic increased by 6.0 to 11.8 in the MTX group, and by 4.8 to 9.4 in the gold treatment arm. There was no statistical difference in the mean X-ray score progression between the 2 treatment groups at 6 and 12 months ($p = 0.66$ and 0.44 , respectively). There was a significant reduction in the X-ray progression rate during the second half year when compared with the first half year in both treatment groups ($p < 0.05$). The mean progression rate decreased from 3.4 during months 0 to 6, to 2.6 during months 7 to 12 with MTX treatment and from 2.6 to 2.2 in the gold group. This corresponds to a reduction of the progression rate from 0.57/month during the first half year to 0.44/month during the second half year in the MTX group, and from 0.43/month to 0.37/month in the IM gold arm. Table 8 summarises the radiographic progression in both treatment groups over 12 months according to responder status (no change, minor change or major change). The results are within expectations for MTX therapy in patients with RA at high risk of X-ray progression, and show no treatment related difference in radiographic progression.

Table 8: Proportion of subjects in each treatment group with radiographic change in study reported by Rau et al 1998 (Intention to treat analysis)

	MTX	GSTM
Radiographic score		
No change	21.4%	25.0%
Change 1–5	37.1%	36.5%
Change > 5	41.5%	38.5%
Number of eroded joints		
No change	20.0%	30.6%
Change 1–4	43.3%	42.0%
Change > 4	36.7%	27.4%

7.1.2. Other efficacy studies

7.1.2.1. Study MC-MTX.10/RH

Design, objectives and study treatment

Study MC-MTX.10/RH was a Phase III, open label, repeat dose, within patient controlled trial conducted in adult patients with active RA which had the primary aim of investigating the patient's satisfaction with a weekly 20 mg SC dose of MTX given as 2 mL of 10 mg/mL solution versus 0.4 mL of 50 mg/mL mixture (both presentations administered as a single prefilled syringe).

Following a screening period of between 1 and 14 days, all patients were planned to receive 20 mg MTX (administered weekly by SC injection) for 6 weeks in total. The end of study visit occurred on Day 43 (that is 1 week after the last scheduled injection visit). For the first 3 drug administrations, syringes containing 2 ml of a 10 mg MTX/ml solution were used. The last 3 injections were performed with syringes containing 0.4 ml of 50 mg MTX/ml. The first and fourth injections were given by the physician or an authorised person. The other injections (2nd, 3rd, 5th and 6th) were performed by the patients themselves. Three injections were administered in the ward or practice, 2 by the physician or an authorised person (1st and 4th) and 1 by the patient (2nd). The 3 other injections were to be given at the patient's home (3rd, 5th and 6th), or in case of patient request, could be administered by the patient in the ward or practice. All patients received oral folic acid once a week, 24 hours after the MTX dose, and drugs known to cause folate deficiency (for example sulfonamides) were contraindicated during the trial.

The study was conducted at 16 centres in Germany. The number of enrolled patients by site varied from 1 to 24. Six centres randomised at least 12 subjects with a total number of 96 patients (72.7% of all 132 subjects). In Study MC-MTX.10/RH, the first subject was enrolled on 22 November 2007, and the last subject procedure for this efficacy dataset occurred on 18 November 2008. There was 1 amendment to the original protocol, which was implemented 3 weeks after the commencement of patient recruitment. The amendment allowed for continuing supply of study medication after Day 43 in subjects tolerating and responding to parenterally administered MTX therapy.

Inclusion and exclusion criterion

To be eligible for inclusion, patients had to be aged between 18 and 75 years of age with a diagnosis of active RA (DAS28 score > 2.6) despite oral treatment with MTX for at least 6 weeks. Only patients who had tolerated MTX at baseline and requiring an intensification of MTX therapy were to be enrolled.

The exclusion criteria included prior treatment with parenteral MTX or biologics, concomitant treatment with another DMARD, renal insufficiency (serum creatinine > 1.5 ULN), hepatic insufficiency (AST or ALT > 2 x ULN, or serum bilirubin > 5mg/dL), impaired haematopoiesis (platelet count < 100 x 10⁹/L, total white blood cell count < 3.5 x 10⁹/L, or haemoglobin < 10 g/dL), alcohol or substance abuse, mouth ulcers or known ulcers of the gastrointestinal tract, infection with Hepatitis B or C virus, HIV or tuberculosis, psychiatric illness, malignancy and those receiving any other subcutaneously administered drug (for example insulin or heparin).

Efficacy outcomes

The primary endpoint of the trial was to determine the patient's decision for future MTX treatment (that is whether 50 mg/mL syringes have the ability to increase patient's satisfaction of SC MTX treatment compared to 10 mg/mL syringes). At the end of the study, patients were asked to decide on their future SC MTX therapy by being asked "which of the prefilled syringes would you prefer from now on?"

Secondary efficacy variables included assessments of:

- Patient satisfaction with the 50 mg/ml syringe versus 10 mg/ml syringe at the end of study (Day 43). The patient was asked “How would you assess, all in all, the small/large syringe at the end of the study?” There were 5 rating categories: very bad, bad, no preference, good and very good.
- Any potential advantages of the fixed needle attached on the 50 mg/ml MTX prefilled syringe in comparison to the prefilled syringe without a fixed needle (10 mg/ml) by the patient. The patient was asked “How do you find the fixed needle (small syringe) in comparison to the one that still has to be attached (large syringe)?” There were 5 possible answers provided: very disadvantageous, disadvantageous, no difference, advantageous and very advantageous.
- Any potential advantages of the 0.4 ml volume of the 50 mg/ml syringe in comparison to 2 ml volume of the 10 mg/ml syringe. The patient was asked “Does it suit you that the injection liquid is 5 times less in the small syringe than in the large syringe?” The patient had to complete the following sentence: In comparison to the solution in the large syringe it is: very disagreeable, disagreeable, indifferent, agreeable or very agreeable.
- Usability of the 10 mg/ml syringes at the 1st injection and of the usability of the 50 mg/ml syringes at the 4th injection rated by the physician on a 100 mm visual analogue scale from 0 (“not convenient”) to 100 (“very convenient”).
- Usability of the 10 mg/ml syringe at the 2nd and 3rd injection and of the 50 mg/ml syringe at the 5th and 6th injection rated by the patient on a 100 mm visual analogue scale from 0 (“not convenient”) to 100 (“very convenient”).

Statistical considerations

All efficacy data was handled by descriptive analyses. The primary efficacy variable (proportion of patients deciding in favour of the 50 mg/ml syringe versus 10 mg/ml syringes) was subjected to statistical testing according to the hypothesis system defined applying a 2 sided, 1 group chi-square test at a significance level of 5%. For all secondary variables evaluating the satisfaction and usability of the small 50 mg/ml syringes compared to the large 10 mg/ml syringes, absolute and relative frequencies were provided.

The number of patients needed in this study was estimated to be 130. A one group chi-square test with a 5% two sided significance level would have 90% power to detect the difference between the null hypothesis rate of 55% and the alternative rate of 70% (that is preferring the 50 mg/mL syringe) when the sample size was 110. The sample size was set to 130 patients to adjust for patients to be excluded from the FAS.

Participant flow and protocol deviations

A total of 132 patients were enrolled into Study MC-MTX.10/RH, but 4 (3.0% of 132) were excluded from the FAS. Of the 4 excluded subjects, 3 only received 1 type of syringe and the other patient was excluded because of a major protocol violation (missed 3 study visits and insufficient source data available). In total, 9 patients (7.0% of 128) recorded significant protocol deviations, all related to violation of inclusion/exclusion criteria. A total of 6 subjects (4.7% of 128) discontinued prematurely from the study; 3 due to AEs, 2 patients withdrew consent and 1 was lost to follow-up.

Baseline data

The mean age of subjects enrolled in Study MC-MTX.10/RH was 54.8 years (range: 18 to 75 years) and the majority (73.4%; 94 out of 128) of subjects were female. The mean body weight of the enrolled subjects was 78.2 kg (range: 49.0 to 116.0 kg). The mean duration of RA prior to study entry was 5.6 years (median 3.0 years; range: 1 to 39 years). The mean and

median baseline DAS28 scores were 4.4 and 4.3, respectively (range: 2 to 8). Of the 128 subjects in the FAS, 63 (49.2%) had previously received MTX therapy. At study commencement, weekly MTX doses ranged from 7.5 to 25 mg, and 85.2% of all subjects (109 out of 128) were taking MTX 15 to 20 mg/week.

Efficacy results

The primary study efficacy endpoint was achieved with 93.0% (119 out of 128) of patients preferring the small 50 mg/mL syringe compared with the larger 10 mg/mL injection (2.3% [3 out of 128]; $p < 0.0001$) at the end of the trial.

The results of the patient questionnaire concerning usability and preference for treatment were:

- 99.1% of the patients assessed the convenience of having a fixed needle with the small syringe (50 mg/mL) as either “advantageous” or “very advantageous” versus 3.1% reporting it as “disadvantageous” or “very disadvantageous”.
- 87.5% of the subjects found that the smaller volume in the 50 mg/mL preparation was more suitable (“agreeable” and “very agreeable”) compared to the larger volume injection (that is 1.6% of patients disagreed with this response).

The results of the physician/study nurse questionnaires concerning usability and preference was:

- All study nurses and investigators assessed the convenience of having a fixed needle with the smaller syringe (50 mg/mL preparation) as “advantageous” and “very advantageous”.
- 87.5% found that the smaller volume in the 50 mg/mL syringe was more suitable (“agreeable” or “very agreeable”) compared to the larger volume with the 10 mg/mL formulation, however, 12.5% of respondents saw no difference in this regard.

Physician and patient global assessments of syringe usability stratified by filling volume was 69.7 mm with MTX 10 mg/mL syringes and 87.3 mm with the smaller syringes (50 mg/mL). The difference was statistically significant ($p < 0.0001$) in favour of the smaller syringes. Overall physician and patient global assessment of syringe usability stratified by visit decreased from 77.0 to 65.5 mm from 1st to 3rd injection (Day 1 versus Day 15) indicating deterioration in satisfaction with repeat 10/mL injections, and the global assessment ratings improved to 89.0, 85.6 and 86.7 mm with 4th, 5th and 6th injections when using small syringes (10 mg/mL). The differences between 1st and 4th, as well as the 3rd and 6th injections, were statistically significant ($p < 0.0001$) in favour of the investigational product (50 mg/mL syringes). However, it should be noted that assessments of the 1st and 4th injection were made by the physician and all others by the patient.

7.1.2.2. Study MC-MTX.5/RH

Design, objectives and study treatment

Study MC-MTX.5/RH was an exploratory Phase II, open label, single group design trial conducted in adult patients with RA which had the primary aim of assessing the local tolerability of repeat SC injections of MTX. Following a screening period of up to 21 days, all patients were planned to receive a stable dose of 15 to 25 mg MTX (administered weekly by SC injection) for 6 weeks in total. The 10 mg/mL solution of MTX was used in this study and it was presented in prefilled syringes. The end of study visit occurred on Day 50 (that is 2 weeks after the last scheduled injection). All injections of MTX were administered at the trial site. The first 2 injections were done by the investigator and the last 4 injections by the patient under the supervision of the investigator. Each of the 6 SC injections was to be made in a pre-specified order into the subcutis of the abdomen.

The study was conducted at 10 centres in Germany. In Study MC-MTX.5/RH, the first subject was enrolled on 2 November 2001, and the last subject procedure for this efficacy dataset occurred on 29 April 2002. There were 2 minor amendments to the original protocol, both of which were implemented after the commencement of patient recruitment. Neither amendment had the potential to affect the study findings.

Inclusion and exclusion criterion

To be eligible for inclusion, patients had to be aged between 18 and 75 years of age with a diagnosis of RA. Only patients who had received a stable weekly dose of MTX 15 to 25 mg (oral or parenteral) were eligible for enrolment.

The exclusion criteria included prior treatment with parenteral MTX, concomitant treatment with another DMARD, renal insufficiency (serum creatinine > 2.0 mg/dL), hepatic insufficiency (AST or ALT > 3 x ULN), impaired haematopoiesis, alcohol or substance abuse, mouth ulcers or known ulcers of the gastrointestinal tract, malignancy and those receiving a broad range of prior or concomitant drugs including phenytoin, tranquilisers, proton pump inhibitors, penicillins, loop diuretics, corticosteroids and NSAID.

Efficacy outcomes

No specific efficacy measures such as ACR or DAS scores were collected in this trial. The primary endpoint of the trial was to determine the local tolerability of repeat SC MTX injections. This was determined by a local tolerance score and was primarily assessed at each study visit whereby an injection of MTX was administered. The local tolerance symptoms of redness, swelling and haematoma (all investigator assessed) as well as pain and itching (patient assessed) were scored for intensity using a 4 point scale (0 = none, 1 = mild, 2 = moderate and 3 = severe). Local tolerability was assumed if the score was ≤ 2 . Time points of assessment of local tolerability occurred on the day of injection and were taken immediately before, as well as 0.5 hours and 1 hour after administration.

The 3 secondary outcome measures included dermal reactions according to the investigator (erythema, oedema, papules and glazing), overall satisfaction with the administration method (as judged by both the patient and investigator) and a global assessment of tolerability (as judged by both the patient and investigator).

Statistical considerations

All outcome data was handled by descriptive statistics. The primary endpoint of the local tolerance score was computed using the maximum intensity score per visit and 2 exact 90% CIs were calculated for the percentage of patients with an overall tolerance score of ≤ 2 and for the proportion of subjects with an overall tolerance score < 2 (stricter standard).

Applying an exact one sided test with a 5% significance level, it was estimated that 57 subjects would have to be enrolled if 95% of patients reported tolerance to MTX injections. However, the sample size was adjusted to 70 patients to allow for a subject dropout rate of 20%.

Participant flow and protocol deviations

A total of 87 patients were consented into Study MC-MTX.5/RH, 82 entered into the treatment phase of the trial and 81 subjects completed the study. One subject withdrew after receiving 5 injections because of an inability to self-inject. One centre, which recruited 13 patients, was excluded from all analyses because of improper completion of case report forms. As such, 69 patients were included in the analysis population. A quarter of subjects (17 out of 69) recorded minor protocol deviations, mainly related to timing of assessments and drug administration, which had no significant impact on the study findings.

Baseline data

The mean age of subjects enrolled in Study MC-MTX.5/RH was 57.3 years (range: 32 to 75 years) and the majority (69.6%; 48 out of 69) of subjects were female and Caucasian (68 out of 69). The mean body weight of the enrolled subjects was 75.9 kg (range: 47.0 to 120.0 kg). The mean duration of RA prior to study entry was 7.5 years (range: 0.3 to 36.4 years). The mean duration of prior MTX treatment was 3.33 years (range: 0.3 to 14.4 years) at a current weekly dose of 16.1 mg (range: 15 to 25 mg). Of the 69 subjects, 32 (46.4%) had previously received MTX as oral therapy at baseline, 31 (44.9%) were receiving intramuscular MTX and 6 subjects (8.7%) were taking MTX by the IV route.

Efficacy results

For 98.6% (68 out of 69) of patients, an overall local tolerance score of < 2 was given, supported by the exact 90% CI (93.3%, 99.9%). Applying a stricter standard of an overall local tolerance score < 2, 89.9% (62 out of 69) of patients recorded this result (90% CI: 81.8%, 95.1%). The reasons for the above scores not reaching 100% was 1 patient recording severe redness; and another 6 subjects recording moderate severity events (4 with redness, 1 with itch and 1 reporting local pain). Mild swelling, mild pain and mild itching were reported at incidences of 10.1%, 5.8% and 7.2%, respectively.

