Clinical effectiveness of 2 treat to target strategies, mimicking standard care compared to early secukinumab for the treatment of Moderate to Severe Psoriatic arthritis: a parallel group randomised controlled trial.

(Strategy Treatments Aiming at MDA in PsA – STAMP)

Versie 3.0

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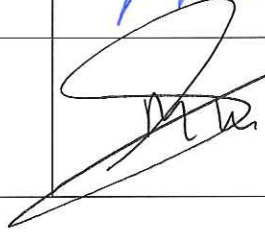
Project leader ***dr. M. Vis, rheumatologist***		11-06-2019

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ACR	**American College of Rheumatology**
AE	**Adverse Event**
AR	**Adverse Reaction**
BRAF	**Bristol Rheumatoid Arthritis Fatigue**
CA	**Competent Authority**
CASPAR	**Classification criteria for Psoriatic Arthritis**
DAPSA	**Disease Activity in Psoriatic Arthritis**
DEPAR	**Dutch Early Psoriatic Arthritis**
DLQI	**Dermatology Life Quality Index**
DMARD	**Disease Modifying Anti- Rheumatic Drug**
DSMB	**Data Safety Monitoring Board**
EQ-5D	**EuroQol 5-Dimensions**
ESR	**Erythrocyte Sedimentation Rate**
EudraCT	**European drug regulatory affairs Clinical Trials**
HAQ	**Health Assessment Questionnaire**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
LDI	**Leeds Dactylitis Index**
LEI	**Leeds Enthesitis Index**
MASES	**Maastricht Ankylosing Spondylitis Enthesitis Score**
MDA	**Minimal Disease Activity**
MTX	**Methotrexate**
MREC	**Medical Research Ethics Committee; in Dutch: Medisch Ethische Toetsings Commissie (METC)**
NSAID	**Non-Steroidal Anti-Inflammatory Drug**
PASDAS	**Psoriatic Arthritis Disease Activity Score**
PASI	**Psoriasis Area & Severity Index**
PCQ	**Productivity Cost Questionnaire**
PPD	**Purified Protein Derivative**
PsA	**Psoriatic Arthritis**
PSAID	**Psoriatic Arthritis Impact of Disease**
QoL	**Quality of Life**
RA	**Rheumatoid Arthritis**
(S)AE	**(Serious) Adverse Event**
SF-36	**Short Form 36 Health Survey**
SHS	**Sharp/van der Heijde score**
SJC	**Swollen joint count**
SmPC	**Summary of Product Characteristics**
SPARCC	**Spondyloarthritis Research Consortium of Canada**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie**

	IB1-tekst
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
T2T	**Treat to Target**
TJC	**Tender Joint Count**
TNF	**Tumor Necrosis Factor**
TWiCs	**Trials Within Cohorts**
VAS	**Visual Analog Scale**
VLDA	**Very low disease activity**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

Over the past couple of years, therapeutic targets for treatment of Psoriatic Arthritis (PsA) are rapidly evolving. Interleukine-17a blockade (e.g. secukinumab) is one of the evolving treatments and plays an important role in the pathophysiology of PsA[1]. In contrast to methotrexate (MTX), in clinical setting it is beneficial on all the effected sites in patients with PsA. It also significantly improves patient reported outcome measures[2]. We hypothesize that treatments covering all features of PsA by early aggressive therapeutic intervention, using secukinumab as an initial treatment strategy will improve Treat to Target (T2T) in PsA.

Objective:

To compare the effectiveness of the administration of secukinumab to standard care in newly diagnosed PsA patients on the ACR50 response at 6 months.

Study design:

The Dutch Early Psoriatic Arthritis (DEPAR) - T2T trial is designed as a randomized, controlled, parallel group, open label, multi-center comparing two T2T strategies within a cohort.

- Arm 1: Standard care. The standard care is based on data from the DEPAR cohort and interviews with Dutch rheumatologists.
- Arm 2: Secukinumab. Patients will be started on Secukinumab 300mg subcutaneous.

Therapy in each arm will be escalated using a 3 monthly scheme in patients not achieving the treatment target Minimal Disease Activity (MDA)[3].

Participants in this study will attend for study visits at baseline and months 3, 6, 9 and 12. After 6 weeks patients will be asked to fill out 5 questionnaires. At the 3-monthly visits, participants will be assessed clinically for disease activity and will be asked to complete patient reported outcomes via questionnaires. Visits in between these will be performed based on clinical need when adjustment to therapy is required.

Study population:

Patients newly diagnosed by the rheumatologist and fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) will be eligible if they present with oligo-arthritis (2 to 5 involved joints) or with poly-arthritis (5 or more joints).

Interventions

ARM 1: Standard care.

Therapy for the cohort is defined by the usual treatment strategy applied by rheumatologists for the treatment of oligo-and polyarticular PsA. The initial therapy (step 1) in this arm is MTX mono-therapy (starting 15mg/week rising escalated to 25mg/week in 6 weeks). In addition, all patients will be administered triamcinolone 80mg intramuscular (IM). In cases of non-response, sulfasalazine twice daily 1000mg will be added to the MTX (step 2). In case of failure of these two Disease Modifying Anti- Rheumatic Drugs (DMARDs), treatment will be escalated by adding a biological DMARD. In this study is opted for a Tumor Necrosis Factor (TNF) blocker (step 3). When the combination of conventional DMARD and a first TNF blocker fails, the TNF blocker will be switched to a second TNF blocker (step 4). The choice of which TNF blocker to use is at the discretion of the treating rheumatologist. The dosing of TNF blockers will be the standard dose for PsA according to current guidelines in line with National reimbursement guidelines. In addition, folic acid 10mg/week will be subscribed in every step of the escalation scheme.

ARM 2: Secukinumab

All participants will be prescribed secukinumab 300 mg every 4 weeks, with a loading scheme of the first four 300 mg injections weekly, in combination with MTX 15mg/week. In addition, all patients will be administered triamcinolone 80 mg intramuscular (IM). (step 1). Secukinumab is not registered for the first line treatment of PsA patients and is not in accordance with national reimbursement guidelines. In case the first step fails (secukinumab 300mg + MTX 15mg/week) treatment will be switched to a TNF blocker (step 2) and to a second TNF blocker if the first TNF blocker fails (step 3). The choice of which TNF blocker to use is at the discretion of the treating rheumatologist. The dosing of TNF blockers will be the standard dose for PsA according to current guidelines in line with national reimbursement guidelines. When a second TNF blocker fails, this drug will be switched to apremilast 30mg twice daily (step 4). Apremilast therapy is in line with national reimbursement guidelines. In addition, folic acid 10mg/week will be subscribed in every step of the escalation scheme

Main study parameters/endpoints:

The ACR50 response will be used to determine efficacy at 6 months. A subject is defined as an ACR50 responder if, and only if, the following three conditions are met:

1. they have a ≥ 50% improvement in the number of tender joints (based on 68 joints)
2. they have a ≥ 50% improvement in the number of swollen joints (based on 66 joints)
3. they have a ≥ 50% improvement in three of the following five domains:

- Patient's global assessment of disease activity (measured on a Visual Analog Scale (VAS) scale, 0-100)
- Physician's global assessment of disease activity (measured on a VAS scale, 0-100)
- Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
- Health Assessment Questionnaire – Disability Index (HAQ-DI©) score
- Acute phase reactant (hsCRP or erythrocyte sedimentation rate [ESR])

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

In our opinion, the implementation of this study is justified when we take into account the number of study visits for the patient/burden of filling out the questionnaires in relation to the knowledge we are expecting to gain from this study

1. INTRODUCTION AND RATIONALE

Psoriatic Arthritis (PsA) is a chronic inflammatory joint disease with an estimated prevalence of 0.5% in the general population. It manifests in skin, joints, enthesis and spine and when left untreated results in joint damage, structural changes in the enthesis and spine[4-6]. Moreover, it can have a dramatic impact on the Quality of Life (QoL). Over recent years treatment options are vastly expanding.