Overall, 14 patients (20.3% of 69) showed 19 dermal reactions, 17 of them were barely perceptible minimal erythema; and 2 were readily visible definite erythema, oedema or papular reactions. In 3 cases of barely perceptible minimal erythema, a slight glazed appearance was additionally described.

In total, 58.0% of the patients were very satisfied with the administration system for self-injection, 36.2% were satisfied, and 5.8% were less satisfied. The majority (87.0%) stated they would like to continue the treatment without weekly visits at their physician, 7.2% were not sure, and 4.3% would not like to continue with injectable MTX treatment without giving any reason. For 44.9% of the patients the investigator judged the self-injection of MTX as very suitable, and as suitable for 52.2% of the patients. For 2 patients, the investigators rated injectable MTX as less suitable.

The global tolerability was assessed as very good by 81.2% of patients, as good by 15.9% of subjects, as moderate and bad by 1.4% each of the patients. One patient rated global tolerability as bad. In 78.3% of patients, the investigator rated the global tolerability as very good, and as good in 20.3% of patients.

7.1.3. Literature based studies in RA

The efficacy of low dose oral MTX for the treatment of RA is well established, with products currently registered for this indication in Australia. Existing MTX products for RA recommend a starting dose of 7.5 mg/week, which can subsequently be titrated up to a maximum weekly dose of 20 mg. The proposed dosing recommendations for Metoject differ by recommending the parenteral route of administration (IM or SC) and having an increased maximum weekly dose of 25 mg.

In the Literature Based Submission (LBS) supporting the use of low dose MTX in RA, the sponsor presented the data in 3 groupings by the route in which MTX was administered in the trials; SC, IM and IV injection. Excluding Study MC-MTX.6/RH, a total of 4 controlled (n = 215 subjects) and 5 uncontrolled studies (n = 170 subjects) examined the effect of SC MTX in controlling active RA in adult subjects, generally over 12 to 26 weeks of treatment follow-up. In addition, Klein et al (2012) reported the retrospective observational data from the German MTX registry involving 411 paediatric patients with various forms of JIA who had received MTX 0.42 mg/kg/week (approximately 12 mg/week) by either SC injection (n = 152) or oral routes (n = 259) for at least 6 months. Parenteral MTX has been used in European children with JIA for > 10 years and this study has been included by the sponsor as supportive evidence of the

efficacy and safety of MTX administered by the parenteral route. JIA is a chronic, autoimmune, inflammatory disease with a response to MTX, which has many similarities to adult RA in terms of immunopathology.

Regarding low dose MTX given by IM injection, the LBS contained 2 randomised, double blind, placebo controlled studies with a total of 29 subjects that compared MTX 10 or 25 mg/week with placebo over 6 to 12 weeks (Thompson et al, 1984; Andersen et al, 1985). Another 5 controlled studies enrolling 311 patients compared IM MTX with either IM gold sodium thiomalate or active therapies. The LBS also contained 2 open label studies in 724 children with active JIA (Ravelli et al, 1998; Ruperto et al, 2004), which used IM MTX. In addition, a total of 390 patients were enrolled in 6 uncontrolled studies, which included 2 studies switching between IM and oral MTX therapy. The most commonly used doses of MTX were 10 to 15 mg/week and most of the studies treated patients for 6 months. Two of the IM dosing studies reported MTX dose increments of 5 mg/week at 3 to 4 week intervals from an initiating dose of 5 mg/week (Andersen et al, 1985; Lambert et al, 2004), depending on RA activity and patient tolerance.

The LBS also contains 6 studies enrolling a total of 80 patients whereby MTX was administered by IV injection for RA. Only 1 of the IV studies was a randomised, blinded trial of 6 months duration but the control arm in this study is not approved in Australia (prospidine IV injection). Hence, the study has been presented by the applicant as an uncontrolled trial (Benenson et al, 1994). Four of the other 5 IV administration studies were for a maximum of 12 weeks, while the study reported by Nicksch et al treated patients with MTX for up to 6 months but subjects only received IV MTX as an induction treatment for the first 4 weeks of that trial.

7.1.3.1. Efficacy in SC MTX studies

There are no placebo controlled studies investigating the efficacy of SC MTX in adult patients with RA. The sponsor has conducted the largest study using SC MTX versus oral MTX in a total of 374 patients over 24 weeks of therapy (Study MC-MTX.6/RH). The details of this trial have already been reviewed. In addition, a total of 4 additional studies involving a total of 367 adult subjects have compared SC MTX with the same dose of oral MTX over 12 to 26 weeks of treatment follow-up. One of those studies (Islam et al, 2013) compared SC with oral MTX in patients with inadequate RA control on oral MTX 15 mg/week, while another trial (Bakker et al, 2010) compared SC MTX to oral CsA in patients with inadequate response to oral MTX. All of the SC switching studies reported improved clinical response with the change in administration route of MTX. In particular, Islam reported a statistically increased percentage of switching patients achieving ACR20 (93% versus 80%) and ACR50 response (89% versus 72%) upon changing from oral to SC MTX ($p < 0.05$).

The German MTX registry study published by Klein et al (2012) involving 411 patients with JIA showed that there was no significant difference in efficacy between oral and SC MTX in achieving the primary efficacy outcome of ACR Pedi 30 improvement after 6 months of therapy (73% [111 out of 152] in the SC MTX group versus 72% [186 out of 259] in the oral arm; $p = 0.75$).

7.1.3.2. Efficacy in IM MTX Studies

Of the 29 adult subjects who participated in the 2 randomized, double blind, placebo controlled studies that compared MTX 10 or 25 mg/week by IM injection with placebo over 6 to 12 weeks (Thompson et al, 1984; Andersen et al, 1985), the majority of subjects completed the study investigational period. The studies show a consistent improvement in joint swelling and tenderness scores relative to placebo of 18 (95% CI 10 to 25) and 25 (95% CI 13 to 37), respectively, over the 6 to 12 weeks treatment period. There was also a statistically significant increase in hand grip strength over the same period of 29 mmHg (95% CI 24 to 33 mmHg) and a reduction in morning stiffness of 2.8 hours (95% CI 1.9 to 3.8 h). The improvement in the clinical measures was supported by statistically significant improvements in the pain score of

the treated groups relative to placebo. Both of these studies also showed a statistically significant decrease in ESR. Estimating the proportion of patients with an ESR reading < 20 mm/hour based on the group variance suggests 25% of MTX treated patients had reached this threshold compared with 7% of subjects in the placebo arm.

In the short term trials (up to 26 weeks of treatment follow-up) investigating the efficacy of IM MTX in adult patients with RA, several of the studies reported the mean change from baseline in DAS28 score and showed to statistically significantly lower values with treatment (that is compared to baseline), but not treatment related difference for this outcome when IM MTX was compared with LEF 20 mg/day at 6 months (Fiehn et al, 2007; n = 21 subjects). Many of the included studies also reported statistically significant decreases over the first 26 weeks in the number of swollen and tender joints in the IM MTX treatment arm (relative to baseline) which were not significantly different from the active comparator therapy, mostly IM gold sodium thiomalate or oral MTX control arms. In addition, a reduction in the duration of morning stiffness was sometimes reported, which was statistically significantly reduced relative to baseline (approximately 30% reduction; $p < 0.05$), but not different from IM gold sodium thiomalate. Other clinical measures, such as hand grip strength and the Lansbury articular index showed consistent trends to improvement with IM MTX.

Excluding the pivotal studies published by Rau et al and his colleagues, a further 196 adult patients with RA in 5 uncontrolled studies received MTX 5 to 25 mg/week by IM injection for 1 to 4 years. The studies did not report the same efficacy parameters as Rau et al, nor did they report sufficient information to permit combined analyses, however, qualitative comparisons were available for consideration. Most of the supporting studies in patients with RA evaluating IM MTX therapy, reported improvements in swollen and tender joint counts in patients able to tolerate MTX up to 2 years, and thereafter changed little. Hand grip strength also improved with IM MTX and morning stiffness decreased to a plateau level after 12 months. Pain scores generally decreased over the first 12 month treatment period and remained constant thereafter for those who could tolerate IM MTX. Global evaluation of RA in responses to questionnaires appears to be less sensitive to changes as a result of therapy and did not change appreciably from baseline. Mobility measures (for example Ritchie Index) and the Lee Index of articular function tended to show a slow decline over the first 12 months of treatment and plateaued thereafter. Most studies reported CRP and ESR values during the studies. With the exception of Sander et al (1999), CRP readings showed a steady decline over 2 years to plateau at approximately 10 mg/L (normal range 1 to 3 mg/L). As observed with CRP changes over time, ESR declined to plateau levels over the first 12 months of IM MTX therapy, and plateaued at approximately 25 mm/hour.

Two studies in children with JIA included oral MTX as a comparator with IM MTX (Ravelli et al, 1998 and Ruperto et al, 2004). Ravelli reported that there was no statistically significant difference in the proportions of patients achieving a 50% reduction in the number of active joints between oral and IM MTX (61% of subjects in the IM MTX group achieved this outcome and 58% of children in the oral MTX group; MTX doses of 10 mg/m² for 6 months). Ruperto reported that with 6 months of oral versus IM or SC MTX 8 to 12.5 mg/m²/week, there was no statistically significant treatment related difference in the rate of achieving ACR Pedi 30 scores. Both Ruperto and Ravelli further examined the response rates of the different subtypes of JIA, and all subtypes showed a favourable response to MTX therapy (administered by any route).

7.1.3.3. Efficacy in IV MTX Studies

Benenson et al (1994) used 30 mg/week of IV MTX in 15 adult patients for 4 weeks, followed by an oral maintenance regimen of MTX 7.5 to 15 mg/week for up to 6 months in patients with refractory RA. The comparator therapy was IV prospidine 500 mg every 3 to 5 days initially followed by a monthly infusion (n = 27 subjects). The study showed that after 4 weeks of treatment, 85% of prospidine treated subjects had demonstrated clinical improvement, which was sustained in 73% of patients at 6 months. In comparison, 40% of the MTX treated cohort

had a significant reduction in disease activity (inflamed joint count, Ritchie articular index and duration of early morning stiffness) after 4 weeks of IV therapy, which improved to 57% of patients at 6 months. Serum inflammatory markers (ESR and CRP) also reduced significantly within 4 weeks of receiving IV MTX, but there was no change in baseline prednisolone use or rheumatoid factor levels over time.

Nicksch et al (1987) used a single IV induction dose of MTX 15 mg followed by low dose MTX 7.5 mg/week given by either the IV or oral route for up to 26 weeks. This trial showed that MTX improved and maintained clinical benefit (for example > 70% improvement in active joint count and walking time) in the majority of treated subjects (n = 28) over 26 weeks. The authors did not report the percentage of doses given by the IV route.

Gabriel et al (1990) also did an IV MTX study (15 to 40 mg/week; mean 26 mg/week) in 10 adult patients with RA, but did not report the clinical efficacy data. However, a decrease in ESR of 21 mm/hour over 12 weeks of IV MTX therapy was stated.

Michaels et al (1982) published a small study of 14 patients who received 10 to 50 mg/week of IV MTX (mean weekly dose of 37 mg) for 7 to 12 weeks. While ESR, joint count and stiffness showed responses to MTX, the study was too small for the differences (change over time from baseline) to reach statistical significance.

Shiroky et al (1988 and 1992) reported 2 small studies using a very high dose MTX therapy by IV infusion (500 mg/m²) with 50 mg/m² of folinic acid rescue therapy every second week, to treat 13 patients with refractory RA who had failed to respond to conventional MTX treatment (low dose oral therapy). Grip strength improved more on the higher MTX dose but the results fell within the expected variance, suggesting the effect was not statistically significant.

7.1.4. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled analyses across the studies has been provided, which is appropriate given the heterogeneity in their design, patient populations and measured outcomes.

7.1.5. Evaluator's conclusions on clinical efficacy for Indication 1

Indication 1: Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAID and one or more disease modifying drugs.

In support of the treatment indication of active RA in adult patients, the sponsor has provided data from 1 sponsor conducted, pivotal phase IV trial (Study MC-MTX.6/RH) as well as 1 literature published cohort (Rau et al, 1991 onwards) as the core evidence of efficacy for the claimed indication. Supportive evidence of efficacy in RA is provided by 2 additional in house studies (MC-MTX.5/RH and MC-MTX.10/RH) and a TGA approved literature search strategy which identified 36 studies involving a total of > 1,000 patients administered parenteral MTX (IM, SC or IV injections) for the treatment of either RA or JIA. The submission meets the requirements of the EMA guideline of relevance, adopted by the TGA, which is CPMP/EWP/556/95 Rev 1 "Points to consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis".

In the pivotal Study MC-MTX.6/RH, a total of 384 subjects were randomised to receive MTX 15 mg/week by either SC injection (n = 194) or as oral therapy (n = 190) for up to 24 weeks. The study also had an early escape provision at 16 weeks if patients failed to demonstrate an ACR20 response, whereby patients receiving SC MTX could have their weekly dose of MTX increased from 15 mg to 20 mg, and those in the oral treatment group were switched to SC MTX 15 mg/week. The choice of comparator treatment in this study is appropriate and consistent with the current standard of care for patients with active RA. The trial design of the pivotal Study MC-MTX.6/RH is appropriate for the claimed treatment indication and the duration of follow-up is sufficient to adequately determine response in RA. The randomisation procedures, strategies to maintain blinding and statistical analysis were

appropriately performed. The trial was performed according to GCP requirements, and the 2 minor protocol amendments did not have a significant impact upon the results.

The population examined in Study MC-MTX.6/RH and the supporting studies are similar in demographics to the subjects that would be treated with RA Australian clinical practice. The vast majority of subjects were middle-aged, Caucasian, and with a female gender predominance. The generalisability of the trial results is satisfactory with some noteworthy caveats. In general, the studies only enrolled patients with moderately to severely active disease, with normal renal and hepatic function, and a relatively low risk of significant infection.

The choice of efficacy endpoints in the pivotal and supporting studies is acceptable, but not ideal. For the pivotal Study MC-MTX.6/RH, the primary efficacy outcome was the percentage of patients in each treatment group who obtained an ACR20 response at 24 weeks. All of the supporting studies used various efficacy endpoints that were relevant at the time of publication such as changes in DAS28 score, remission or response rates, and changes in CS dose requirements. The primary efficacy endpoint in the pivotal MC-MTX.6/RH trial was achieved. At 24 weeks, 78.2% (147 out of 188) of patients in the SC MTX group achieved ACR20 response compared to 70.1% (131 out of 187) of patients in the oral treatment arm, which met the protocol specified, statistical margin of treatment difference ($p = 0.0412$ by CMH test). Therefore, SC MTX demonstrated superiority to oral MTX in the treatment of active RA in adult patients who were naïve to MTX. Various secondary efficacy endpoints in Study MC-MTX.6/RH supported the primary efficacy outcome, such a higher rate of ACR70 response, median DAS28 score change over time and the proportion of patients meeting EULAR response criteria.