With more emergent effective treatments for inflammatory arthritis, the concept of T2T is growing to its full potential. T2T is a treatment strategy in which treatment is optimized to reach and maintain explicitly specified goals, by the doctor and the patient, such as remission or low disease activity. In rheumatoid arthritis (RA), this treatment approach has proven to be effective, leading to less erosive progression, more drug free remission and better QoL[7-9].

In PsA, the T2T principle is less often applied and has only been studied by Coates *et al*[10]. The TICOPA trial used a step-up approach in the tight control arm. In this study, patients were started on MTX, sulfasalazine and subsequently a TNF blocker was added if patients did not meet the pre-specified target MDA. Patients in the tight control group had a higher odds of achieving an ACR 20 response than the standard care group (odds ratio 1·91, 95% CI 1·03–3·55; p=0·04). ACR 50, ACR 70, and Psoriasis Area & Severity Index(PASI)75 responses were also achieved more frequently in the tight control group than in the standard care group. However, there was little difference in resolution of dactylitis and enthesitis in the tight control group as compared to the standard care group, and there was no difference in damage progression. This indicates that a T2T approach is feasible in the treatment of PsA, but not all disease features respond well on the TICOPA regime suggesting that better treatment strategies are needed[10].

Studies in patients with RA established that early aggressive treatment in a T2T strategy improves outcome. For instance, in the BEST-study and the TREACH-study combination therapy arms outperformed the mono therapy arms on joint damage and drug free remission[8, 9]. However, up to date there is ample to no data on early aggressive T2T treatment in PsA.

The initial drug used in the TICOPA trial was MTX[10]. The effect of MTX on skin psoriasis has been proven extensively[11], however there is little to no evidence for the efficacy of MTX in PsA treatment for other disease features[12, 13]. This could implicate that early strategies using

treatment covering all PsA disease features will improve outcome in T2T studies.

Secukinumab, an interleukine-17a blocker, is a new treatment. Il-17 plays an important role in the pathophysiology of PsA[1] and blocking Il-17 improves all of the disease features in patients with PsA in contrast to MTX [2]. We therefore hypothesize that, using secukinumab as an initial treatment in a T2T strategy will dramatically improve the management of PsA.

In the current proposal we aim to investigate the effect of an early aggressive T2T strategy using secukinumab as a first line drug and its outcome compared to a strategy mimicking current daily clinical practice in recently diagnosed PsA patients.

2. OBJECTIVES

Primary Objective:

To compare the effectiveness in a T2T setting of the administration of secukinumab to standard care in newly diagnosed PsA patients on the ACR 50 response at 6 months.

Secondary Objectives:

To compare effectiveness in a T2T setting of the administration of secukinumab to standard care in newly diagnosed PsA patients 6 and 12 months:

- Patients achieving ACR 20 and 70 at 6 months
- Patients achieving ACR 20, 50, 70 at 12 months
- Patients achieving MDA[3] and Very low disease activity (VLDA) at 6 and 12 months
- Disease Activity in Psoriatic Arthritis (DAPSA) and Psoriatic Arthritis Disease Activity Score (PASDAS) scores at 6 and 12 months

To compare QoL in a T2T setting of the administration of secukinumab to standard care in newly diagnosed PsA patients at 12 months:

- SF-36[14]
- Psoriatic Arthritis Impact of Disease (PSAID)[15]
- Bristol Rheumatoid Arthritis Fatigue (BRAF)

To compare work performance (presenteeism and absenteeism) in a T2T setting of the administration of secukinumab to standard care in newly diagnosed PsA patients at 12 months.

To compare progression of radiological damage in a T2T setting of the administration of secukinumab to standard care in newly diagnosed PsA patients at 12 months:

- PsA-modified Sharp/van der Heijde score (SHS)[16] at 12 months

To assess the cost-effectiveness between two treatment arms, standard care (arm 1) and early secukinumab arm (arm 2).

3. STUDY DESIGN

The DEPAR-T2T trial is designed as a randomized, controlled, parallel group, open label, multi-center trial comparing two T2T strategies within a cohort.

Arm 1: Standard care.

The standard care is based on data from the DEPAR cohort and interviews with Dutch rheumatologists.

Arm 2: Secukinumab

Patients will be started on Secukinumab 300mg subcutaneous

Therapy in each arm will be escalated using a 3-monthly scheme in patients not achieving MDA [3]. (Figure 1 and 2)

TWiCs design:
For this research we will use a Trials Within Cohorts (TWiCs) design. This method recruits a central cohort having “treatment as usual” with regular observations and then adds pragmatic trials of alternative therapies in which a random group of eligible patients are selected. This allows robust generalizability from studies to routine health care, avoids attrition and disappointment bias from controls in open label studies as patients receive only information relevant to their care, aids recruitment to trials, allows routine collection of long term outcomes and increases efficiency with multiple trials within one cohort.

DEPAR:
The currently running DEPAR (NL42453.078.12) cohort will function as the central cohort for STAMP. The DEPAR cohort is a prospective observational cohort set up for newly diagnosed patients with PsA. 13 general hospitals and one academic hospital in the South West Part of the Netherlands participate in the DEPAR cohort. The recruitment started in 2013 and we expect to include 800 patients in 6 years. Each new patient will be invited by their doctor to participate and if they consent to the study they will be assessed by a research nurse for all clinical parameters.

Data is collected at baseline and every 3 months during the first year, every 6 months in the second year and then once a year. At each study visit patients are required to fill in the same questionnaires as STAMP and the nurse does the same physical examinations as STAMP (see Table 1; study assessments). Patients will be asked to participate in either DEPAR or STAMP, so they will not have a double study burden.

STAMP:
Patients fulfilling the inclusion criteria for the T2T trial will be offered to participate in the study. Patients diagnosed by the rheumatologist and fulfilling the CASPAR will be eligible if they present with oligo-arthritis, defined as 2 to 5 swollen joints (SJ) or with polyarthritis, defined as 5 or more swollen joints.

Participants in this study will attend study visits at baseline and months 3, 6, 9 and 12. At these 3-monthly visits, participants will be assessed clinically for disease activity and will be asked to complete patient reported outcomes via questionnaires. Visits in between these will be performed based on clinical necessity when adjustment of therapy is required.

Based on the evaluations, MDA[3] will be calculated and therapy will be escalated or continued (Figure 1).