The study reported by Rau et al (1991 onwards) was the other trial nominated by the sponsor as being pivotal in this application. The trial was a randomised, double blind, parallel group study of 174 adult patients with early active erosive RA comparing IM MTX 15 mg/week with IM gold sodium thiomalate 50 mg/week (87 subjects in each treatment arm). The key efficacy findings were:

- 40 to 50% reduction in the mean number of tender and swollen joints over 6 to 12 months of treatment (statistically similar in both treatment groups)
- approximately 50% reduction in the duration of morning stiffness and serum inflammatory markers after 6 months of therapy (statistically similar in both treatment groups) and
- X-ray data showing a slowing of radiographic progression (similar to that observed with IM gold therapy) over 12 months.

The literature search identified a total of 36 published studies (some controlled, many uncontrolled, and some abstracts and case reports) in which patients with RA or JIA received low dose parenteral MTX therapy in a regimen similar to that being requested by the sponsor. The data shows that injectable MTX therapy results in clinically important improvements in RA and JIA disease activity (for example ACR 20 or Pedi 30 responses). This data provides further support for the claimed indication. The sponsor has also submitted 2 additional in house studies (MC-MTX.10/RH and MC-MTX.5/RH) which support the utility and tolerability of injectable MTX in adult patients with RA.

Overall, the data in this submission supports the efficacy of SC MTX in the treatment of adult patients with active RA, but there is no evidence that it is superior to the currently available conventional DMARDs. Parenteral MTX offers another treatment strategy in area of medicine with an unmet therapeutic need.

7.2. Indication 2

Indication 2: Symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment.

The clinical efficacy of low dose weekly MTX given by any administration route (orally, SC, IM or IV injection) as a treatment for PSOR is well established, with several oral and injectable products currently listed on the Australian Register of Therapeutic Goods (ARTG). Existing products for this indication prescribe starting doses as low as 10 mg/week, which can subsequently be titrated up to a maximum weekly dose of 50 mg. The proposed dosing recommendations in this application differ from MTX therapies currently approved in Australia by the addition of the SC administration route, reducing the starting dose to 7.5 mg/week and reducing the maximum weekly dose to 25 mg.

In this submission, the clinical efficacy of low dose MTX (7.5 to 30 mg/week) when given by SC injection in adult patients with PSOR is supported by 1 randomised controlled trial (Gumusel et al, 2011) and 2 case series (Zackheim et al, 1992 and Arthur et al, 2001). The application also contains another 9 randomised controlled studies, which provide supporting data for the use of low dose MTX (oral administration; 5 to 30 mg/week) in patients with PSOR. All of the additional supporting studies used a MTX dosing regimen, which incorporates at least some of the key components of the regimen proposed in this submission. In 4 of the 9 studies, a dosing schedule very similar to that proposed in this submission was used, including a low initiation dose (7.5 mg) followed by a gradual escalation in dose, according to response, up to a maximum of 25 mg/week. Two of those 4 studies included a placebo control arm.

7.2.1. Pivotal efficacy studies

7.2.1.1. Study reported by Gumusel et al (2011)

This publication describes a single centre (Turkey), single blind, randomised and controlled trial comparing the efficacy and safety of SC MTX with oral cyclosporine in 37 patients with moderate to severe PSOR with nail involvement. MTX was administered by SC injection as a single 15 mg weekly dose for the first 3 months. For the second 3 months of the trial, the MTX dose was reduced to 10 mg weekly (administered by SC injection). The comparator therapy was oral cyclosporine given in an initial daily dose of 5mg/kg for 3 months (divided into 2 daily doses), reducing to 2.5 to 3.5mg/kg for the second 3 month period. The study was conducted between January and November 2007.

The recruitment population was restricted to subjects aged 25 to 68 years. Patients were required to have moderate to severe PSOR at baseline with associated nail involvement, diagnosed by irregular pitting, salmon coloured patches and onycholysis with erythematous borders. Other eligibility criteria included > 10% BSA involvement with PSOR, baseline PASI score ≥ 10 and a nail psoriasis severity index (NAPSI) score of ≥ 10 . If nail involvement was distressing, or treatment resistant to topical treatment, patients with BSA and PASI score < 10 could also be included. The NAPSI is a validated way of determining severity of nail PSOR affecting the nail bed and nail matrix. It has range of 0 to 80 (each of the 10 nails are scored 0 to 8) with a higher score indicating more severe nail PSOR. The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (< 10%) to six (90 to 100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease).

All patients had previously received phototherapy or systemic or topical treatments. The 2 treatment groups were similar at baseline with respect to demographic and baseline disease characteristics. The mean age of subjects in the MTX group was 42.5 years, and 38.4 years in the cyclosporine arm. About half of all subjects were male with a slightly higher frequency in the MTX group (59% [10 out of 17] versus 47% [8 out of 17]). Patients had long standing PSOR with mean duration of disease being 12.6 years in the MTX arm and 13.6 years in the cyclosporine

group. The mean baseline NAPSİ and PASI scores were 39.1 and 10.7 (respectively) for the MTX group, compared with 42.1 and 12.9 (respectively) for the cyclosporine arm.

Study treatment was open label, but blinded assessors performed the efficacy evaluations. Randomisation was performed by the throw of a dice without subjects knowing their subsequent treatment allocation. Sample size was appropriately calculated using the mean reduction in NAPSİ score as the key efficacy outcome. Efficacy analyses were performed on data from the per protocol population. A total of 37 patients (18 subjects in the MTX group and 19 patients in the cyclosporine arm) were randomised into this trial. One patient discontinued MTX before 24 weeks because of raised serum transaminases, and 2 subjects prematurely cease cyclosporine because of increased serum creatinine levels and increased lipid profiles.

The primary efficacy endpoint was the mean reduction in NAPSİ scores from baseline to 24 weeks. NAPSİ and PASI scores were evaluated every 4 weeks during the study. At the end of the 24 week treatment period, the mean NAPSİ score decreased from 39.1 to 18.3 in the MTX treatment group (43.4% reduction from baseline) and from 42.1 to 25.4 in the cyclosporine arm (37.2% reduction from baseline). The reduction in PASI score over the study period was the major secondary efficacy endpoint. At Week 12, prior to the decrease in MTX dose, the mean PASI score had improved from 10.7 to 4.0 (that is an approximate mean reduction of 63% in PASI score) in the MTX treated cohort. At Week 12, the mean PASI score in the cyclosporine group had improved from 12.9 to 3.8 (that is an approximate mean reduction of 70% in PASI score). At Week 24, the mean PASI score was 6.2 in the MTX treatment group and 5.0 in the cyclosporine arm.

In the MTX group, 10 patients (58.8%) showed mild improvement in the clinical signs of PSOR and 7 (41.1%) demonstrated moderate improvements. In the cyclosporine group, 8 subjects (47%) showed mild clinical improvement using the same response criteria, 7 (41.1%) demonstrated moderate improvement and 1 subject (5.8%) had complete resolution of PSOR. One patient (5.8%) showed no clinical benefit to cyclosporine. The results indicate that SC MTX 10 to 15 mg/week is beneficial in the treatment of patients with moderate to severe PSOR with associated nail involvement.

7.2.1.2. Case series using MTX by SC injection

The publication by Zackheim et al (1992) reports a series of 7 adult patients with PSOR (and 3 with cutaneous T cell lymphoma) treated with SC MTX, and the case series by Arthur et al (2001) details 2 adult patients with psoriatic arthritis (and 6 other patients, including 4 with RA, 1 with polymyositis and 1 with Wegener's vasculitis) treated with SC MTX. In both of the case series, the efficacy and safety of weekly MTX given by the SC route of administration is compared to the same dose of therapy given by IM injection. Treatment allocation in both reports was not randomized or compared prospectively. The publications provide a low quality level of evidence supporting the risk: benefit of SC MTX as it relies on subjective prescriber and patient opinion to assess clinical response and tolerability rather than objective, quantified data obtained in a blinded manner.

Of the 10 patients included in the report by Zackheim, 9 patients received once weekly injections of MTX, while the remaining patient received fortnightly treatment. The dose of MTX ranged from 5 mg to 87.5 mg. Six of the 10 patients had previously received MTX by IM injection prior to the study period. Their current dose was continued by IM injection for 3 weeks while under surveillance, prior to switching to the SC route of administration. No specific efficacy results are reported in this publication.

The report by Arthur of 8 patients treated with SC MTX compared the safety and efficacy of SC MTX to the IM route. The mean age of the patients in this case series was 43 years (range: 36 to 58 years), with 6 male and 2 female subjects. The mean duration of inflammatory arthritis was 11.33 years. The efficacy results indicate no significant difference in pain, fatigue, early

morning stiffness and tender joints for SC versus IM injection. Patients reported preferring the SC route as it was less painful and it enabled self-injection of therapy.

7.2.2. Other efficacy studies (low dose oral MTX in PSOR patients)

7.2.2.1. Study reported by Saurat et al (2008)

This study was a multi-centre, double blind, double dummy, placebo controlled trial comparing the efficacy and safety of adalimumab monotherapy (n = 108) with oral MTX (n = 110) and oral placebo treatment (n = 53) in 271 patients with moderate to severe PSOR. This study has been included in this submission as it evaluates the safety and efficacy of MTX when administered according to the dosage regimen proposed for Metoject, in a patient population reflective of the targeted group, and due to the quality of the study design and analysis. Adalimumab is approved in Australia as a treatment option for moderate to severe, chronic plaque PSOR in adult patients who are candidates for systemic therapy of phototherapy.

The dosage regimen for MTX used in this trial uses a 7.5mg initiation dose, followed by a stepped titration phase over 12 weeks (increasing by 5 mg every 3 weeks), as determined by individual patient efficacy and safety response, with a maximum weekly dose of 25 mg. This posology is identical to the proposed Metoject regimen. However, in this study MTX was administered orally rather than parenterally. At baseline, 80 mg of adalimumab was administered followed by 40 mg every 2 weeks from Week 1 through to 15. The mean weekly dose of MTX in the MTX group was 14.2 mg at Week 4, 16.8 mg at Week 8, 18.8 mg at Week 12 and 19.2 mg at Week 15. In total, 94% (89 out of 95) patients in the MTX group received a weekly dose of > 15 mg at Week 12.

The patient population in this trial was restricted to those ≥ 18 years of age with objective measures of PSOR severity consistent with moderate to severe disease. Patients were required to have a diagnosis of PSOR for at least 12 months prior to inclusion. Eligible patients must be candidates for systemic therapy or phototherapy as well as had active PSOR despite treatment with topical agents. They must have at least 10% BSA affected by PSOR and have a baseline PASI score of ≥ 10 .

Eligible patients were randomized in a 2:2:1 ratio to receive subcutaneous adalimumab, oral MTX or oral placebo. Patients were co-prescribed oral folic acid 5 mg weekly. Matching placebo injection solutions or oral capsules were conjointly administered to conceal treatment allocation.

The 3 treatment groups were similar at baseline with respect to demographic and baseline disease characteristics. The mean age of enrolled subjects was 41.6 years, and 66% of all subjects were male. Patients had long standing PSOR with mean duration of disease being 18.5 years and 86% of subjects had previously received systemic and/or phototherapy for PSOR. The mean baseline PASI score was 19.7 and the mean affected BSA with PSOR was 32.1% for the entire population. About 20% of all subjects had psoriatic arthritis as well as PSOR.

The primary efficacy variable was the proportion of patients achieving at least a 75% reduction in PASI score at Week 16 relative to the baseline score (that is PASI 75 response). At the end of the 16 week treatment period, 35.5% of patients receiving MTX achieved $\geq 75\%$ reduction in their PASI score. This outcome compared to 79.6% in the adalimumab group ($p < 0.001$ for adalimumab versus MTX) and 18.9% in the placebo arm. Of the 64 patients in the MTX group who achieved a $\geq 50\%$ reduction in PASI score at Weeks 8 or 12, and then continued on the 20 mg weekly dose, 37 (57.8%) achieved a PASI 75 response by the end of the 16 week study.

7.2.2.2. Study reported by Reich et al (2011)

This 52 week study was a multi-centre, randomised, double blind, controlled trial designed to evaluate the safety and efficacy of SC briakinumab given every 4 weeks (monoclonal antibody against the p40 molecule shared by interleukin-12 and interleukin-23) and oral MTX in 317 patients with moderate to severe PSOR. Briakinumab is not registered as a treatment for

PSOR in Australia. The sponsor included this study in the submission because the trial was a well-designed study that evaluates the safety and efficacy of MTX when administered according to dose regimen proposed for Metoject in the target patient population. In this study, oral MTX was given as a 5 mg initiation dose, followed by a stepped titration phase up to a maximum dose of 25 mg weekly. MTX was administered orally with oral folate 5 mg weekly. A total of 154 patients were assigned to receive briakinumab and 106 (68.8%) completed through to Week 52 of the study. In the MTX group, 163 were assigned to this treatment at baseline but only 45 (27.6%) completed 52 weeks of therapy.

The patient population was restricted to those ≥ 18 years of age with objective measures of PSOR severity consistent with moderate to severe disease at baseline. Patients were required to be diagnosed with PSOR at least 6 months previously and have stable plaque disease for at least 2 months prior to enrolment. Eligible patients must be candidates for systemic or phototherapy, with at least 10% BSA affected by PSOR, have a baseline PASI score ≥ 12 , as well as a Physician's Global Assessment (PGA) score of ≥ 3 . The 2 treatment groups were similar at baseline with the mean age of enrolled subjects being 44 years, and 70% of all subjects were male. Patients had long standing PSOR with mean duration of disease being 18.9 years and $> 90\%$ of subjects had previously received systemic and/or phototherapy for PSOR. The mean baseline PASI score was 18.2 and the mean affected BSA with PSOR was 26.1% for the entire population.

The primary efficacy endpoints of this trial were the percentage of patients in each of the treatment groups with PASI 75 response at 24 weeks, a score on the PGA of 0 or 1 at Week 24, PASI 75 response at Week 52, and a score on PGA of 0 or 1 at Week 52. At Week 24, 39.9% of MTX patients achieved PASI 75 improvement and 34.4% of subjects had a PGA score of 0 or 1. This compared to 81.8% and 80.5% of patients in the briakinumab arm achieving these endpoints. Both results confirmed the statistical superiority of briakinumab to MTX. At Week 52, 23.9% of MTX patients achieved PASI 75 improvement and 20.2% of subjects had a PGA score of 0 or 1. This compared to 66.2% and 63.0% of patients in the briakinumab arm achieving these endpoints at Week 52. Both results confirmed the statistical superiority of briakinumab to MTX at Week 52.

7.2.2.3. Study reported by Ho et al (2010)

This was a 6 month, randomised, single blind, controlled trial conducted at 2 dermatology hospitals in Hong Kong, which evaluated the safety and efficacy of oral MTX (n = 20 subjects), traditional Chinese medicine (n = 21 patients) and placebo (n = 20 subjects) in adult patients with moderate to severe plaque PSOR. The study was included in this submission because it had a placebo controlled arm, which allows for the evaluation of the efficacy and safety of low dose MTX in PSOR. Traditional Chinese medicine (multiple ingredients) was given as a fixed oral therapy throughout the trial, however MTX was given at an initial dose of 2.5 to 5 mg/week and was slowly up-titrated over 9 weeks to a maximum weekly dose of 30 mg (all received concurrent folic acid 5 mg/week). Randomisation was undertaken but patients in the MTX treatment arm received unblinded therapy.

Patients were required to be diagnosed with PSOR at least 12 months previously and have at least 20% BSA affected by PSOR. Eligible patients must have previously tried topical CS, systemic and phototherapy. The treatment groups were similar at baseline with the mean age of enrolled subjects being 43 years, and 82% (50 out of 61) of all subjects were male. A total of 50 patients completed the study follow-up of 6 months (including 19 of 20 subjects in the MTX group). The rate of discontinuation was highest in the traditional Chinese medicine treatment group (33%; 7 out of 21).

The primary efficacy variable was the mean change from baseline to 6 months in the PASI score for each treatment group. For the patients who completed the study, the mean PASI score at baseline was 22.0 in the MTX group, 18.9 in the traditional Chinese medicine arm and 20.4 in the placebo group. After 6 months of treatment, the mean PASI scores were 5.7, 16.0 and 13.9

(respectively), which is an improvement from baseline of 74%, 15% and 32%, respectively. The difference in response between MTX and both other treatment groups were statistically significant. Secondary efficacy measures supported the primary outcome observation. Patients treated with MTX had greater improvements in PGA scores, PSOR related disability and PASI responses compared to the 2 other treatment groups. The PASI 50 response rate at 6 months was 79% in the MTX group, 14% in the traditional Chinese medicine arm and 24% in the placebo group. The PASI 75 response rate at 6 months was 63% in the MTX group, 0% in the traditional Chinese medicine arm and 18% in the placebo group.

7.2.2.4. Study reported by Akhyani et al (2010)

This publication describes a single centre (Iran), randomized, open label trial comparing the efficacy and safety of oral MTX 7.5 to 20 mg/week with oral mycophenolate mofetil in 38 patients with moderate to severe chronic plaque PSOR. MTX was started at a dose of 7.5 mg (given in 3 divided doses over 24 hours), increased to 15 mg weekly for 3 doses after the first dose, and then was given at a dose of 20 mg/week until Week 12. The up-titration regimen used in this study is similar to that proposed for Metoject, except MTX was given orally in this trial (versus by injection). The comparator therapy was oral mycophenolate mofetil given at a daily dose of 2,000 mg. The study was conducted between 2005 and 2007. To be eligible for inclusion, patients were required to be at least 18 years of age, have a baseline PASI score of at least 10 and were not to have received systemic or phototherapy within 3 months of recruitment. Central randomisation in a 1:1 ratio by computer was employed. No sample size calculation was provided. Treatments were not concealed during the study.

A total of 38 subjects were enrolled (18 in the MTX arm and 20 in the mycophenolate group), and 3 patients in each treatment group did not complete until 12 weeks. Patients enrolled in the MTX group had a mean age of 45.7 years (36% male) and those in the mycophenolate arm had a mean age of 39.9 years (40% male). Of the 15 MTX treated subjects who completed to 12 weeks, only 2 received 20 mg/week of MTX and the majority of patients took 15 mg/week.

Although not clearly stated, the primary efficacy outcome was the mean PASI score in each treatment group (using the per protocol population) at Week 12 compared to baseline. The mean PASI scores at baseline were 17.43 in the mycophenolate group and 16.46 in the MTX cohort. At 12 weeks, the mean PASI scores in each treatment group had decreased to 3.97 in the mycophenolate group and 3.17 in the MTX arm. As a secondary efficacy outcome, 73.3% of patients in the MTX group achieved a PASI 75 response at Week 12 (53.3% of patients sustained this level of response for a further 12 weeks after discontinuing MTX) compared to 58.8% of subjects treated with mycophenolate (33.3% of subjects maintained PASI 75 response at Week 24).

7.2.2.5. Study by Flystrom et al (2008)

This publication reports a multicentre, single blind, randomized controlled trial comparing the efficacy and safety of oral cyclosporine 3 to 5 mg/kg/day with oral MTX 5 to 15 mg/week in the treatment of moderate to severe PSOR over 12 weeks. MTX was initiated at a dose of 7.5 mg/week (given in 3 divided doses over 24 hours), which was gradually increased to 15 mg/week. At Week 12, only 12 of the 31 MTX treated patients still in the study were receiving the maximum weekly MTX dose of 15 mg (6 were still on 5mg or 7.5 mg/week). Central randomisation in a 1:1 ratio by computer was employed. Blinded assessors performed the PASI assessments at baseline, and every 4 weeks for 12 weeks. However, treatments were not concealed to subjects. To be eligible for inclusion, patients were required to be at least 18 years of age, and have a history of insufficient response to topical and/or phototherapy. There was no lower limit of qualifying baseline PASI score in the study protocol.

A total of 84 subjects were enrolled (41 in the MTX arm and 43 in the cyclosporine group), and 4 patients in the MTX group and 12 subjects in the cyclosporine arm did not complete until 12 weeks. Patients enrolled in the MTX group had a mean age of 48 years (76% male) and those in

the cyclosporine arm had a mean age of 45 years (87% male). The mean baseline PASI scores were 15.5 in the cyclosporine group and 14.1 in the MTX cohort. The primary efficacy outcome was the mean PASI score in each treatment group (using the per protocol population) at Week 12 to 3.6 in the cyclosporine group and 5.6 in the MTX arm. As a secondary efficacy outcome, 24% of patients in the MTX group achieved a PASI 75 response at Week 12 compared to 58% of subjects treated with cyclosporine.

7.2.2.6. Study by Heydendael et al (2003)

This study was a multicentre (Netherlands), single blind, randomised controlled trial comparing the efficacy and safety of oral cyclosporine 3 to 5 mg/kg/day with oral MTX 15 to 22.5 mg/week in the treatment of moderate to severe PSOR over 16 weeks. MTX was initiated at a dose of 15 mg/week (given in 3 divided doses over 24 hours), which was increased to 22.5 mg/week at Week 4 if less than PASI 25% improvement was recorded. Only 4 of 44 patients randomized to MTX had their dose escalated above 15 mg/week. Randomisation was done centrally by computer in blocks of 8 subjects. Blinded assessors performed the PASI assessments and treatments were not concealed to subjects. To be eligible for inclusion, patients were required to be at least 18 years of age, have a baseline PASI score of at least 8, and demonstrated insufficient response to topical and/or phototherapy.

A total of 88 subjects were enrolled (44 in each treatment group), and a total of 3 patients (1 in the MTX group and 2 subjects in the cyclosporine arm) did not complete until 16 weeks. Patients enrolled in the MTX group had a mean age of 41.6 years (65% male) and those in the cyclosporine arm had a mean age of 38.3 years (69% male). The mean baseline PASI scores were 14.0 in the cyclosporine group and 13.4 in the MTX cohort. The primary efficacy outcome was the mean percentage reduction in the PASI score for each treatment group (using the per protocol population) at Week 16; 72% reduction for the cyclosporine group and 64% decrease in the MTX arm. As a secondary efficacy outcome, 60% of patients in the MTX group achieved a PASI 75 response at Week 16 compared to 71% of subjects treated with cyclosporine.

7.2.2.7. Study by Fallah Arani et al (2011)

This was 16 week, multicentre, randomised controlled trial comparing the effectiveness and safety of orally administered low dose MTX with fumarates in 54 adult patients with moderate to severe PSOR. Fumarates are not a registered therapy in Australia for PSOR. The sponsor included this publication because the MTX arm had a dosing regimen similar to that proposed for Metoject; initial dose of 5 mg, which was gradually increased up to 15 mg/week by Week 12 and then progressively reduced thereafter until cessation at Week 17. Oral fumarate treatment was commenced at a dose of 30 to 120 mg/day, which was gradually increased up to 720 mg/day by Week 9 and continued at that dose until Week 16. Central randomisation was performed but allocation of study treatment was not concealed. Efficacy assessments were performed at Weeks 4, 12, 16 and 20. Analyses were conducted using data from the intention to treat population.

To be eligible for inclusion, patients were required to be at least 18 years of age with a baseline PASI score of at least 10. A two week washout period as required for those who had received preceding topical therapies and a 4 week washout was required for those who had received previous systemic or phototherapy. A total of 54 subjects were enrolled (27 in each treatment group), and a total of 3 patients (2 in the MTX group and 1 subject in the fumarate arm) did not complete until 12 weeks. Patients enrolled in the MTX group had a mean age of 41 years (59% male) and those in the fumarate arm had a mean age of 43 years (74% male). Patients had long standing PSOR with mean duration of disease being 16.5 years and more than two thirds of all subjects had previously received systemic and/or phototherapy for PSOR (90% had prior topical therapy as well).

The mean baseline PASI scores were 14.7 in the MTX group and 18.0 in the fumarate cohort. The primary efficacy outcome was the difference from baseline to Week 12 in the mean

PASI score. After 12 Weeks of MTX therapy, the mean PASI score was 6.7 (n = 25 evaluable subjects). In the subjects treated with fumarate, the mean PASI score was 10.5 at 12 Weeks. As a secondary efficacy outcome, 24% (6 out of 25) of patients in the MTX group achieved a PASI 75 response at Week 12 compared to 19% (5 out of 26) of subjects treated with fumarate. Three patients (1 in the fumarate group and 2 treated with MTX) achieved PASI 90 response at Week 12. At Week 20, 72% (13 out of 18) of patients in the fumarate group and 53% (10 out of 19) of patients in the MTX arm still had a PASI 50 response, and 39% (7 out of 18) of subjects in the fumarate group and 32% (6 out of 19) of patients in the MTX arm had a PASI 75 response. One patient in the fumarate group and 2 subjects in the MTX cohort maintained PASI 90 response at Week 20. However, once MTX ceased at Week 12, 3 patients in the MTX group showed a worsening in PASI at Week 20 as compared to their baseline assessment versus no patients in the fumarate group demonstrating PSOR rebound.

7.2.2.8. Study by Barker et al (2011)

This trial was an open label, Phase IIIb study conducted in 106 European centres that aimed to evaluate the effectiveness and safety of infliximab (IFX) with orally administered MTX in 868 adults with moderate to severe PSOR who were MTX naive. Patients were centrally randomized 3:1 to receive IV infusions of IFX 5 mg/kg at Weeks 0, 2, 6, 14 and 22 or oral MTX 15 mg/week for the first 6 weeks, increasing to 20 mg/week if less than a 25% improvement in baseline PASI score was not achieved. Subjects not reaching PASI 50 response at 16 weeks, or who were intolerant, could switch treatment groups. The total treatment period was 22 weeks. The use of concomitant folic acid with MTX was recommended but not mandated in the protocol (39% of patients [84 out of 215]). The trial was initiated in September 2005 and completed the last patient assessment in June 2008.

To be eligible for inclusion, patients were required to be between 18 and 75 years of age with moderate to severe PSOR of at least 6 months duration. The baseline PASI score had to be at least 12 and subjects were required to have at least 10% BSA involvement with PSOR. Approximately two-thirds of all subjects had received previous systemic (63%) and/or biological therapy (8%). A total of 868 subjects were enrolled (653 in the IFX and 215 in the MTX treatment group). The 2 treatment groups were well matched for baseline demographic and disease characteristics. Patients enrolled in the MTX group had a mean age of 41.9 years (69% male) and those in the IFX arm had a mean age of 44.1 years (67% male). Patients had long standing PSOR with mean duration of disease of 18 years. The baseline PASI score in both groups was 21 and the baseline %BSA involvement was 31 to 32%.

A total of 541 patients (83% in the IFX group) and 127 subjects (59% in the MTX arm) completed the 22 week treatment phase of the study. Among those who completed the trial, 9 patients in the IFX group and 63 in the MTX arm (29% of 215) switched therapy at 16 weeks. In the MTX group, 54 of 215 patients (25%) increased their weekly dose to 20 mg at Week 6. The primary efficacy endpoint was the rate of PASI 75 response at Week 16. The major secondary efficacy outcomes were the rate of PASI 75 response at 26 weeks, as well as the proportion of subjects achieving PGA score of 0 or 1 at Weeks 16 and 26. All efficacy analyses were performed using the intention to treat population.

The primary efficacy endpoint (rate of PASI 75 response at Week 16) was observed in a statistically higher proportion of subjects in the IFX group (78% [508 out of 653]) compared with MTX (42% [90 out of 215]; $p < 0.001$). At Week 26, 31% (66 out of 215) of patients in the MTX group achieved a PASI 75 response compared to 77% (502 out of 653) in the IFX arm ($p < 0.001$). At Weeks 16 and 26, the percentage of subjects with a PGA score of 0 or 1 was 38% (Week 16) and 28% (Week 26) in the MTX group; and 76% (Week 16) and 73% (Week 26) in the IFX arm. The low PGA score comparison at both time points was statistically in favour of IFX versus MTX.

7.2.2.9. Study by Dogra et al (2012)

This was a 12 week, single centre, prospective, randomized, double blind, parallel group trial conducted in India which aimed to identify the most effective fixed single dose of oral MTX in patients with severe plaque type PSOR. After screening 108 subjects, the study enrolled 60 patients (30 in each cohort) aged between 18 and 62 years, with 1 group randomised to take MTX 10 mg/week and the other arm to receive 25 mg/week. Folic acid 5 mg twice weekly was given to all participants.

Recruited patients were required to have at least 10% BSA involvement with PSOR at baseline. The mean baseline PASI score was 12.6 in both treatment groups. Patients had 23 to 24% mean %BSA affected at baseline. Patients in the MTX 25 mg/week group were slightly younger with a mean age of 35 years (versus 39.4 years in the MTX 10 mg/group), were more likely to be male (86.7% versus 73.3%) and had a shorter mean duration of PSOR (5.7 years versus 8.3 years) than those in the MTX 10 mg/week cohort. Of the 60 enrolled patients, 51 (85%) completed the 12 week study. Four subjects (3 in the MTX 25 mg/week group) withdrew due to side effects and the other 5 non completing subjects either withdrew consent or were lost to follow-up.

The primary efficacy outcome was the difference in the mean PASI scores between the 2 groups from baseline to 12 weeks (intention to treat analysis). The main secondary efficacy variable was the mean number of weeks in each group to achieve a PASI 75 response. In both groups, there was a mean clinical improvement with MTX treatment, which was statistically greater in the 25 mg versus the 10 mg arm. The mean PASI score at 12 weeks was 0.36 in the 25 mg group versus 2.03 in the 10 mg arm ($p = 0.01$). At 12 weeks, 24 patients (92.3% of 26) in the MTX 25 mg group had achieved a PASI 75 response compared with 18 subjects (72% of 25) in the MTX 10 mg cohort ($p > 0.05$). The mean time to achieve PASI 75 response was significantly shorter in the MTX 25 mg group (7.92 weeks) versus the MTX 10 mg arm (9.47 weeks; $p < 0.05$).

7.2.3. Analyses performed across trials (pooled analyses and meta-analyses)

This submission also contained a systematic review published by Montaudie (2011) evaluating the dose and administration route of MTX in PSOR. The review evaluated all studies investigating the use of low dose MTX in adult patients with PSOR published between 1980 and March 2010. The severity of PSOR was not quantified. The authors declare financial support for the publication by a pharmaceutical company. After filtering the searched articles, only 6 randomized controlled trials designed to assess the efficacy of MTX in PSOR were included in the systematic review (4 of which are included in this submission; Saurat [2008], Akhyani [2010], Heydendael [2003] and Flystrom [2008]). None of the PSOR studies have compared the effect of oral versus SC MTX, and they reported various MTX dosing regimens with starting doses between 5 and 10 mg, increasing over a minimum of 4 weeks to a target dose of 15 to 25 mg/week.