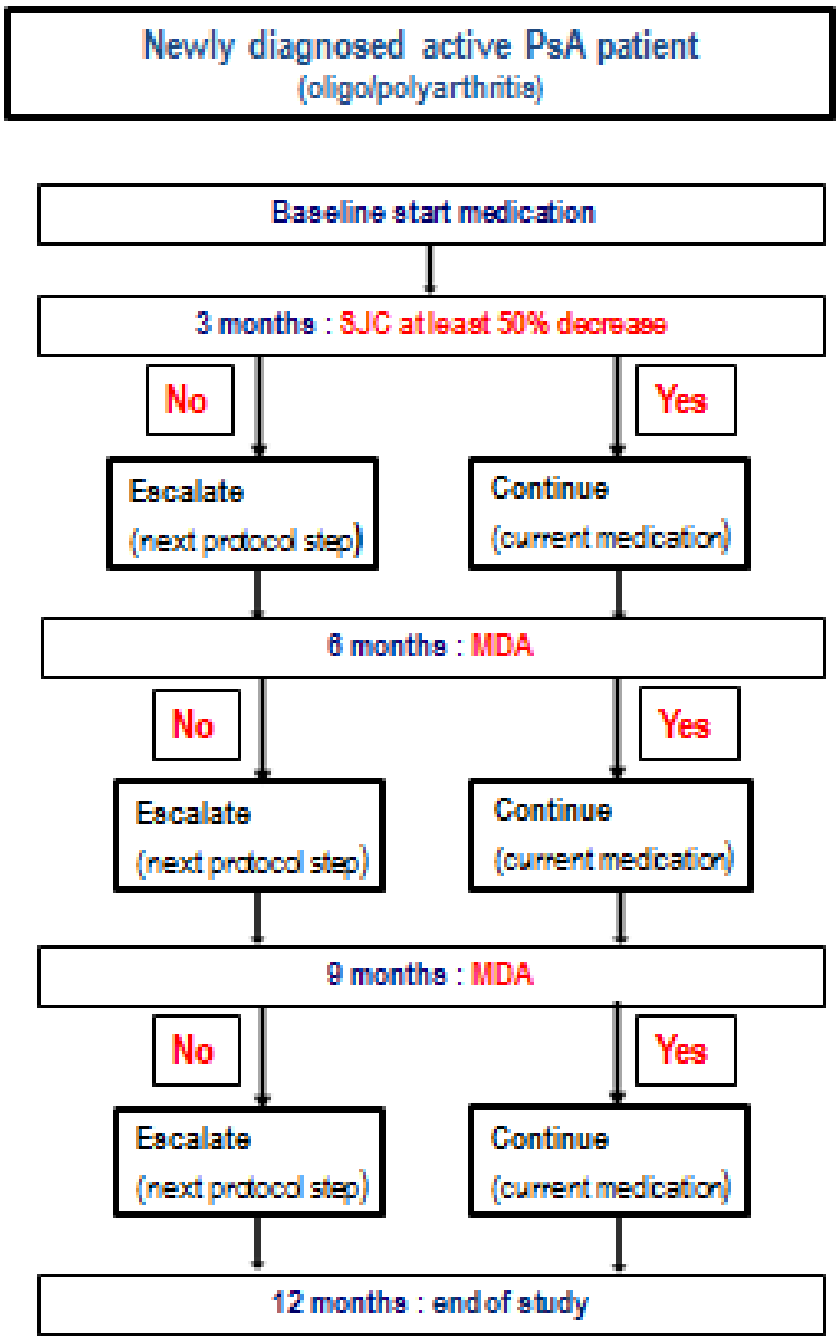

Figure 1: Treat to target evaluation points

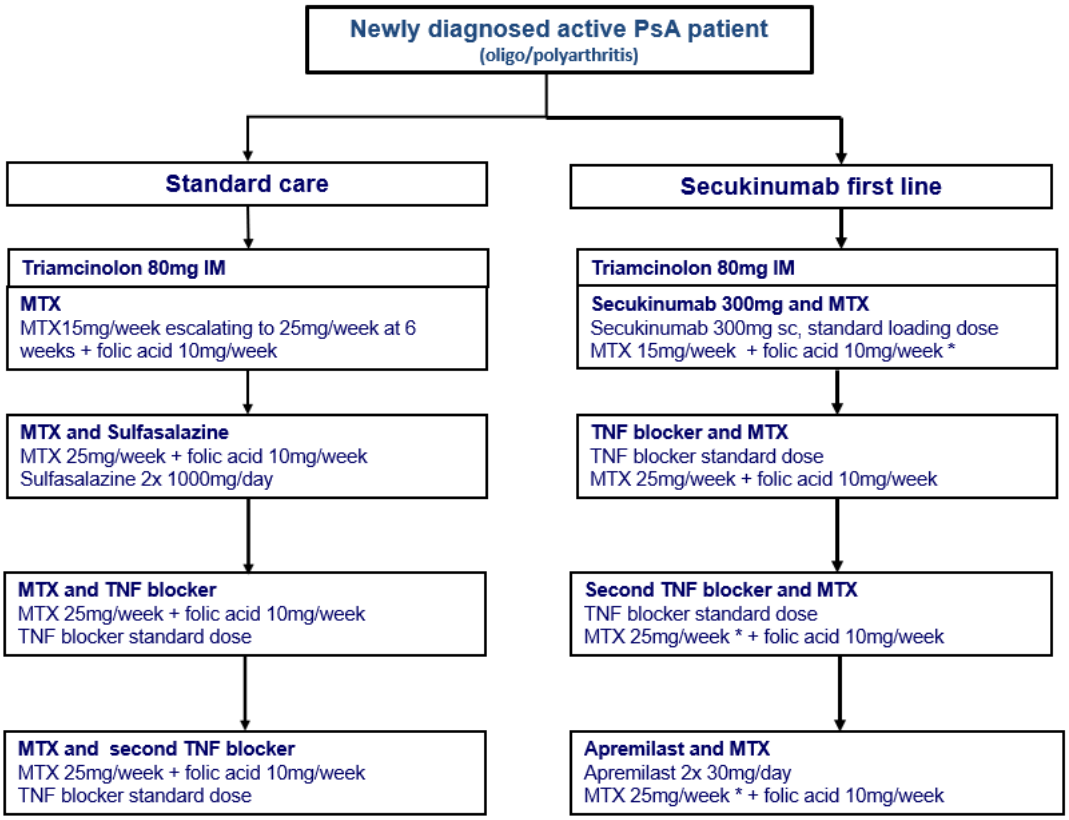

Figure 2: Treatment escalation steps

4. POPULATION

4.1 Population (base)

This trial will recruit participants from the DEPAR cohort with newly diagnosed PsA who have not previously received treatment with DMARDs for their articular disease. For this trial, only participants with oligo- or polyarticular disease will be eligible.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. A new diagnosis of PsA as per CASPAR <3 months.
2. A minimum of two swollen joints.
3. Patients must be able to understand and communicate with the Investigator and comply with the requirements of the study and must give a written, signed and dated informed consent (IC) before any study assessment is performed.
4. Male or female patients between 18 and 80 years of age.
5. In the Investigator's opinion, the patient is able and willing to comply to all trial requirements.
6. Female participants of child bearing potential and male participants whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception during the trial and for 3 months thereafter as in standard practice.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be ineligible:

1. Evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified health care professional.
2. Current or previous treatment of arthritis with DMARDs (including MTX, leflunomide or sulfasalazine) or biologics (including TNF, IL12/23 or IL17 inhibitor therapies)
3. Use of any investigational drug and/or devices within 4 weeks prior to randomization or a period of five half-lives of the investigational drug, whichever is longer in duration.
4. Pregnant or nursing (lactating) women, in which pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
5. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator

immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
6. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes.
7. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) of e.g. aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, and/or serum bilirubin. The Investigator should be guided by the following criteria: Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
8. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a glomerular filtration rate (GFR) < 30 ml/min.
9. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
10. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive Purified Protein Derivative (PPD) skin test or a positive QuantiFERON TB-Gold test untreated or insufficiently treated according to the national guideline.
11. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at screening or randomization.
12. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
13. Current severe progressive or uncontrolled disease, which in the judgment of the clinical Investigator renders the patient unsuitable for the trial.
14. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins).
15. Any medical or psychiatric condition which, in the Investigator’s opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
16. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization

4.4 Sample size calculation

The primary outcome is the proportion of patients achieving an ACR 50 response at 6 months. The ACR 50 response at 6 months in DEPAR was 25% (the TICOPA usual care arm was 23% at 12 months[10]). We will use this as ACR 50 response for at 6 months in the standard care arm group.
The ACR 50 response at 6 months in the secukinumab 150mg arm in biologic naive patients was 44% in the future2 trial. For the power calculation, we expect the ACR 50 to be at least 9% higher, as we include DMARD naive patients instead of MTX failures.
Using this 28% difference in outcomes between the 2 groups in a power calculation with a power of 80% and a significance of 5%; 47 patients per arm are needed. Estimated sample sizes for a two-sample proportions test were evaluated by Pearson's chi-squared test using STATA 15. To allow for dropouts and to answer secondary outcomes we will include 60 patients per arm.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment:

This is a 2-arm strategy study.