7.2.4. Evaluator's conclusions on clinical efficacy for Indication 2

Indication 2: Symptomatic control of severe, recalcitrant, disabling psoriasis in adults, which is not adequately responsive to other forms of treatment.

In support of the proposed indication of symptomatic control of severe PSOR, which is not adequately responding to other forms of treatment (particularly, after topical treatment has failed), the sponsor has provided data from 10 randomised controlled trials, 2 small case series and 1 systematic review. Only 1 of the submitted trials (Gumusel 2011) used a SC dosing regimen of low dose MTX, but many of the other included studies had elements consistent with the proposed Metoject posology, such as the initiation of low dose MTX 5 to 7.5 mg/week with an up titration of dose to 25 mg/week. Although the studies reported different efficacy outcomes, the majority reported PASI 75 response as an outcome. For patients with moderate to severe PSOR, PASI 75 response is considered to be clinically relevant. According to the TGA adopted guideline of relevance (EU guideline – CHMP/EWP/2454/02), PASI 75 response in the target population is appropriate to define efficacy. The current submission for Metoject meets

the requirement of demonstrating sufficient efficacy for low dose MTX therapy compared to placebo in treating the symptomatic manifestations of moderate to severe PSOR, in individuals who have failed to respond to other therapies (mainly, prior topical treatment and varying rates of systemic and/or phototherapy).

The included studies have administered MTX for periods ranging from 12 to 52 weeks, which is a sufficient duration of treatment follow-up to ascertain the effectiveness of MTX in PSOR. Some of the studies reported maintenance of treatment effect after the cessation of therapy, which is an element recommended in the EU guideline. The studies also show that MTX is frequently inferior to biological therapies (for example IFX) but there is a place for MTX (oral and injectable) as a treatment option for adult patients with moderate to severe PSOR.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data.

8.1.1. Pivotal efficacy studies

The sponsor has provided a single pivotal efficacy study (MC-MTX.6/RH) in adult patients with RA, which collected the following safety data:

- General adverse events (AEs) were assessed by adverse event reporting and physical examinations, both of which occurred weekly for the first 4 weeks, every 2 weeks between Weeks 6 and 12 and thereafter every 4 weeks until Week 24.
- Injection Site Reactions (ISR) were an AE of particular interest, assessed at each scheduled visit.
- Laboratory tests, including haematology and biochemistry, as well as urinalysis testing were performed at baseline, weekly for the first 4 weeks, every 2 weeks between Weeks 6 and 12 and thereafter every 4 weeks until Week 24.

All AEs were coded with MedDRA version 8.1 and reported according to their overall incidence in each treatment group using the safety analysis set, which included all patients who received at least 1 dose of study medication.

8.1.2. Pivotal studies that assessed safety as a primary outcome

There were no studies in this submission that assessed safety as the primary outcome.

8.1.3. Non-pivotal efficacy studies

The non-pivotal efficacy studies providing safety data are as follows:

- Study MC-MTX.10/RH provided data on 131 adult patients with RA treated with SC MTX 20 mg/week for up to 6 weeks (up to 4 of the 6 injections were self-administered by the patient).
- Study MC-MTX.5/RH provided data on 87 adult patients with RA treated with SC MTX 15 to 25 mg/week for up to 6 weeks (the first 2 weekly injections were done by the investigator and the last 4 injections were done by the patient under supervision).
- Population cohort published in various journals (mainly Rau et al, 1997) provided data over 12 months of follow-up in 184 subjects (87 subjects in each treatment group) with RA treated with either IM MTX or IM gold.

- Both the RA and PSOR literature based submissions provided safety data as well on general AEs, serious AEs and laboratory abnormalities.

8.1.4. Other studies evaluable for safety only

Not applicable.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable in this submission.

8.3. Patient exposure

The safety of low dose orally administered MTX therapy is well established in RA and PSOR, as is the relative safety of IM and IV injections of MTX in PSOR. The currently available parenteral formulations of MTX in Australia are of the 10 mg/mL or 25 mg/mL concentration. Safety considerations relevant to this submission is the impact on of the proposed 50 mg/mL concentration for Metoject, and the use of the SC route of administration in addition to the IM and IV injection routes in adult patients with active RA.

The sponsor has provided 3 in house studies in this submission of particular relevance. Two of the studies compared the safety of the proposed 50 mg/mL injection with the 10 mg/mL injection (Studies MC-MTX.5/RH and MC-MTX.10/RH). These 2 trials recruited a total of 223 patients, who received up to 6 weeks of SC MTX therapy 15 to 20 mg/week. The sponsor has also provided a third study (MC-MTX.6/RH), which compared the safety of the MTX 10 mg/mL injection with orally administered MTX. This trial followed a total of 384 patients for 6 months (194 in the SC group and 190 subjects in the oral arm).

For the total RA dataset (that is combining the sponsor studies with the literature based submission trials), the overall extent of MTX exposure can be divided into the 3 route of administration:

- IM Injection; based on the reported mean doses and the numbers of patients recruited in the studies, 78% of patients received MTX 5 to 20 mg/week, with 71% of these patients being treated for 6 to 12 months. A total of 235 patients (21% of all patients) were followed beyond 2 years.
- SC Injection; 73% of patients received MTX 10 to 20 mg/week for 6 to 12 months. No analysis of outcomes beyond 12 months of therapy is available in this treatment subgroup.
- IV Injection; 52% of patients received MTX 5 to 15 mg/week for a total of 12 weeks with the remainder receiving 30 to 45 mg/week for 4 to 12 weeks. A total of 55% of patients have been followed up to 24 weeks.

The PSOR safety dataset (based on the publications in the LBS) represent a total of 343.3 patient years of exposure to MTX in weekly doses ranging from 2.5 to 30 mg, for durations of follow-up ranging from 12 to 52 weeks. In the submitted trials, MTX was administered by both the SC and oral routes to adult subjects with moderate to severe PSOR.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, no significant difference over 24 weeks of treatment follow-up was observed in the overall incidence of patients with any documented AE; 66.3% (128 out of 193) in the SC group and 61.7% (116 out of 188) in the oral arm. In both cohorts, gastrointestinal disorders were the most common type of AE by SOC (System Organ Class) affecting 42% of all subjects (160 out of 381). This result is within expectations as gastrointestinal complaints are a common side effect of MTX (by any route of administration). Gastrointestinal AEs affected a slightly proportion of subjects in the SC group (45.6%; 88 out of 193) compared to the oral arm (38.3%; 72 out of 188), but this was not statistically significant ($p = 0.149$). All other types of AEs by SOC occurred at a similar frequency in each of the MTX treatment groups. Infections were the second most frequently occurring AE at an incidence of 19.7% in each of the treatment group. Abnormal investigation results was the third most frequently reported AE affecting 17.1% (33 out of 193) of subjects in the SC group and 18.6% (35 out of 188) of patients in the oral MTX arm. In this SOC category, abnormal liver function tests comprised 12% of AEs in total (at a similar frequency in both groups), which is to be expected with MTX. Other common types of AEs by SOC were metabolism and nutrition disorders (13.4%, mainly, anorexia), skin and subcutaneous disorders (11.1%) and nervous system disorders (8.1%, mainly, headache). The majority of gastrointestinal AEs (abdominal pain, diarrhoea, nausea, vomiting, stomatitis and dyspepsia) as well as anorexia were reported in the first 4 weeks of the trial, and then reduced in frequency thereafter up until 24 weeks.

Approximately 40% of all AEs in both groups were rated as moderate in severity, and the only individual type of AE of moderate severity different between the 2 treatment groups was diarrhoea (higher in the oral group [6.9%; 13 out of 188] compared to the SC arm [2.6%; 5 out of 193]; $p < 0.05$); refer to Table 11. Moderate severity anorexia was reported at a higher incidence in the SC group (7.3%; 14 out of 193) versus 3.2% (6 out of 188) in the oral arm, but this difference did not reach statistical significance ($p = 0.076$).

Table 9: Summary of adverse events during Study MC-MTX.6/RH (safety analysis set)

	No. (%) of patients receiving SC MTX (n = 193)	No. (%) of patients receiving oral MTX (n = 188)
Adverse events		
Any adverse event	128 (66)	116 (62)
At least a moderate adverse event	79 (41)	77 (41)
Adverse event possibly related to study drug	102 (53)	90 (48)
Serious adverse event	11 (5.7)	8 (4.3)
Adverse event leading to withdrawal	18 (9.3)	8 (4.3)
At least moderate adverse events reported at a $\geq 3\%$ incidence		
Gastrointestinal		
Abdominal pain	17 (8.8)	20 (10.6)
Diarrhea	5 (2.6)	13 (6.9)
Dyspepsia	13 (6.7)	11 (5.9)
Loss of appetite	14 (7.3)	6 (3.2)
Nausea	32 (16.6)	23 (12.2)
Stomatitis	6 (3.1)	7 (3.7)
Vomiting	7 (3.6)	6 (3.2)
Increased alanine aminotransferase	3 (1.6)	8 (4.3)
Bronchitis	4 (2.1)	7 (3.7)
Headache	4 (2.1)	8 (4.3)
Nasopharyngitis	9 (4.7)	10 (5.3)

* Methotrexate (MTX) was administered subcutaneously (SC) or orally.

Between Weeks 16 and 24, overall AEs were reported at a slightly higher incidence in the SC 20 mg group versus the SC 15 mg cohort, with the difference attributable to an increased

frequency of gastrointestinal AEs (mainly abdominal pain in the higher SC MTX dose group; 22.7% [5 out of 22] in the 20 mg dose group versus 10.0% [3 out of 30] in the 15 mg dose arm).

Published cohort of Rau et al (1997)

In this adult RA treatment cohort, AEs were reported in 66.7% (58 out of 87) of patients in the IM MTX group and 83.9% (73 out of 87) of subjects in the IM gold arm. Most of the AEs were of mild severity and self-limiting. Table 12 (extract from paper by Rau et al, 1997) provides a summary of the overall AEs reported in this cohort in the first 12 months of therapy. The most frequently observed AEs were elevations of serum transaminases, nausea, hair loss and stomatitis in the MTX group compared with rash, stomatitis, proteinuria and nausea in the IM gold arm. In both groups, a higher incidence of AEs was reported in the first 6 months of treatment versus the second 6 months of treatment follow-up.

Table 10: Summary of adverse events in Rau et al safety cohort (published 1997)

Side-effect	MTX (n = 87)	GSTM (n = 87)
Transaminase increase (<3 times normal)	30	8
Nausea	18	8
Hair loss	12	7
Stomatitis	6	19
Rash	3	48
Cough/dyspnoea	4	3
Leucocytopenia (<3000/m)	2	0
Eosinophilia (>10%)	6	9
Thrombocytopenia (<100 000)	0	2
Proteinuria	0	9

GSTM=Gold Sodium Thiomalate

8.4.1.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

In Study MC-MTX.10/RH, AEs were reported in 19.1% (25 out of 131) of subjects included in the safety dataset. The proportion of patients reporting AEs was similar in both of the treatment groups; 10.7% (14 out of 131) with the 10 mg/mL injection and 11.5% (15 out of 131) with the MTX 50 mg/mL injection. The most frequent types of AEs were gastrointestinal disorders (6.0%) followed by abnormal investigation results (3.8%) and administration site conditions (3.1%). All but 3 of the recorded AEs were of mild or moderate severity.

A total of 10 AEs were reported among the 82 subjects who received MTX in Study MC-MTX.5/RH. The most frequently reported AE was nausea (5 AEs).

RA Literature

The studies included in the RA LBS reported on 1,147 patients receiving 7.5 to 30 mg/week of MTX by IM injections, 850 receiving 5 to 45 mg/week of MTX by SC injection and 80 patients receiving 7.5 mg/week 500 mg/m²/week of MTX by IV bolus or a 1 hour infusion. From the control arms of these studies, 750 patients received oral MTX as well other active treatments (mainly, IM gold injections). The safety data from these control therapies have been used for comparison purposes.

From the published RA studies, the SC route of administration appears to be consistently associated with a higher frequency of gastrointestinal side effects relative to other routes of administration (36% incidence with SC MTX versus 11% with IM therapy and 13% with oral MTX). The published trials report a similar incidence and type of gastrointestinal AEs from the SC route to that observed in Study MC-MTX.6/RH. There is a range of frequencies across the

studies for gastrointestinal AEs with oral MTX therapy, ranging from 6 to 18% in JIA patients and 28 to 38% in adult RA subjects. The pivotal sponsor study MC-MTX.6/RH found no statistically significant difference between gastrointestinal AEs in patients receiving oral versus SC MTX (38.3% versus 45.6%, respectively).

Studies using IM MTX administration reported more renal events (proteinuria and increased serum creatinine). Relative to other routes of administration, IV MTX therapy appears to be associated with increased incidence of skin AEs (mainly alopecia and rash, at a total incidence of 20% in 3 small studies) and metabolic effects (anorexia).

Comparison of the AE profile by dose for all parenteral routes combined showed the expected relatively higher frequency of gastrointestinal, respiratory, skin and nervous system related AEs. Nervous system AEs consisted mainly of headache and dizziness (non-specific CNS symptoms). The small numbers of patients receiving high doses (> 30 mg/week of MTX) may have inflated the apparent frequencies of these AEs (affecting 11 out of 62 patients in 3 studies). The skin related AEs were hair loss, rash and sweats (affecting a total of 12% of 35 patients in 2 small studies). There were no consistent trends with increasing dose and the profile of AEs in the sponsor conducted studies.

The active control groups used in the published studies were either oral MTX or IM gold injections. The placebo controlled studies were small and short term (total of 29 patients for 6 weeks) and do not provide sufficient information on safety for reliable comparison. Comparison of the AE profiles show that the frequency of the gastrointestinal AEs from SC MTX is also higher than from IM gold (36% versus 13%, respectively). However, gold injections appear to produce more skin reactions (hair loss, exanthema and rash; total 26%) than either oral or SC MTX (9% and 5%, respectively).

PSOR Literature

There is some limitation to the reported PSOR data involving AEs as not all trials tabulated their AE experience and in other studies, only AEs with an incidence > 5% were reported. In the well-controlled studies like Saurat et al (2008) and Reich et al (2011), the overall incidence of AEs in MTX treated subjects was approximately 85%, which was comparable to that reported in the biological therapy arms. The profile of most common AE types in the PSOR population is similar to that observed in the adult RA population. The most common types of AEs are gastrointestinal disorders (mainly, diarrhoea, nausea and abdominal pain), non-serious infections (mainly nasopharyngitis and viral infections), nervous system related (mainly headache) and musculoskeletal (non-specific arthralgia and myalgia). In the PSOR population, there is low incidence of reported pruritus (approximately 2%) which is less common in the RA group. ISRs are an uncommonly reported AE (< 1.5%) in the PSOR population receiving parenteral MTX.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, the majority of recorded AEs were rated by the site investigators as being at least possibly related to MTX (52.8% [102 out of 193] for the SC group and 47.9% [90 out of 188] for the oral arm). Drug related anorexia and nausea were more frequent in the SC group (anorexia 15.5% and nausea 33.7%) than in the oral group (anorexia 8.5% and nausea 23.9%). Both of these individual types of drug related AEs were statistically higher ($p = 0.03$) with the SC route of administration versus oral taking of MTX.

ISRs were an AE of special interest in Study MC-MTX.6/RH. Patients in the oral MTX treatment group were given placebo injections to maintain the blind. The overall incidence of ISRs was similar (6.5% to 7.1%) between the 2 treatment groups over the 24 week trial. ISRs of swelling, haematoma and pain were similar between the 2 treatment groups, but redness and itching was

documented to occur at a slightly higher frequency with MTX versus placebo injections. All but a few of the ISRs were rated as either mild or moderate in severity, and no patient withdrew from the study because of an ISR.

Published cohort of Rau et al (1997)

The publications reported all treatment emergent AEs (as detailed above) and did not report information as to whether or not the investigators considered the AEs to be drug related or not.

8.4.2.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

Treatment related AEs were reported in a total of 18.3% (24 out of 131) of patients involved in Study MC-MTX.10 out of RH. In each treatment sequence, 10.7% (14 out of 131) of subjects recorded treatment related AEs. Like the overall AE profile, gastrointestinal disorders (mainly nausea and diarrhoea) and abnormal investigations (mainly abnormal serum transaminases) were the most frequent types of drug related AEs. Only two drug related AEs in 2 patients were rated as being of severe intensity. In Study MC-MTX.5/RH, 5 of the 10 AEs were considered to be drug related the most common of which was nausea.

RA and PSOR Literature

The published trials didn't specifically present AE data by relationship to MTX. The majority of studies reported treatment emergent AEs, which has already been presented in this report.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

Study MC-MTX.6/RH

No death was recorded in Study MC-MTX.6/RH. A total of 22 serious AEs (SAE) were reported in the trial affecting 19 subjects. The overall incidence of SAEs was similar in both treatment groups: 5.7% (11 out of 193) in the SC group and 4.3% (8 out of 188) in the oral MTX arm. The most frequently reported SAEs belonged to the SOC of cardiac disorders (2 patients in each treatment group: 1 patient in each group with coronary ischaemia and 1 patient in each arm with cardiac arrhythmia) and those requiring surgical procedures (affecting 4 patients in the oral therapy group only: hip arthroplasty, ruptured tendon repair, pelvic floor operation and removal of benign thyroid nodule). Only 1 SAE was considered by the investigator to be at least possibly related to MTX. A 74 year old female patient being treated with SC MTX 15 mg/week developed pneumonitis at Week 11 to 12, which is a rare but known potential side effect of MTX, but can also be also due to RA itself or infection. One patient in the SC MTX group was recorded as suffering from deep vein thrombosis, but this SAE was not considered to be drug related. Another patient in the SC treatment group was identified as having prostate cancer and another subject in the same cohort had a stroke (all considered to be not related to MTX).

Published cohort of Rau et al (1997)

Three deaths were recorded in the first 12 months of this treatment. All deaths occurred in MTX treated subjects. A 61 year old female with a past history of hypertension died from brain stem bleeding 4 months into MTX treatment. Two male patients (57 and 59 years old) died from acute myocardial infarction 4 and 5 months after commencing IM MTX. One of those subjects had no history of cardiac disease but the other patient had a background history of significant cardiac arrhythmia. Overall, 2 AEs in the MTX group and 13 in the IM gold arm were graded as being of grade III or IV severity (according to WHO classification of toxicity criteria).

8.4.3.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

There were no fatalities or malignancies reported in either of these studies. One SAE was reported in Study MC-MTX.5/RH. This involved a patient stumbling over his doormat, suffering a scalp laceration and requiring overnight observation in a local hospital. The SAE was appropriately assessed as not being drug related. A total of 3 SAEs were reported in Study MC-MTX.10/RH. One patient (62 year old male) experienced a cheekbone fracture, which was considered to be unrelated to MTX. Another subject (58 year old female) developed left ear mastoiditis 28 days after receiving her last study injection of MTX and this SAE was evaluated as being possibly related due to the immunosuppressive potential of MTX. The third SAE case (51 year old female) involved non-specific back pain requiring hospital admission, which was considered as unlikely to be related to MTX.

RA Literature

No fatalities have been reported in the studies whereby SC and IV MTX were investigated, but the majority of these trials were of < 6 months duration (apart from 1 JIA study of 12 months duration). A total of 35 deaths have been reported in the IM MTX studies (including 3 deaths in the Rau et al cohort), which involve significant longer durations of treatment follow-up (1 to 3 years). The body systems most frequently associated with the suspected cause of death are cardiac (12 deaths), respiratory (6 fatalities), vascular (6 deaths), neoplasms (2 fatalities) and infection (1 death). Patients with active RA are at higher risk of atherosclerotic cardiovascular death. There are 6 reports of cancer in the published literature (2 cases each of acute leukaemia and colon cancer; and single cases of gastric neoplasm and oropharyngeal carcinoma). None of the authors specifically attributed death or malignancy to MTX, and with often the lack of control arms it is difficult to ascertain the precise risk of death and malignancy with parenteral MTX. However, the figures do not appear to indicate a higher risk of those events with parenteral versus oral MTX use in patients with RA.

PSOR literature

A total of 18 SAEs were noted in patients receiving MTX in the published PSOR trials, including 1 death due to oesophageal rupture. The report by Reich et al (2011) reported 12 SAEs in 10 MTX treated patients (6.1% of 163) compared with 19 SAEs in 14 briakinumab treated subjects (9.1% of 154). These figures included 6 infection related SAEs in the briakinumab group and 3 infection related SAEs in the MTX arm. The 10 MTX treated patients with SAEs included 2 episodes of diverticulitis and abnormal liver function tests; and single cases of oesophageal rupture (resulting in death), intestinal polyp, sacroiliitis, erythrodermic PSOR, vertigo, angioedema, urticaria and intermittent claudication. Barker et al (2011) reported 4 infection related SAEs in 211 MTX treated patients. The study by Saurat et al (2008) reported 2 SAEs in MTX treated subjects, including 1 case of hepatitis.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, the rate of permanent discontinuation was higher in patients in the SC group (9.3%; 18 out of 193) compared to subjects in the oral treatment group (4.3%; 8 out of 188). In the SC treatment group, the most common AEs leading to withdrawal were gastro-intestinal disorders (4.7% [9 out of 193]: 3 with diarrhoea, 9 with nausea, 4 with abdominal pain, 2 with vomiting and 1 with stomatitis), infections (1.6% [3 out of 193]: single cases each of bronchitis, nasopharyngitis and gastrointestinal fungal infection), nutrition disorders (2.1% [4 out of 193]: all cases of anorexia) and psychiatric disorders (1.6% [3 out of 193]: single cases each of anxiety, confusion and sleep disorder). In the oral MTX treatment arm, the most common AEs resulting in treatment discontinuation were gastro-intestinal disorders (1.6%

[3 out of 188]; 3 cases of nausea, 1 with vomiting, 2 cases of diarrhoea and 1 with abdominal pain) and nutrition disorders (1.6% [3 out of 188]; all with anorexia). The data relating to treatment discontinuations due to AEs shows a higher incidence of gastro-intestinal disorders in the SC versus oral group, mainly due to a greater number of patients who reported nausea (9 in the SC group versus 3 in the oral arm).

Published cohort of Rau et al (1997)

During the first 6 months of this treatment group, 4 patients (4.6% of 87) in the MTX group and 26 subjects (29.9% of 87) in the IM gold arm withdrew from therapy. In the second months of treatment follow-up, an additional 2 MTX treated subjects and 6 IM gold treated patients discontinued. In both groups, it is unclear as to why patients permanently discontinued therapy.

8.4.4.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

Three subjects discontinued prematurely from Study MC-MTX.10/RH due to AEs. These included single cases of coughing, dizziness and nausea with dry mucosa and pain. All of these AEs were considered to be non-serious and possibly related to MTX. Only 1 of 82 subjects enrolled into Study MC-MTX.5/RH withdrew prematurely and this was not related to an AE.

RA literature

The included studies reported widely varying rates of patient discontinuation from parenteral MTX. Most of the IM MTX studies reported rates of withdrawal between 9 to 35% with MTX < 20 mg/week. In the IM MTX trials where IM gold was the comparator treatment, the rate of discontinuation from IM gold therapy was consistently higher (28 to 59%) than with IM MTX. In the IV MTX trials, the rate of subject discontinuation varied between 30 to 37.5%. In the SC MTX trials, the rate of subject discontinuation from therapy varied between 9 to 18%, and where oral MTX was the comparator therapy, the rate of discontinuation from oral MTX was generally lower than SC MTX.

PSOR literature

Overall, the rate of discontinuation from MTX due to AEs was low in the controlled PSOR studies at a median rate of 5% over the first 6 months of therapy (range: 0 to 28%). In comparison, the proportion of subjects withdrawing in active control treated subjects was 1 to 13% and for placebo control trials was 2%. Discontinuations from MTX in PSOR patients (like RA subjects) were mainly due to raised serum transaminases or gastrointestinal AEs such as nausea, vomiting and abdominal pain.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

Study MC-MTX.6/RH

During the course of Study MC-MTX.6/RH, the number of patients who developed increased AST and/or ALT values reached 21.3% (35 out of 164) in the SC group and 22.5% (38 out of 169) in the oral MTX treatment arm. A small percentage of individuals recorded at least 1 ALT reading > x 2 ULN during the 24 week study: 1.6% (3 out of 193) of subjects in the SC group and 4.3% (8 out of 188) of patients in the oral treatment arm. Mean ALT and AST results increased during the study in both groups. In the SC group, the mean ALT level increased from 0.60 to 0.82 Upper Limit of Normal (ULN) and in the oral arm from 0.63 to 0.78 the ULN. A similar pattern was observed for mean AST values. In the SC group, the mean AST level increased from 0.75 to 0.89 the ULN and in the oral arm from 0.78 to 0.85 the ULN. The observed incidence and pattern

of mean and abnormal transaminases is to be expected with low dose MTX use in patients with RA. In addition, low dose MTX treatment had no influence on GGT or alkaline phosphatase values (expected observation); mean change or the frequency of significantly abnormal values.

Published cohort of Rau et al (1997)

Up until 12 months of treatment follow-up, a total of 30 patients (34.5% of 87) in the IM MTX group and 8 subjects (9.2% of 87) in the IM gold arm developed increases in serum transaminases up to 3 x ULN. In the MTX group, 8 of these laboratory abnormalities were classified as grade III severity and 4 were deemed as grade IV (according to WHO classification of toxicity criteria). In the IM gold group, no abnormalities of liver function tests were classified as being of grade III or IV severity.

8.5.1.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

In Study MC-MTX.5/RH, no individual subject developed a significant deviation in liver function tests over the course of the study. A total 4 subjects in Study MC-MTX.10/RH were recorded as developing a new post-baseline increase in serum AST during this trial but none of those abnormalities were considered to be clinically significant.

RA literature

Nearly all of the RA studies reported elevations in 1 or more hepatic transaminases, but often the extent of these changes was not specified. There were some references to these changes being transient, and rarely was the abnormality sufficient to require withdrawal of the patient from the trial. Overall, a total of 8 to 14% of patients receiving parenteral MTX reported liver enzyme abnormalities compared to approximately 9% associated with oral MTX use and approximately 5% with adult patients receiving IM gold treatment.

In 1 study published by Hoffmeister et al (1983) the results of serial liver biopsies from 34 RA patients treated with MTX for periods ranging from 3 to 15 years was reported. Fifty of the 67 biopsy specimens in this cohort were normal. The remaining 17 liver biopsies showed mild to moderate fatty changes, 7 revealed a mild increase in portal fibrosis and in 5 specimens there was a slight variation in size of hepatocyte nuclei. No specimens showed evidence of necrosis or cirrhosis. None of the patients whose specimens showed increased fibrosis had prior normal biopsies. The minor histologic changes found in liver biopsies were stated to be also commonly found in RA patients not treated with MTX.

PSOR literature

A total of 63 reports of elevated or abnormal liver function tests (mainly raised serum transaminases) were listed in the PSOR study reports. This is consistent with observations in the adult RA population and the known toxicity of MTX (given by any route of administration). In a small percentage of patients, there were confounding factors for hepatotoxicity such as obesity, alcohol consumption, Type 2 diabetes mellitus or chronic infection with hepatitis B or C virus. Most of the abnormalities of liver function tests involved < x 3 ULN rises in serum transaminases which had a mean onset 5 to 6 weeks after commencing MTX and returned to normal within 4 to 8 weeks of ceasing MTX. Often abnormalities of liver function tests were asymptomatic, although some patients did complain of concurrent non-specific symptoms such as fatigue and nausea. In < 10% of subjects with abnormal liver function tests, MTX was permanently discontinued.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, mean serum creatinine levels remained almost constant during the trial with no treatment related difference (SC versus oral MTX) being observed. Serum creatinine levels in the SC group were 0.67 ULN at baseline and were 0.69 ULN at Week 24. In the Oral MTX group, the mean serum creatinine levels were 0.71 ULN at baseline and 0.72 ULN at Week 24. No individual subjects developed an acute deterioration in renal function during the 24 week study.

Published cohort of Rau et al (1997)

No patients in the MTX treatment group were reported to have abnormalities of kidney function or upon urinalysis. However, in the IM gold treatment group, 9 of 87 (10.3%) patients developed proteinuria within the first 12 months, which is an expected toxicity finding of parenteral gold.

8.5.2.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

In Study MC-MTX.10/RH, no individual subject developed a significant abnormality in kidney function over the course of the trial. One subject in Study MC-MTX.5/RH was recorded as developing proteinuria but with a normal serum creatinine. Another subject with pre-existing diabetes mellitus had glucose detected in their urine at the final study visit. A further patient had a significant increased number of erythrocytes in urine at visit 1, which had resolved spontaneously at the end of the study.

RA Literature

The published studies contain sporadic reports of increases in serum creatinine and/or proteinuria affecting up to 4% of all patients receiving MTX (from 7 studies), which is an AE incidence lower than the most frequently reported active comparator therapy, IM gold (up to 9% of treated developing kidney problems).

PSOR literature

No specific concerns about abnormalities of renal function were noted in MTX treated subjects in the PSOR literature. In contrast, alternative active treatments (in particular, CsA) were associated with elevated serum creatinine levels, occasionally requiring discontinuation from therapy (Flystrom et al, 2008).

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

Study MC-MTX.6/RH

There were no significant differences between the 2 treatment groups for the number of patients with out of range results for other clinical chemistry parameters (for example phosphate) that were tested. In addition, the pattern of change from baseline in the mean biochemical values was similar for both treatment groups.

Published cohort of Rau et al (1997)

No specific information on this safety endpoint was reported.

8.5.3.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

Mean biochemistry parameter changes were minor and no clinical relevant changes were observed in any clinical chemistry test.

RA and PSOR literature

No specific concerns relating to blood chemistry abnormalities have been identified in the published literature.

8.5.4. Haematology

8.5.4.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, no differences were observed between the 2 treatment groups for the number of patients with abnormal haematological results. No particular individual subjects developed significantly abnormal haematology such as leukopenia or thrombocytopenia. In addition, the pattern of change in mean haematology values was similar for both treatment groups.

Published cohort of Rau et al (1997)

Up to 12 months of treatment follow-up, 2 patients in the MTX treatment arm developed leukopenia (white cell count $< 3 \times 10^9/L$) and 2 subjects in the IM gold group developed thrombocytopenia (platelet count $< 100 \times 10^9/L$). In addition, 6 patients in the IM MTX group and 9 subjects in the IM gold arm developed peripheral blood eosinophilia ($> 10\%$ of total white cell count), which is not unexpected in the gold treatment group.