ARM 1: Standard care.
Therapy for the cohort is defined by the usual treatment strategy applied by rheumatologists for the treatment of oligo- and polyarticular PsA (Figure 2). The initial therapy (step 1) in this arm is MTX mono-therapy (starting 15mg/week rising escalated to 25mg/week in 6 weeks). In addition, all patients will be administered triamcinolone 80mg intramuscular (IM). In cases of non-response, sulfasalazine twice daily 1000mg will be added to the MTX (step 2). In case of failure of these two DMARDs, treatment will be escalated by adding a biological DMARD. In this study is opted for a TNF blocker (step 3). When the combination of conventional DMARD and a first TNF blocker fails, the TNF blocker will be switched to a second TNF blocker (step 4). The choice of which TNF blocker to use is at the discretion of the treating rheumatologist. The dosing of TNF blockers will be the standard dose for PsA according to current guidelines in line with National reimbursement guidelines.

ARM 2: Secukinumab
All participants will be prescribed secukinumab 300 mg every 4 weeks, with a loading scheme of the first four 300 mg injections weekly, in combination with MTX 15mg/week (Figure 2). In addition, all patients will be administered triamcinolone 80 mg intramuscular

(IM) (step 1). Secukinumab is not registered for the first line treatment of PsA patients and is not in accordance with national reimbursement guidelines. In case the first step fails (secukinumab 300mg + MTX 15mg/week) treatment will be switched to a TNF blocker (step 2) and to a second TNF blocker if the first TNF blocker fails (step 3). The choice of which TNF blocker to use is at the discretion of the treating rheumatologist. The dosing of TNF blockers will be the standard dose for PsA according to current guidelines in line with national reimbursement guidelines. When a second TNF blocker fails, this drug will be switched to apremilast 30mg twice daily (step 4). Apremilast therapy is in line with national reimbursement guidelines.

Rationale for choice of therapy

In this study we compare two treatment strategies. “Standard care applies” to the sequence in with the different drugs (MTX, sulfasalazine, TNF blocker, secukinumab, apremilast) are given. It does not apply to the drugs themselves because in arm 2 (intervention arm) many of the same drugs as in standard care are given, just in a different order. In arm 2, secukinumab is administered at a different time point than it would have been given in “standard care”, which is why this arm is the intervention arm. We have chosen to give a TNF blocker after secukinumab because in our opinion it would not be “escalation” of therapy if we would only increase MTX dosage or add sulfasalazine (Figure 2). The same is true for apremilast.

Early escalation

Early escalation is defined as making the next step in the treatment arm prior to the scheduled study visit used for evaluating the achievement of the treatment target. Early escalation is allowed under specific circumstances, which are:

- Intolerance to the medication in the current step of the treatment.
- Active disease, meaning not in MDA and judged by the rheumatologist as very severe, where postponing escalation cannot wait until the next study visit.

In case of early escalation, an extra study visit is scheduled ad hoc. Regular study visits are not rescheduled. In case of early escalation, no medication escalation will be advised at the next regular study visit.

Protocol violation

A protocol violation is defined as not complying with the predefined medication protocol by the rheumatologist. Protocol violations are prohibited.

In case a rheumatologist does not want to comply with the escalation and/or continuation of medication based on the evaluation of the treatment target, a new evaluation of the treatment

target is scheduled 2 weeks later to ensure that the evaluation of the target is true. When the rheumatologist still does not want to comply with the medication advice, a protocol violation is scored.
A protocol violation will also be recorded when the treating physician administers rescue medication, other than the prespecified allowed rescue medication (for instance administering trimacinolon either IM or intra-articular will be recorded as a protocol violation)

Compliance with Trial Treatment

Non-compliance will be assessed at each clinical trial visit and any missed dose reported by the participants will be recorded.

Rescue Medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/exacerbation of their disease. Only the following prespecified rescue medication is allowed:

- Aminocetophenomen
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (or an increase in dosage)

Treatment at end of trial

This is a one-year study, continuation of medication at the end of the trial is left to the discretion of the rheumatologist.

Treatment targets

This is a T2T strategy trial meaning that if a certain target is not achieved (treatment failure), treatment will be increased. Achievement of targets will be defined at 3, 6 and 9 months.

At 3 months, the predefined target is a decrease of swollen joints of at least 50%. The treatment target at 6 and 9 months is the MDA criteria. These assess 7 different outcomes in which patients should meet at least 5 of the 7 items to be classified as being in MDA. The MDA criteria are shown in the box below[3]:

Outcome Measure (see Section 8)	**Score +1 for each outcome measure which is below the value below. Total score of ≥5 indicates MDA achieved**
Tender joint count (TJC) (using 68 joint count)	≤1
Swollen joint count (SJC) (using 66 joint count)	≤1
Enthesitis count (using Leeds Enthesitis Index [LEI] or SPARCC)	≤1
Skin assessment	PASI≤1 or BSA≤3%
Patient global VAS (mm)	≤20
Patient pain VAS (mm)	≤15
HAQ[17]	≤0.5

The rationale for using a decrease of 50% in SJC instead of MDA is that the response to MTX is slow and the full response is not expected to be achieved at 12 weeks.

Visits

All study visits are scheduled every 3 months, based on the date of the baseline visit. The study visits should take place in a 2-week window of (before and after) the prescheduled study visit. In case a study visit does take place outside this window, this will be recorded, but data collection and assessment of escalation will still be done.
In case of a visits outside the study window, the next visit still takes place according to the prespecified visit schedule based on the date of the baseline visit. If a subject for any reasons discontinues with the study early, a discontinuation visit will be scheduled, This visit will be scheduled within a 2-week window of the subject announcing its discontinuation.

5.2 Use of co-intervention (if applicable)

DMARDs

No other conventional DMARD or biologic DMARD therapy is allowed other than those prescribed in the protocol.

Corticosteroids

Corticosteroids, either intramuscular or oral, are not allowed during the study.

NSAIDs

NSAIDs in the standard dose are allowed as co-treatment.

Other medication

There are no specifically excluded concomitant medications, although some drugs are contraindicated alongside Investigational Medicinal Products (IMPs) in this protocol (e.g. sulphonamides). Any new therapies for other conditions should only be prescribed if safe alongside their therapy. Participants and their GP will be aware of participants' treatments as this trial is open label.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

Secukinumab is supplied as an IMP for specific use within this trial as it is to be prescribed outside the reimbursement rules in the Netherlands.
Formulation and storage of the IMPs is in line with the manufacturers' recommendations. For further details refer to the Summary of Product Characteristics (SmPC secukinumab 12-11-2018). A reference copy can be found in the Investigator and Pharmacy Site Files.

All medications used in this study are commercially available products routinely used in patients with PsA. Generic ('off the shelf') commercial supplies are to be used for MTX, sulfasalazine, TNF blockers (infliximab, adalimumab, certoluzimab, golimumab or etanercept) and apremilast as determined by individual hospital sites. MTX, sulfasalazine, TNF blockers and apremilast will be off the shelf supplies. The pharmacy will be responsible for labelling the IMPs in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994.

6.1 Name and description of investigational product(s)

In this study, two treatment strategies are compared. This means no head-to-head comparison between separate drugs is made. All drugs that could be prescribed in this trial (except secukinumab) are introduced in chapter 7.1. We classify secukinumab as the sole IMP, since this is the drug that is given at another time point, compared to standard care.

Secukinumab

Secukinumab is a human anti-interleukin-17A monoclonal antibody, which has shown efficacy in immune-mediated inflammatory diseases, such as psoriasis, PsA and ankylosing

spondylitis[18-20]. Common side effects include upper respiratory tract infections, such as nasopharyngitis and rhinorrhea, but also oral herpes, diarrhea and urticaria[21]. Every 4 weeks 300 mg secukinumab will be administered subcutaneously after an initial standard loading dose of weekly 300mg secukinumab for 4 weeks (arm 2). Secukinumab is registered for PsA patients with active disease failing MTX.

In this study we have chosen a dosage of 300mg per 4 weeks. This has two reasons. The first reason is that we have chosen a treat to target strategy with MDA as the target. One of the criteria for MDA is psoriasis and a dosage of 300mg per 4 weeks is the standard dosage secukinumab for psoriasis. Secondly, the aim of this study is to investigate whether a strategy treatment with an early aggressive therapeutic intervention using secukinumab will improve T2T in PsA. For this reason we have chosen the highest registered dosage of secukinumab.

6.2 Summary of findings from non-clinical studies

All medication used in this T2T trial is registered for PsA. Non-clinical data revealed no special risk of secukinumab for humans (see SmPC Secukinumab 12-11-20198, Chapter 5.3).

6.3 Summary of findings from clinical studies

All medication used in this T2T trial is registered for PsA. A summary of the clinical efficacy and safety of secukinumab is provided in the SmPC Secukinumab version 12-11-2019, page 10-14.

6.4 Summary of known and potential risks and benefits

All medication used in this T2T trial is registered for PsA. Potential risks, contraindications and adverse effects of secukinumab are mentioned in the SmPC Secukinumab 12-11-2018, chapter 4.3, 4.4-4.8. For benefits observed in clinical trials, see page 10-14.

6.5 Description and justification of route of administration and dosage

Secukinumab will be administered by subcutaneous injections in the recommended dose of 300mg for subjects with moderate to severe PsA. Each 300mg dose is given as two subcutaneous injections of 150mg/1mL. If possible, areas of the skin affected by psoriasis will be avoided as injection sites.

6.6 Dosages, dosage modifications and method of administration

Subjects in the secukinumab arm will receive 300mg monthly starting with a loading dose the first month of 300mg weekly.

6.7 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the investigational medicinal products will be done according to the relevant GMP guidelines by the pharmacy of the Erasmus MC. See annex 13 of the guideline Good Manufacturing Practice (2003/94/EG, via http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf)

6.8 Drug accountability

Secukinumab will be dispensed by one central pharmacy: Erasmus MC. The drug will be dispensed by the pharmacy to each individual patient using a certified courier. Accountability will be assessed each visit by the investigator by counting the unused syringes.

7. NON-INVESTIGATIONAL PRODUCT

All drugs, except for secukinumab (see chapter 6), will be prescribed through the normal route. That is, patients will be handed a prescription by their treating rheumatologist to pick up the medication in their pharmacy.

7.1 Name and description of non-investigational product(s)

Methotrexate

MTX is considered one of the group of synthetic DMARDs (s-DMARDs) and is the most commonly prescribed first line therapy in PsA. It is an immune suppressant licensed for the treatment of psoriasis and RA. Common side effects include nausea, fatigue, mouth ulcers, elevated liver enzymes and leucopenia. It is given orally or subcutaneously in doses from 5-25mg per week. It is the most commonly prescribed first line treatment for PsA and is also used as the default first line therapy for all patients in the clinic. In the standard care arm, it will be prescribed at 15mg per week for the first 2 weeks, 20mg per week for the next 2 weeks and 25mg per week thereafter as tolerated. In the secukinumab arm the dose will not be escalated beyond the initial dose of 15mg/week.

Sulfasalazine

Sulfasalazine is considered as one of the members of the group of s-DMARDs and is one of the commonly prescribed second line therapies in PsA. It is an immune suppressant licensed for the treatment of RA. Common side effects include nausea, fatigue, rash and leucopenia. It is given orally in doses ranging from 500mg to 2g daily in two or three divided doses. It is one of the second line DMARDs that may be used in combination with MTX in

arm 1 of the trial. It will be prescribed with a standard increasing dose over the first 4 weeks aiming for a dose of 100mg twice daily.

TNF blockers

TNF inhibitors, such as infliximab, etanercept and adalimumab selectively block the role of the cytokine TNF-α. TNF-α is elevated in the skin and synovium of patients with PsA and multiple trials have shown efficacy of anti-TNFα agents[22]. Common side effects are respiratory complaints; pneumonia, sinusitis, pharyngitis, also headache, abdominal pain, nausea, vomiting, anemia, leucopenia, neutropenia, elevated liver enzymes and injection site reactions. The type of TNFα agent and dosage for individual patients will be selected by the treating rheumatologist (arm 1 and 2) in line with national reimbursement guidelines.

Apremilast

Apremilast is a targeted synthetic DMARD, which acts as a phosphodiesterase 4-inhibitor. It has shown a moderate efficacy on joints, skin and entheses in PsA[23]. In the Netherlands, this immunosuppressive drug is currently only indicated in patients with plaque psoriasis. It may be prescribed to patients with PsA when prior treatment with DMARDs has failed. Common side effects are gastro-intestinal complaints, such as nausea, vomiting and diarrhea, but also weight loss and respiratory tract complaints like coughing, nasopharyngitis and bronchitis. Headache, depression and insomnia have been reported as well. During the trial it will be prescribed orally is a dosage of 30mg twice a day (arm 2).

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

This study is a strategy treatment trial, not a drug trial. For this reason we only monitor drug accountability of the IMP (see Chapter 6.8).

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

ACR 50 response at 6 months.

8.1.2 Secondary study parameters/endpoints (if applicable)

- ACR 20 and 70 at 6 months and ACR 20, 50 and 70 at 12 months.
- MDA[3], VLDA, DAPSA and PASDAS at 6 and 12 months.
- Short Form 36 Health Survey (SF-36)[14], BRAF and PSAID[15] at 12 moths.
- Productivity Cost Questionnaire (PCQ)[24] at 12 months.
- The PsA-modified SHS at 12 months.

8.1.3 Other study parameters (if applicable)

Not applicable.

8.2 Randomisation, blinding and treatment allocation

Patients will be randomized to one of the two treatment arms, using variable block randomization stratified for center, by an independent call-center.
Treatment allocation is not blinded for patients, treating physicians nor nurses. Trained research nurses will calculate the score on which the decision to escalate therapy will be based.

8.3 Study procedures

During the duration of the study, from inclusion to month 12, assessments must be performed as indicated in Table 1, see next page.
Subjects should be seen for all visits on the designated day, or as closely as possible to the

originally planned visit schedule. If subjects refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason.

Screening will take place before baseline measurements and includes:
- CASPAR criteria
- Eligibility criteria
- Hepatitis B and C: to determine possible viral hepatitis.
- Chest X-ray: to determine possible latent tuberculosis.
- PPD skin test or a Quantiferon test: to exclude possible latent tuberculosis.
- Urine pregnancy test

Subjects who prematurely withdraw after randomisation from the study will not be replaced.

	Base	6 wk	3 m	6 m	9 m	12 m	Discontinuation
Inclusion/exclusion criteria	x						
Demographic data	x						
Comorbidity	x			x		x	x
Medication	x		x	x	x	x	x
Adverse events			x	x	x	x	x
Physical exam							
general (height, weight etc)	x			x		x	x
66/68 joint count[25]	x		x	x	x	x	x
LEI/Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [26]	x		x	x	x	x	x
Leeds Dactylitis Index (LDI)[26]	x		x	x	x	x	x
PASI[27]	x		x	x	x	x	x
PRO							
PSAID-12[15]	x	x	x	x	x	x	x
MCQ	x	x	x	x	x	x	x
PCQ[24]	x	X	x	x	x	x	x
HAQ[17]	x	x	x	x	x	x	x
Skindex-17[28]	x	X	x	x	x	x	x
EQ5d 5L[29]	x		x	x	x	x	x
SF36-PCS[14]	x	x	x	x	x	x	x
SF36-MCS[14]	x	x	x	x	x	x	x
VAS	x	x	x	x	x	x	x
BRAF MDQ/NRS	x	x	x	x	x	x	x
Laboratory							
Standard (i.e. ESR, ALAT, GFR, FBC)	x		x	x	x	x	x
Radiology							
X-ray of hands and feet[16]	x					x	x

Table 1: Study assessments

Demographics

The core demographic dataset will include age, sex, ethnicity, marital status, work status, education, smoking and alcohol use.

Disease duration: Information will be gathered about the presence and onset of arthritis, psoriasis, back pain and/or enthesitis.