8.5.4.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

In both trials, absolute mean changes from baseline to the study end were small and tended to decrease slightly for all haematology parameters except for minor changes in monocyte and basophil counts. One patient in Study MC-MTX.5/RH developed bicytopenia (leukopenia and thrombocytopenia), which resolved at study conclusion.

RA literature

A total of 10 studies in the RA LBS have reported leukopenia and thrombocytopenia as side effects occurring in subjects taking MTX. This is an uncommon but known AE with low dose MTX use. In general, the severity of the cytopenia was not accurately presented but some of the reports state there was associated fevers and/or infections, suggest significant leukopenia had probably occurred at the low doses of MTX administered in RA therapy. Overall, the frequency of abnormal haematology results was low at 0.8 to 3% for parenteral MTX compared to 0.7% for oral MTX and up to 9% with IM gold therapy.

PSOR literature

There were 2 reports of significant haematological abnormalities with MTX use in the PSOR literature. This included 1 case each of transient thrombocytopenia (Fallah Arani et al, 2011) and anaemia (Akhyani et al, 2010).

8.5.5. Vital signs

8.5.5.1. Pivotal studies

Study MC-MTX.6/RH

In Study MC-MTX.6/RH, no clinically relevant mean changes in vital signs (pulse, blood pressure or weight) were reported in either treatment group over 24 weeks of treatment follow-up.

Published cohort of Rau et al (1997)

No specific information on this safety endpoint was reported.

8.5.5.2. Other studies

Studies MC-MTX.10/RH and MC-MTX.5/RH

No significant changes in vital signs were recorded in either of these studies.

RA and PSOR literature

In general, no specific information on this safety endpoint was reported.

8.6. Post-marketing experience

The most recent PSUR (covering data collected between 2008 and 2012) identifies a total of 185 case reports of AEs with parenteral MTX therapy in treating patients with RA, polyarthritic forms of JIA or PSOR. The estimated exposure to Metoject 50 mg/ml from sales data has been calculated as 329,879 patient years of treatment (assumes average weekly MTX dose of 17.5 mg). A total of 60 AE reports have also been received for off label treatment indications including inflammatory bowel disease, SLE, dermatomyositis, Wegener's granulomatosis, pemphigoid, ankylosing spondylitis and temporal arteritis. The post-marketing experience with Metoject did not identify any new safety concerns with low dose MTX use, or an increased frequency of known side effects with parenteral therapy. In particular, the expected incidence of malignancies (solid cancers and lymphoproliferative disorders) appears to be within expectations for the target treatment populations. Injection site reactions from either SC or IM injection of MTX appears to be an uncommon AE affecting < 1% of subjects and rarely resulting in treatment discontinuation. However, lipoatrophy at the injection site does appear to be more common in women and when injections are given in a thigh location.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

Increased serum transaminases are a relatively laboratory abnormality associated with low dose MTX therapy in adult patients with RA or PSOR. The liver function test abnormalities are usually transient and asymptomatic. Chronic hepatotoxicity (including fatty change, periportal fibrosis and cirrhosis) has been associated with chronic cumulative use of low dose MTX in the requested treatment indications in this submission. Parenteral MTX does not appear to have an increased risk of hepatotoxicity compared with chronic low dose oral MTX therapy. The proposed PI for Metoject contains information on the risk of liver toxicity associated with MTX and the risk factors for its development. This report contains details of the incidence and pattern of abnormal liver function tests observed with low dose parenteral MTX in adult patients with RA and PSOR.

8.7.2. Haematological toxicity

Myelosuppression including neutropenia, thrombocytopenia and anaemia are an uncommon but significant toxicity associated with low dose MTX therapy (given by any route of administration). This is reflected in the current submission and the parenteral administration of

MTX does not appear to change the risk of significant haematological toxicity compared to administration of same dose MTX therapy by oral ingestion. The risks of low dose MTX with respect to myelosuppression are contained in the proposed Metoject PI.

8.7.3. Risk of infection

Low dose MTX treatment is associated with an increased risk of severe or serious infection, including opportunistic infection, and the current submission for parenteral MTX is consistent with expectations (incidence and pattern of serious infection) for low dose weekly therapy in the target treatment populations. More details about infection related SAEs is provided in this report.

8.7.4. Injection site reactions

The submission contained data showing a similar incidence of ISRs (6.5 to 7.1% of subjects) in the 2 treatment groups (SC MTX versus oral MTX with placebo injections) in the pivotal RA Study MC-MTX.6/RH. The supporting literature and trials in both RA and PSOR patients report a low incidence of ISRs, typically rated as mild in severity, and rarely resulting in a patient having to cease MTX.

8.8. Other safety issues

8.8.1. Safety in special populations

Low dose MTX therapy (by any route of administration) should be avoided in any pregnant or lactating women. Older patients (> 65 years of age) do not appear to be at an increased risk of toxicity from low dose weekly therapy if their renal and hepatic function is normal, and their body folate stores are replete. The Metoject PI contains the same information as other MTX approved medicines on this issue.

8.8.2. Safety related to drug-drug interactions and other interactions

Low dose MTX treatment has been associated with many potential drug-drug interactions including those with probenecid, various antimicrobial drugs (such as ciprofloxacin, doxycycline and trimethoprim with sulfamethoxazole), folic acid and proton pump inhibitors. Although not specifically examined for in the Metoject clinical development program, the reported incidence of drug-drug interactions was low and would not be expected to occur at a higher incidence if patients receive parenteral versus oral low dose weekly MTX for RA or PSOR.

8.9. Evaluator's overall conclusions on clinical safety

The sponsor did not include an integrated analysis of safety data in this submission, which is appropriate because of the heterogeneity of the studied populations and different methods of data collection. The total clinical safety dataset for the RA consists of a patient exposure of 1,147 patients who have IM MTX 7.5 to 30 mg/week, 850 subjects who have received SC MTX 5 to 45 mg/week and 80 patients who have received IV MTX 7.5 to 500 mg/week. The RA control data also includes 750 patients who have taken low dose, weekly, oral MTX. The PSOR safety dataset comprises 343 patient years of information published in the literature.

The current safety dataset provides sufficient information about the short and medium term risks (up to 2 years) associated with parenteral MTX in the 2 target populations such as liver and haematological toxicity, infections, injection site reactions, and discontinuations due to adverse events. However, the extent of long term follow-up (several years) is relatively small and may not be adequate to assess for some potential AEs of concern that may have a long latency between drug exposure and AE occurrence, particularly malignancy, some opportunistic infections and cardiovascular safety. The study populations had baseline characteristics, disease

activity and concomitant medications indicative of the intended target populations for the claimed indications.

Key safety conclusions identified in the pivotal RA Study MC-MTX.6/RH safety dataset are as follows:

- At 24 weeks, the overall incidence of AEs, drug related AEs, SAEs and serious infections were similar in the oral and SC MTX treatment groups.
- Most common individual types of AEs (occurring in > 5% of patients in either treatment group) were nausea, abdominal pain, abnormal investigation results, anorexia, diarrhoea and non-serious infection, all of which occurred at a similar incidence in both MTX groups apart from a higher incidence of gastrointestinal AEs with SC versus oral MTX (45.6% versus 38.3%).
- Permanent discontinuations from MTX due to AEs were more frequent in the SC MTX group (9.3% at 6 months) than the oral MTX arm (4.3% at 6 months), mainly due to a higher incidence of gastrointestinal AEs.
- At 6 months of follow-up, the overall incidence of SAEs was similar in the 2 treatment groups (4.3 to 5.7%) with the most frequent type of SAE being major cardiovascular events (coronary ischemia and stroke).
- The most frequent type of investigation abnormality in both treatment groups involved elevated serum transaminases, which occurred at a similar frequency in both arms (21.3 to 22.5%). Most of these abnormalities were asymptomatic and transient, and infrequently prompted permanent discontinuation from MTX.

In the supportive RA studies (including the published cohort by Rau et al), more than 2,000 subjects in total have received parenteral treatment with MTX (with doses ranging from 5 to 45 mg/week), and treatment follow-up was typically limited to 6 to 12 months. The overall incidence and pattern of AEs in these studies is similar to that observed in the pivotal sponsor initiated trial MC-MTX.6/RH. In particular, a higher frequency of gastrointestinal AEs is associated with the SC administration of MTX in patients with RA (versus IM and oral therapy) and treatment discontinuations occur at a frequency of 5 to 10% over 6 to 12 months. The published data does not identify any new potential safety concerns with MTX. In the PSOR studies, a similar pattern and incidence of AEs was generally observed with low dose MTX. Gastrointestinal AEs, non-serious infections and headache are the most common AEs, as well as low incidence of pruritus and non-specific musculoskeletal pain (which is different to the RA experience). The consistent, key safety finding from all of these supportive studies is that major cardiovascular events and occasional serious infections are the most common type of SAE.

Death has been reported in at least 38 subjects with RA and in 1 patient with PSOR exposed to parenteral MTX (35 in the RA LBS, 3 in the publication by Rau et al and 1 PSOR patient in the published literature. Fifteen of the deaths (all in RA subjects) have resulted from major cardiovascular events (myocardial ischemia or stroke). However, the mortality rates and types of deaths observed in the RA and PSOR studies is probably consistent with those expected in the target populations. A total of 6 malignancies in RA treated patients have also been identified, which is also within expectations. No specific type of malignancy was observed at a heightened frequency.

MTX is associated with an increased risk of opportunistic infection, including pneumocystis pneumonia (although no confirmed cases have been reported in patients in this submission dataset), but major infections (including 1 reported fatality) have been recorded in this population.

All of the studies (in both RA and PSOR) have demonstrated a relatively high frequency of abnormal liver function tests with low dose MTX (by any route of administration) which is a

known AE of such therapy. The incidence of abnormal liver function tests does not appear to be affected by the route of administration of low dose MTX. There are also sporadic reports of thrombocytopenia, leukopenia and anaemia in this submission affecting both patients with RA and PSOR. This is known uncommon AE of MTX therapy.

Injection site reactions occurred in 6.5 to 7.1% of subjects in the pivotal RA Study MC-MTX.6/RH, with a similar proportion of reported AEs in each of the treatment groups (SC MTX versus oral MTX with placebo injections). The supporting literature and trials in both RA and PSOR patients report a low incidence of ISRs with patient rarely having to cease treatment due to an ISR.

In summary, the safety data indicates that parenteral MTX has an overall comparable safety profile to the current standard of care (oral MTX or other active comparator therapies) in patients with moderately to severely active RA or PSOR. There are some significant safety concerns including the risk of serious infection, abnormalities of liver function, malignancy potential and cytopenias (leukopenia and thrombocytopenia). Significant pharmacovigilance would be recommended if approval were granted for Metoject. This would include vigilance for opportunistic infections, malignancy, all cause death, and significantly abnormal laboratory results.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Metoject in the proposed usage are:

- Slightly higher rate of ACR20 response (which is the minimal clinically detectable improvement) in MTX naïve RA patients with early disease when given low dose weekly MTX (15 to 20 mg/week) by SC injection versus oral therapy (as observed in Study MC-MTX.6/RH).
- Injectable MTX achieves a clinical response (improvement) in adult patients with RA that is superior to placebo therapy, but similar in magnitude to other conventional DMARD treatment, such as IM gold.
- For the proposed indication of moderate to severe PSOR, low dose MTX by SC injection was only examined in 1 study (Gumusel et al, 2011) and was found to be equivalent to oral CsA. The majority of supporting efficacy data in PSOR compared low dose oral MTX to a variety of active treatments and showed a clinical effect better than placebo but inferior to biological treatment.
- Patients with RA report high levels of satisfaction and local tolerance with self-administered Metoject injections.
- The availability of colour coded, prefilled syringes in multiple doses and specific to patients with RA and PSOR has the potential to reduce the risk of medication administration errors.
- Potential for improved response to low dose MTX therapy in RA and PSOR patients who have failed to adequately respond to oral therapy; and therefore subsequent treatment with biologic agents may be avoided or delayed.

9.2. First round assessment of risks

The risks of Metoject in the proposed usage are:

- Higher incidence of gastrointestinal AEs and discontinuations from therapy with SC versus orally administered low dose weekly MTX in adult patients with active RA and PSOR.
- Low risk of serious infections and injection site reactions with parenteral low dose MTX.
- High incidence of abnormal liver function tests with regular low dose MTX in both RA and PSOR patients, which is not affected by the route of administration.
- Potential for off-label use in adult patients with other autoimmune conditions such as inflammatory bowel disease, psoriatic arthritis and systemic lupus erythematosus.
- Potential for off-label use in paediatric patients with JIA. MTX is frequently used in JIA and Metoject is approved in several countries (including the EU) for use in polyarthritis subtypes of JIA.
- Potential for overdose with serious clinical consequences if Metoject is given at an inappropriate dose schedule such as daily for several days versus the recommended once weekly regimen.
- Currently available parenteral preparations of MTX in Australia include 2.5 mg/mL, 25 mg/mL and 100 mg/mL. The availability of Metoject will add another MTX presentation (50 mg/mL), which has the potential to increase the risk of medication error (dispensing and administration).
- Potential for cytotoxic exposure to healthcare workers and consumers (including pregnant women) if handling and drug disposal recommendations are not correctly adhered.

9.3. First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Metoject, given the proposed usage (low dose weekly therapy given by SC or IM administration) in the target populations of adults with moderately to severely active RA or PSOR, is favourable.

10. First round recommendation regarding authorisation

10.1. Overarching issues

The evaluator recommends acceptance of the sponsor's proposed indications for Metoject subject to satisfactory response to the questions in section 11, and regular periodic safety update reports (PSURs). The sponsor is applying for registration for 3 routes of parenteral administration (SC, IM and IV injection). There is a sufficient volume of data with Metoject to recommend registration of the SC and IM routes of administration (in both treatment indications) but only a small volume of data from other injectable formulations of MTX to support the IV route of administration. The evaluator did not recommend registration of the IV route of administration for Metoject. In addition, the submission does not provide sufficient clarity about the appropriate clinical setting for the IV administration of Metoject to occur, nor whether the presentation device is suitable for IV administration.

The sponsor proposed commercial formulation (50 mg/mL) of Metoject has only been studied in Studies MC-MTX.9/PH (bioequivalence trial) and MC-MTX.10/RH (patient satisfaction study). The pivotal study in this submission (Study MC-MTX.6/RH) investigated the 10 mg/mL

formulation of MTX. Nonetheless, there is sufficient volume of supporting data to suggest that the 50 mg/mL formulation is acceptable for registration.

The submission contains a sufficient volume of data to support the sponsor proposal for self-administration of Metoject by SC or IM administration. The supporting evidence for such practice is provided by data in Studies MC-MTX.10/RH (patient satisfaction trial) and MC-MTX.5/RH (local tolerability trial). In both of these in house studies, MTX was self-administered by SC injection for up to 6 weeks in adult patients with RA at a dose of 15 to 25 mg/week. The results show that self-injection of MTX did not result in a higher incidence of AEs (specifically, local injection reactions) compared with administration by a healthcare professional, and were acceptable by patients. In both studies, the self-administration of MTX did not identify any new or more frequent safety concerns with low dose MTX use in adult patients with RA. The LBS also contained 3 small studies in paediatric patients with rheumatic disease whereby trained parent or carer SC administration of weekly low dose MTX was acceptable to patients and parents.