Family history: PsA, RA, ankylosing spondylitis, psoriasis, inflammatory bowel disease, diabetes and cardiovascular disease

Comorbidities

Ankylosing spondylitis, inflammatory bowel disease, lymphoma, uveitis, diabetes and cardiovascular disease.

General physical examination

Height, weight, abdominal girth and blood pressure.

Arthritis (66/68 joint count[25])

Joint tenderness and swelling will be classified using the 66/68 SJC/ TJC[25]. Joint pain (68 joints) and swelling (66 joints) is graded on a 0-1 scale.

The following joints are evaluated bilaterally:

- Upper body: temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, meta-carpophalangeal, proximal interphalangeal and distal interphalangeal.
- Lower body: hip (only tenderness), knee, ankle, tarsus, metatarsophalangeal and proximal interphalangeal joints are evaluated.

Psoriasis (PASI[27])

Skin disease will be evaluated with the PASI score. The PASI examines four body regions: i) the head and neck, ii) the hands and arms, iii) the chest, abdomen and back (trunk) and iv) the buttocks, thighs and legs. The area score can range from 0 (no psoriasis) to 6 (all of the skin affected). The severity score for each region is reached by adding scores for redness, thickness and scale, each of which is graded from 0 to 4, giving a maximum of 12. An area and severity score for each region is calculated by multiplying the area score by the severity score (maximum 6 x 12 = 72). The amount each region contributes to the final PASI is then weighed according to how much of the total body skin surface it represents. The head and neck contribute 1/10, the hands and arms 1/5, the trunk 3/10 and the buttocks, thighs and legs 2/5. The region scores are each weighed by the given amount and then added to give

the final PASI score[27].

Enthesitis (LEI/ MASES[26])

Enthesitis will be graded with the Leeds Enthesitis Index (LEI) and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).

LEI

In the LEI 6 entheseal points are examined:

- bilaterally the lateral epicondyle of the humerus at the common extensor origin.
- bilaterally the medial condyle of the femur, superior to the joint line, at the origin of the medial collateral ligament.
- bilaterally the posterior prominence of the calcaneum at the insertion of the Achilles tendon.

MASES

In the MASES 13 entheseal points are examined:

- bilaterally 1st Costochondral joint
- bilaterally 7th Costochondral joint
- bilaterally posterior superior iliac spine
- bilaterally anterior superior iliac spine
- bilaterally Iliac crest
- bilaterally proximal insertion of Achilles tendon
- 5th Lumbar spinous process

Pressure is exerted at the enthesis sufficient to blanch the finger nail of the examiner (approximately 4 kg). If pain is experienced during examination, the enthesis is graded as 1, otherwise as 0. Therefore, the maximum scores are 6 and 13 points for the LEI and MASES respectively.

Dactylitis (LDI)[26]

Dactylitis will be evaluated with a modified Leeds Dactylitis Index (LDI). The modified LDI scores a digit as dactylitis, when the digit is swollen and painful when pressed. LDI assesses all 20 digits (max. score 20)[26].

Patient reported outcomes

The following patient reported outcomes will be used. We are aware that it will require a certain effort and amount of time for patients to fill in this number of questionnaires. From experience of the DEPAR cohort we know that per study visit it will take approximately 30

minutes for a patient to fill in all the questionnaires. For most patients this does not pose as an obstacle to participate in the study. Since patients will participate in either DEPAR or STAMP, they are not required to fill in the questionnaires twice per study visit.

The PsA Impact of Disease questionnaire (PsAID-12)

The PsAID-12 is the first PsA-specific questionnaire developed in cooperation with patients and is based on their experience of the impact of the disease on dimensions of health. The 12 items are scored on a 0-10 scale. A higher score on the PsAID indicates more impact of the disease. Its validity, responsiveness to change and its performance in composite disease activity measures will be investigated.

Productivity Cost Questionnaire (PCQ)[24]

Work performance will be evaluated using the iMTA PCQ (iPCQ). The iPCQ includes three modules measuring productivity losses of paid work due to 1) absenteeism and 2) presenteeism and productivity losses related to 3) unpaid work. The iPCQ adopts a 4-week recall period[24].

Short form 36 (SF-36)[14]

QoL will be assessed with the Short Form 36 Health Survey (SF-36). The SF36 is a generic 36-item questionnaire covering 8 dimensions: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning and mental health. From these dimensions summary scores will be calculated to provide a global measure of physical (PCS) and mental (MCS) functioning[14]. The SF-36 performs well in PsA and is frequently used.

Skindex-17[28]

The Skindex-17 is a dermatology-specific QoL instrument and constitutes two subscales, symptoms and psychosocial. It consists of 17 items (12 psychosocial; 5 symptoms) and answers are given on a 5-point scale: never, rarely, sometimes, often and always[28]. The recall period is 7 days. It is suggested that the Skindex-17 performs better in case of mild psoriasis, which is more often the case in PsA. Its superiority compared to the Dermatology Life Quality Index (DLQI) and its performance in composite disease activity measures will be investigated.

EuroQol 5 dimensions (EQ-5D)[29]

The EQ-5 provides a simple descriptive profile and a single index value for health status. It comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and unable to/extreme problem[29].

BRAF

A combination of the Multi-Dimensional questionnaire (BRF-MDQ) and the Numeric Rating Scale (NRS) will be used. The MDQ is a 20-item questionnaire giving an overall global score and four subscale scores reflecting physical fatigue, living with fatigue, cognitive fatigue and emotional fatigue. The NRS consists of three single item scales measuring fatigue severity, effect and coping using numerical rating scales.

HAQ-DI

The HAQ-DI, assesses a subject's level of functional disability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity and activities that involve both lower and upper extremities. There are 20 questions in eight categories of functioning, including dressing, rising, eating, walking, hygiene, reach, grip and usual activities. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty[0]), some difficulty (1), much difficulty (2) and unable to do [3]).

Visual Analog Scale (VAS) 0–100 mm

Patient

- The patient will fill out a VAS on their arthritis, psoriasis, both combined and pain.

Rheumatologist

- The rheumatologist will assess the severity of the patients arthritis, psoriasis and both combined.

Laboratory

As part of routine clinical practice, the following parameters are measured in the local laboratories of the participating hospitals:

- Acute phase reactants: ESR, CRP
- Hematology: hemoglobin, red blood cell count, white blood cell count, thrombocytes
- General chemistry: ALT(SGPT)
- Antibodies: Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) only at baseline

Radiographic damage (X-rays of hand and feet)[16]

The PsA-modified SHS will be used to evaluate radiographic joint damage. To assess PsA-specific radiological damage, scores for the distal interphalangeal hand joints and pencil-in-cup/gross osteolysis deformities are added to the original SHS. The total PsA-modified SHS (0-528) is a sum of erosion (0-320) and joint space narrowing (JSN, 0-208) scores in 40 hand joints and 12 feet joints[16]. Taking radiography of hand and feet is part of routine clinical practice.

Disease activity measures

ACR response criteria

The ACR response will be used to determine efficacy. A subject is defined as an ACR 20 responder if, and only if, the following three conditions are met:

1. they have a ≥ 20% improvement in the number of tender joints (based on 68 joints)
2. they have a ≥ 20% improvement in the number of swollen joints (based on 66 joints)
3. they have a ≥ 20% improvement in three of the following five domains:

- Patient's global assessment of disease activity (measured on a VAS scale, 0-100)
- Physician's global assessment of disease activity (measured on a VAS scale, 0-100)
- Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
-HAQ-DI© score
- Acute phase reactant (hsCRP or ESR)

ACR 50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.
ACR 70 = 70% improvement in at least 3 of the 5 measures and 70% improvement in the swollen and tender joint count.
The ACR response is to be assessed at the visits/time points shown in Table 6-1 and Table 6-2.

MDA[3]

The proportion of subjects achieving MDA, which is defined as 5 of the following 7 domains: ≤ 1 TCJ, ≤ 1 SJC, PASI ≤ 1 or BSA≤3%, patient pain VAS ≤ 15, patient global assessment of disease activity VAS ≤ 20, HAQ-DI© ≤ 0.5, tender entheseal points ≤ 1[3].