10.2. Specific treatment indications

10.2.1. Rheumatoid Arthritis

Although the proposed indication wording in RA is consistent with other injectable formulations of MTX registered in Australia, the indication wording could be amended (shortened) to be consistent with contemporary literature and worldwide best clinical practice. The treatment indication should simply state:

“Treatment of moderately to severely active rheumatoid arthritis in adults”.

Low dose weekly MTX (oral or parenteral) should be considered first line therapy in adult patients with RA of moderate to severe activity, and not only be considered after a trial of NSAID and/or other conventional DMARDs. The use of concurrent NSAID and/or low dose CS is acceptable (and supported by the current submission as well as literature) but the evaluator would view this additional information as being of limited value in the treatment indication wording.

The sponsor proposes the following dosage regimen for Metoject in RA: *“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 not be exceeded. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.”*

The posology wording is highly similar to that for low dose oral MTX in Australia, as well as the overseas registration wording of injectable MTX. However, the dosing regimen wording could be simplified to be consistent with contemporary literature and worldwide best clinical practice. The dosage regimen should simply state *“that a weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability”*. The evaluator also agreed with keeping the last proposed sentence relating to the back-titration of MTX to the lowest effective maintenance dose once disease remission is achieved. Published evidence does not support the slow upward titration of MTX from 7.5 mg/week in RA patients with severely active disease, and starting doses as high as 15 mg/week have been investigated.

10.2.2. Psoriasis

The evaluator concurred with the sponsor proposed treatment indication wording for PSOR.

The sponsor proposes the following dosage regimen for Metoject in PSOR: *“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. 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. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 to 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.”* Like RA, the posology wording could also be amended (shortened). The dosage regimen should state *“that a weekly dose of 7.5 to 30 mg is recommended, depending on response and tolerability”*. The evaluator would also agree with keeping the last proposed sentence relating to the back-titration of MTX to the lowest effective maintenance dose once clinical remission is achieved.

11. Clinical questions

11.1. Safety

1. The current application is proposing the administration of Metoject by the subcutaneous (SC), intramuscular (IM) and intravenous (IV) routes of administration in adult patients with RA and psoriasis. Can the sponsor clarify if it wishes to seek registration for administration by the IV route, and if so comment on the suitability and safety of self-administration of Metoject (pre-filled syringes; possibly presented in a pen device) by the IV route. If the IV route administration is being requested, can the sponsor outline the clinical setting for safe and appropriate administration of Metoject, and how this may differ from the proposed SC and IM administration setting?
2. Can the sponsor also clarify the suitability of the presentation device and safety of self-administration of Metoject (pre-filled syringes) by the IM route as the data included in this submission (Studies MC-MTX.10/RH and MC-MTX.6/RH; as well as the supporting literature based trials) about self-administration relates principally to SC administration of low dose MTX?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor's response dated 30 January 2015 responds to 3 questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Q1. The current application is proposing the administration of Metoject by the subcutaneous (SC), intramuscular (IM) and intravenous (IV) routes of administration in adult patients with RA and psoriasis. Can the sponsor clarify if it wishes to seek registration for administration by the IV route, and if so comment on the suitability and safety of self-administration of Metoject (pre-filled syringes; possibly presented in a pen device) by the IV route. If the IV route administration is being requested, can the sponsor outline the clinical setting for safe and appropriate administration of Metoject, and how this may differ from the proposed SC and IM administration setting?

The sponsor intends to register 2 distinct presentations of a prefilled syringe for administration by the SC route: one with an embedded needle (suitable for self-administration) and another with an enclosed needle (suitable for administration by a healthcare professional only).

The sponsor is also wishing to register Metoject for IM and IV administration (to be performed by a healthcare professional only) and plans to provide this product in separate distinct

packaging. The sponsor has declined to provide additional clinical setting or safety instructions for IM and IV administration.

The latest proposed PI (version 2) has made amendments (page 23 of 23) to the “Presentation and Storage Condition” section to reflect the above information. However, the information relating to the enclosed needle presentation does not specifically state this preparation should only be administered by a healthcare professional. I recommend a statement reflecting such practice be added to the proposed PI.

Q2. Can the sponsor also clarify the suitability of the presentation device and safety of self-administration of Metoject (pre-filled syringes) by the IM route as the data included in this submission (Studies MC-MTX.10/RH and MC-MTX.6/RH; as well as the supporting literature based trials) about self-administration relates principally to SC administration of low dose MTX?

The sponsor does not propose the self-administration of Metoject by the IM route and if used in this manner (for administration by a healthcare professional only), the drug will be supplied in different packaging to the SC administered medicine.

Q3. Can the sponsor clarify in the Dosage and Administration section of the proposed PI, the appropriate clinical settings for the safe and appropriate administration of Metoject? The proposed PI does not mention the potential for self-administration (presumably only SC and possibly IM administration), and does not distinguish the administration setting according to route of administration.

The sponsor states that the administration setting should be in the care of a physician familiar with the various characteristics of MTX and that he or she should only delegate SC administration of Metoject to the patient when appropriate. The initial dosing and monitoring is the same irrespective of route of administration. This is a correct statement. The sponsor has added 2 sentences to version 2 of the PI to reflect the appropriate delegation of SC administration (page 17 of 23). The sponsor does not propose the self-administration of Metoject by the IM route.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical efficacy information was requested or submitted in the sponsor’s response. Accordingly, the benefits of Metoject are unchanged from those identified in the first round assessment of benefits.

13.2. Second round assessment of risks

In response to questions, the sponsor has provided clarification regarding the clinical setting for self-administration (SC route only) and the presentation packaging of Metoject for use by various routes of administration. Despite these clarifications, the risks of Metoject are unchanged from those identified in first round assessment of risks.

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed the first round assessment of benefit-risk balance. The benefit-risk balance of Metoject in the proposed treatment indications of adult patients with RA and PSOR is favourable when the drug is given by the SC or IM route of administration. In addition, there is sufficient data to support the proposal for self-administration by the SC route of administration in

selected patients using the embedded needle device. The evaluator would not recommend registration of Metoject by the IV route of administration. The current submission does not contain a sufficient volume of directly obtained clinical data to support the safe use of Metoject in this setting.

14. Second round recommendation regarding authorisation

The evaluator recommends acceptance of the sponsor's proposed treatment indications for Metoject that is, adult patients with RA or psoriasis. The sponsor is applying for registration by 3 routes of parenteral administration (SC, IM and IV injection). There is a sufficient volume of data with Metoject to recommend registration of the SC and IM routes of administration. In addition, there is a sufficient volume of data to support the registration of self-administration by the SC route. However, there is only a small volume of data from other injectable formulations of MTX to support the IV route of administration. The evaluator did not recommend registration of the IV route of administration for Metoject. In addition, the evaluator would recommend the dosage regimen for Metoject use in RA and PSOR be amended as per the recommendations outlined in section 10 of this report.

15. References

- Akhyani M, et al. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology*. 2010; 24: 1447-1451.
- Andersen PA, et al. Weekly pulse methotrexate in RA. Clinical and immunologic effects in a randomized, double-blind study. *Ann Intern Med* 1985; 103: 489-496
- Arthur V, et al. Self-injection of gold and methotrexate. *Journal of Rheumatology*. 2001; 28: 1.
- Auvinet B. et al. Compared bioavailability of methotrexate administered orally or intramuscularly in rheumatoid arthritis. *Presse medicale* 1992; 21: 822
- Bakker MF. et al. Utrecht Arthritis Cohort Study Group. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. *Annals of the rheumatic diseases* 2010; 69: 1849-1852
- Barker J, 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). *British Journal of Dermatology*. 2011; 165: 1109-1117
- Benenson EV. Timina OB. Prospidine versus methotrexate pulse in highly active rheumatoid arthritis: a controlled 6-month clinical trial. *Clinical Rheumatology*, 13(1): 54-9, (1994)
- Bressolle F, et al. Total and free methotrexate pharmacokinetics in elderly patients with rheumatoid arthritis. A comparison with young patients. *J Rheum* 1997; 24: 1903-1909
- Bressolle F, et al. Effects of moderate renal insufficiency on the pharmacokinetics of methotrexate in rheumatoid arthritis patients. *Ann Rheum Dis* 1998; 57: 110-113
- Brooks PJ, et al. Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1990; 33: 91-94
- Carmichael SJ, et al. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J Rheum* 2002; 29: 2077-2083
- Dogra S, et al. Efficacy and safety of systemic methotrexate in two fixed doses of 10mg and 25mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study. *Clinical and Experimental Dermatology* 2012; 37: 729-734
- Fallah Arani S, et al. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled trial. *British Journal of Dermatology* 2011; 164: 855-861
- Fiehn C. et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. *Rheumatology international* 2007; 27: 975-979
- Flystrom I, et al. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *British Journal of Dermatology*. 2008; 158: 116-121
- Gabriel S. et al. Treatment of rheumatoid arthritis with higher dose intravenous methotrexate. *Journal of Rheumatology* 1990; 17: 460-465

- Gumusel M, et al. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one- blind, randomised study. *Journal of the European Academy of Dermatology and Venereology* 2011; 25: 1080-1084
- Hamilton RA. Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. *British Journal of Rheumatology* 1997; 36: 86-90
- Herborn G et al. Interim report on 102 patients after two years in a double blind comparison of intramuscular methotrexate and gold sodium thiomalate in early erosive rheumatoid arthritis. *Zeitschrift für Rheumatologie* 1992; 51: 163-171
- Herman R.A. et al. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. *Journal of Pharmaceutical Sciences* 1989; 78: 165-171
- Heydendael VMR, et al. Methotrexate versus cyclosporine in moderate-to- severe chronic plaque psoriasis. *New England Journal of Medicine* 2003; 349: 658-665
- Ho SGY, et al. Methotrexate versus traditional Chinese medicine in psoriasis a randomised, placebo-controlled trial to determine efficacy, safety and quality of life. *Clinical and Experimental Dermatology* 2009; 35:717-722
- Hoekstra M. et al. Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients with Rheumatoid Arthritis. *Journal of Rheumatology* 2004; 31: 645-648
- Hoekstra M. et al. Splitting high-dose oral methotrexate improves bioavailability: A pharmacokinetic study in patients with rheumatoid arthritis. *Journal of Rheumatology* 2006; 33: 481-485
- Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. *American Journal of Medicine*, 75(6A): 69-73, (1983)
- Islam MS, et al. Comparative Efficacy of Subcutaneous versus Oral Methotrexate in active Rheumatoid Arthritis *Mymensingh Med J* 2013; 22: 483-488
- Jones SK, et al. Methotrexate pharmacokinetics in psoriatic patients developing hepatic fibrosis. *Arch Dermatol* 1986; 122: 666-669.
- Jundt JW, et al. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *Journal of Rheumatology* 1993; 20: 1845-1849
- Lambert CM. et al. Dose escalation of parenteral methotrexate in active rheumatoid arthritis that has been unresponsive to conventional doses of methotrexate: a randomized, controlled trial. *Arthritis & Rheumatism* 2004; 50: 364-371
- Menninger H, et al. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. *British journal of rheumatology*, 37(10): 1060-8, (1998)
- Michaels RM. et al. Weekly intravenous methotrexate in the treatment of rheumatoid arthritis. *Arthritis & Rheumatism* 1982; 25: 339-341
- Montaudie H, et al. Methotrexate in psoriasis: a systemic review of the treatment modalities, incidence, risk factors and monitoring of liver toxicity. *Journal of the European Academy of Dermatology and Venereology* 2011; 25: 12-18
- Mouterde G, et al. Optimizing methotrexate therapy in rheumatoid arthritis: a systematic literature review. *Joint Bone Spine* 2011; 78: 587-592
- Nicksch E., Wittenborg A. Low-dose methotrexate therapy in intractable rheumatoid arthritis. *Clin. Exp Rheumatol* 1987; 5: 541

- Rau R. et al. A double blind randomized parallel trial of intramuscular methotrexate and gold sodium thiomalate in early erosive rheumatoid arthritis. *Journal of rheumatology* 1991; 18: 328-333
- Rau R-2. et al. A double-blind comparison of parenteral methotrexate and parenteral gold in the treatment of early erosive rheumatoid arthritis. an interim report on 102 patients after 12 months. *Seminars in arthritis and rheumatism* 1991; 21: 13-20
- Rau R. et al. Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis. 12 month data of a double-blind parallel study of 174 patients. *British journal of rheumatology* 1997; 36: 345-352
- Rau R-2. et al. Treatment of destructive rheumatoid arthritis with methotrexate. *Journal of Rheumatology* 1997; 24: 1881-1889
- Rau R, et al. Progression in early erosive rheumatoid arthritis. 12 month results from a randomized controlled trial comparing methotrexate and gold sodium thiomalate. *British journal of rheumatology* 1998; 37: 1220-1226
- Rau R-2. et al. Longterm combination therapy of refractory and destructive rheumatoid arthritis with methotrexate (MTX) and intramuscular gold or other disease modifying antirheumatic drugs compared to MTX monotherapy. *Journal of Rheumatology* 1998; 25: 1485-1492
- Rau R et al. Radiographic outcome after three years of patients with early erosive rheumatoid arthritis treated with intramuscular methotrexate or parenteral gold. Extension of a one-year double-blind study in 174 patients. *Rheumatology* 2002; 41: 196-204
- Ravelli A. et al. Oral versus intramuscular methotrexate in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. *Clinical & Experimental Rheumatology* 1998; 16: 181-183
- Reich K, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *New England Journal of Medicine* 2011; 365: 1586-1596
- Ruperto N, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; 50: 2191-2201
- Sander O. et al. Prospective six year follow up of patients withdrawn from a randomised study comparing parenteral gold salt and methotrexate. *Annals of the Rheumatic Diseases* 1999; 58: 281-287
- Saurat J-H, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. (CHAMPION). *British Journal of Dermatology* 2008; 158: 558-566
- Seideman P, et al. The pharmacokinetics of methotrexate and its 7-hydroxy metabolite in patients with rheumatoid arthritis. *British Journal of Clinical Pharmacology* 1993; 35: 409-412
- Shiroky J. et al. High dose intravenous methotrexate with leucovorin rescue in rheumatoid arthritis. *Journal of Rheumatology* 1998; 15: 251-255
- Shiroky JB. et al. High dose intravenous methotrexate for refractory rheumatoid arthritis. *Journal of Rheumatology* 1992; 19: 247-251
- Skeith KJ, et al. Lack of significant interaction between low dose methotrexate and ibuprofen or flurbiprofen in patients with arthritis. *J Rheum* 1990; 17: 1008-1010
- Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509

Stewart CF, et al. Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharm and Therap* 1990; 47: 540-546

Stewart CF, et al. Aspirin alters methotrexate disposition in rheumatoid arthritis patients. *Arthritis and Rheumatism* 1991; 34: 1514-1520

Swierkot J and Szechinski J. Methotrexate in rheumatoid arthritis. *Pharmacol Rep* 2006; 58: 473-492

Thompson RN. et al. A controlled two-centre trial of parenteral methotrexate therapy for refractory rheumatoid arthritis. *Journal of Rheumatology* 1984; 11: 760-763

Visser K, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. *Ann Rheum Dis* 2009; 68: 1086-1093

Zackheim HS. Subcutaneous administration of methotrexate. *Journal of the American Academy of Dermatology* 1992; 26: 1008

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