PASDAS

Seven components are: Patient reported measures (excluding mental component summary score (MCS) of the medical outcomes survey Short Form-36 (SF-36-PCS)), skin, peripheral joint counts (TJCs and SJCs), Dactylitis (LDI), Enthesitis (LEI), acute phase response (CRP) and Patient & Physician global VAS scores.
PASDAS = (0.18 x √Physician global VAS)
+ (0.159 x √Patient global VAS)
- (0.253 x √SF36-PCS)
+ (0.101 x LN (SJC + 1))
+ (0.048 x LN (TJC + 1))
+ (0.23 x LN (Leeds Enthesitis Count + 1))

+ (0.377 LN (Dactylitis count + 1))
+ (0.102 x LN (CRP + 1)) +2)*1.5.

DAPSA

DAPSA adds the SJC66, TJC68, VAS global (0-10 scale), VAS pain (0-10 scale), and CRP in a total score.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The Investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1. Specific criteria for withdrawal (if applicable)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

No replacement will be made for subjects withdrawing from the trial after randomisation. The reason for withdrawal, where provided, will be recorded in the Case Report Form (CRF).

8.6 Follow-up of subjects withdrawn from treatment

If the participant or Investigator withdraws from active treatment, participants will still be asked to complete follow-up with data collected at planned time points, unless they indicate that they wish to withdraw from follow-up. Withdrawn participants will not be replaced.
If the participant is withdrawn from treatment due to an adverse event, the Investigator will arrange for additional follow-up visits or telephone calls as required until the adverse event has resolved or stabilised.

8.7 Premature termination of the study

The Investigator may discontinue a participant from treatment within the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent

- Loss to follow-up

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (dutch; WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited MREC (Medical Research Ethics Committee) without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The Investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether considered related to the investigational products. All AEs reported spontaneously by the subject or observed by the Investigator or his staff will be recorded.

AEs of special interest occurring during the study will be collected at each study visit through patient questionnaires and/or physician reports. Such AEs include:

- Patient reported: nasopharyngitis, upper respiratory tract infection, headache, nausea, diarrhea, vomiting, injection site reaction.
- Physician reported: hypercholesterolemia, hypertension, infections, neutropenia/leucopenia, liver function test abnormalities.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All SAEs occurring during the trial and until 4 weeks after the final visit that are observed by the Investigator or reported by the participant, will be recorded and reported to the study team on a digital trial-specific SAE Form. All SAEs must be reported on the digital SAE reporting form and the study team, within 24 hours of the Site Study Team becoming aware of the event. They will perform an initial check of the report, request any additional information, and ensure it is reviewed correctly. Additional and further requested information (follow-up or corrections to the original case) will be detailed on the same digital SAE form (where changes are signed and dated) or on a new SAE Report Form (if too many changes) .

Reporting Obligations to Novartis

In addition to compliance with all reporting requirements above, the PI shall:

a) Report to Novartis all SAEs experienced by a study subject receiving a Novartis product within 24 hours of learning of the event regardless of the relationship of the event to the Novartis product. The PI shall make available to Novartis promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by Novartis, and,

b) Copy Novartis on the submission to the country regulatory agency of events meeting the definition of an expedited safety report at the time of submission to the agency; and,

c) Notify Novartis upon any subjects receiving a Novartis Product who are pregnant.

Novartis' contact for reporting serious adverse drug experiences, pregnancy experiences, and communications of country regulatory agency submissions for expedited safety reports shall be bijwerkingen.phlnar@Novartis.com.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited MTEC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a maximum period of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions (ARs) are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected ARs are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the AR must be unexpected, that is to say, the nature and severity of the AR are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure (IB) for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal *Eudravigilance* or *ToetsingOnline* is sufficient as notification to the competent authority (CA).

The sponsor will report expedited all SUSARs to the CAs in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the ARs. For fatal or life threatening cases the term will be maximum 7 days for a preliminary report with another 8 days for completion of the report.

This study is not blinded, so therefore codebreaking is not necessary.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, (local) CA, CAs of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious ARs, along with an aggregated summary table of all reported serious ARs, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till the end of the study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

A DSMB will be appointed to safeguard the interests of the trial participants, to assess the safety and efficacy of the interventions during the trial and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMB will be independent of the trial investigators and sponsor and will adopt a charter that defines its terms of reference and operation in relation to oversight of the trial. It will meet at least every 12 months over the duration of the trial. The DSMB will not be asked to perform any formal interim analyses of effectiveness. It will, however, review accruing data and summaries of that data presented by treatment group. It will also consider emerging evidence from other related trials or research and review any related SAEs that have been reported. The DSMB may advise the chair of the TSC at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety or clear evidence of the effectiveness of one of the treatments. The DSMB will comprise an independent medically qualified clinician, statistician, and other researchers.

10. STATISTICAL ANALYSIS

Primary and secondary efficacy analyses will include all patients according to the treatment assigned at randomization, i.e. intention-to-treat analysis, also known as full analysis. For the binary primary endpoint (ACR 50) the intervention will be compared to the control arm using logistic regression. Secondary outcomes will be evaluated as appropriate regarding the distribution of the data. Endpoint analysis at 6 and 12 months will be performed, as well as analysis of outcome evolvement over time. The latter using repeated-measures mixed models. Missing data will be dealt with using multiple imputation and a sensitivity analysis will be performed by imputing non-response as worst case scenario and response as best case scenario. All analysis will be performed using STATA.

10.1 Primary study parameters

All analysis will be performed in STATA15 or higher version. The main analysis will be performed from an intention-to-treat perspective. In addition, a per protocol analysis will be performed. Missing value will be dealt with as described below. Reporting the results will follow the Consort Statement.

Primary Objective:

To compare effectiveness, using the proportion of patients achieving an ACR 50 response, between two treatment regimens (1) standard care and (2) secukinumab in an early stage at 6 months.

Technique:

The difference in proportions response between the two arms will be tested by a two-sample proportion test [prtest in STATA]. In addition, logistic regression will be performed.

10.2 Secondary study parameters

Secondary Objective:

To compare effectiveness at 6 and 12 months between two treatment strategies, standard care (arm 1) and early secukinumab arm (arm 2) using:

- Patients achieving ACR 20 and 70 at 6 months
- Patients achieving ACR 20, 50, 70 at 12 months
- Patients achieving MDA and VLDA at 6 and 12 months
- DAPSA and PASDAS scores at 6 and 12 months

Technique

As many comparisons will be made, we create a multiple testing problem for which no elegant solution is available. Although the two-sample proportion test could be used to compare the equality of proportions for binary response and a t-test for continuous outcomes we risk to find relationships that do not exist due to the type 1 errors inheritably related to statistical testing.

Therefore, the second objective will be rephrased as:
To compare effectiveness **over the first year of treatment** between the two treatment strategies, standard care (arm 1) and secukinumab (arm 2) **by assessing the evolvement of** ACR 20-50-70, MDA,[3] VLDA, DAPSA and PASDAS

The two treatment arms will be compared using statistical techniques for longitudinal data to assess the evolvement of the treatment response over time. This will include mixed effects logistic regression for binary outcomes and mixed effects linear regression for continuous outcomes.

Secondary Objective:

To compare QoL at 12 months between two treatment strategies, standard care (arm 1) and secukinumab (arm 2) using:

- SF-36[14]
- PSAID[15]
- BRAF

Technique:

Simple t-tests for the difference between baseline and 12 months follow up will be used to compare the two treatment arms. In addition, mixed effects linear regression will be used to assess the compare the evolvement over time between the two groups.

Secondary Objective:

To compare work performance (presenteeism and absenteeism) at 12 months between between two treatment strategies, standard care (arm 1) and secukinumab (arm 2)

Technique:

Work performance is often skewed. Depending on the distribution we will use either a t-test or Mann-Whitney U test for the difference between baseline and 12 months follow-up to

compare the two treatment arms. For work absence, a binary outcome, the difference in proportions response between the two arms will be tested by a two-sample proportion test. In addition, mixed effects linear, logistic and/or poison regression will be used to assess the evolvement over time between the two groups.

Secondary objective:

To compare progression of radiological damage at 12 months between two treatment strategies, standard care (arm 1) and secukinumab arm (arm 2) using:

- PsA-modified SHS[16] at 12 months

Secondary objective:

To assess the cost-effectiveness between two treatment strategies, standard care (arm 1) and secukinumab (arm 2).

Technique:

Alongside the clinical trial, an economic evaluation will be performed conform the guidelines of the Health Care Institute Netherlands (ZIN, 2015). This evaluation will be conducted from a societal and payer's perspective. When adopting the societal perspective resource, inputs into the treatment arms will be recorded as part of the trial and will be costed using a micro-costing approach. This will involve calculation of the costs of all individual elements (drugs and intervention materials), as well as relevant overheads (administration, managerial, capital, etc.) and adjustment for indirect time (non-face-to-face working time which cannot easily be allocated to specific individuals). All other services used will be costed by applying nationally applicable unit costs, including reference costs for secondary care services, as well as published costs for primary care, social care and education services. Indirect non-medical cost data related to production losses through work loss days and work days with less productivity will be assessed by the PCQ[24]. Outcomes for the economic evaluation will be measured using the EQ-5D-5L[29] measure of health-related QoL. When adopting the payer's perspective only the costs covered by the basic health care insurance will be included. Savings in health care costs are expected to result from reduced sickness absence and productivity loss. The difference in total costs between the two groups will be related to the difference in outcomes to calculate the following incremental cost-effectiveness ratios (ICER): costs per QALY, costs per treatment failure avoided and costs per additional patient with an ACR 50 response. Bootstrapping will be performed to estimate the uncertainty around the ICERs and the results will be shown in cost-effectiveness planes and acceptability curves. Sensitivity analysis will be performed to assess the main drivers of cost-effectiveness.

Missing value analysis:

Pattern of missings will be visualised using M-graphs. Missing follow-up values will be imputed with chained equation multiple imputation using data from the patients randomized in the same arm. This assumes that the missing value pattern is Missingness At Random (MAR). In addition, we will perform a sensitivity analysis with adding the worst scores for those who dropped out in the intervention arm and the best scores in the control arm and vice versa to present the range in which the outcome can fluctuate depending on the missing value mechanism.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 Recruitment and consent

Newly diagnose patients fulfilling the entry criteria and whom have consended to the DEPAR trial will be offered to participate in the trial by their rheumatologist.

If they are interested they will be given the full PIF for this intervention as well as a verbal explanation of the trial. They will be allowed as much time as they wish to consider their participation. If they decline to consent then they will be followed only in DEPAR (in line with their previous consent) assuming their consent for DEPAR remains valid.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

We hypothesize that treatment subjects receive in the secukinumab arm will be beneficial to them. Treatment will not imply that they are under any greater risks, compared to the other

treatment arm, since secukinumab is already registered for PsA.
This study does not include minors nor capacitated adults and is not group related.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data collection
Data will be collected electronically using GemsTracker and Limesurvey. GemsTracker (GEneric Medical Survey Tracker) is a software package for (complex) distribution of questionnaires and forms during clinical research and quality registrations in healthcare developed by the Erasmus Medical Center. The software allows you to set up your own website for data collection. On a GemsTracker site different users are able to submit, view and send information. Within GemsTracker it is possible to configure the rights and roles within the system and it is possible to decline access to certain access for certain roles. GemsTracker can be accessed through depar.ciceroreumatologie.nl. The data entered into GemsTracker will be seen as the source and thus the electronical cares report form (eCRF). The access and role within the eCRF - thus GemsTracker - will be assigned by project coordinator/ IT- coordinator. All rights and roles of those being able to log in to the eCRF are being logged.
LimeSurvey is an open source software to securely create and use online questionnaires.

All participants and a selection of designated and trained research nurses will complete online questionnaires. Patients will not have access to the eCRF and thus to the data, whereas research nurses only have access to the patients included from the hospital they are assigned to. Patients will receive an email including a link to complete the questionnaires. That link does not contain any personal data.
Patients without an email address or who are not willing to complete the questionnaires online will receive a paper version of the questionnaires. After completion, the questionnaires will be sent back to the investigator centre and the answers will be copied in the eCRF.
Those paper versions do not contain any personal data. The original paper questionnaire will be stored in a closed closet at the investigator centre.
Besides the (online) questionnaire, data from the patients file at the hospital will be (automatically) collected. By using a query structured search in the hospitals database, a set of data will be collected and uploaded to the server through a secure FTP connections.

Data storage
The software packages and all data are stored on a server hosted by VANAD Enovation – ISO 27001, ISO 27799 and NEN 7510 certified. Only a dedicated selection of programmers have access to the database on the server and the server is being protected by a whitelist of IP-addresses. Each hospital participating in the trial has a SSH access to the server linked to their own folder where the data is being stored and imported. Thus they can upload their data to the server through a protected connection.

Hosting party	VANAD Enovation
IP-adres	IP: 92.42.238.14 domain: ciceroreumatologie.nl SSL: RapidSSL sha256
Server	Apache2: Apache/2.2.15 OS: CentOS 6.9 (Final) CPU: Intel(R) Xeon(R) CPU X5670 @ 2.93GHz 1 Core Memory: 4gb memory
Software	PHP version 5.5.38 Mysql versie: 5.1.73 PHPMyadmin: 2.11.11.3 (https://depar.ciceroreumatologie.nl/phpmyadmin)
Web installation	● Depar: https://depar.ciceroreumatologie.nl version 1.8.1p5

	Database: depar_gems ● Limesurvey: https://depar.ciceroreumatologie.nl/ls version: 2.05+ build 150520 Database: depar_ls ● CMS ExpressionEngine: https://www.ciceroreumatologie.nl versie: v2.5.5 - Build: 20121220 Database: pixeldeluxe Note: all database users have access to all databases.
Access	Software developers (ENGON, THRANX) can access the var/www/sites data on the server via SSH and the PHP Myadmin url. The access is protected by a whitelist of IP-addresses. Each hospital has a SSH access linked to their own folder where the data is being imported. They can upload data to the server.

Data export, analysis and sharing

In order to conduct scientific research the data will be downloaded from the server to a local computer. This will be done by a designated researcher – the data manger/ project coordinator – as the first step contains data that can be traced to the participants. The data manager will remove personal data and will create a pseudonymized dataset that can be used by other researchers.

The key file linking the patient to its study number will be stored at the local network (password protected) of the project manager/ data manager at the investigator centre.

Software used to analyse the data are STATA and R/R Studio both running on the local desktop of the computer.

Data confidentiality

All data will be handled confidentially and all medical centres will be asked to sign a confidentiality agreement. In addition, all staff will be trained before having access to the GemsTracker/eCRF.

12.2 Monitoring and Quality Assurance

All aspects of the study will be carefully monitored for compliance with applicable government regulations with respect to current good clinical practice and SOPs.

Study Monitoring and Source Data Verification

The principal investigator ensures that appropriate monitoring procedures are performed before, during and after the study.

All aspects of the study are reviewed with the local Investigator and the staff at a study Initiation visit and/or at an Investigators' Meeting.

Prior to enrolling subjects into the study, a member of the central study team will train local staf on the procedures for obtaining IC, record keeping, and reporting of AEs/SAEs with the investigator.

Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by a member of the central study team in accordance with the Study Monitoring Plan. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that ICs, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the MREC and to the CA.

Non-substantial amendments will not be notified to the accredited MREC and the CA, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MREC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious ARs, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited MREC and the CA of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited MREC and the CA within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the CA.

12.6 Public disclosure and publication policy

The results of this scientific research will be disclosed unreservedly.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable.

13.2 Synthesis

All medicinal products used in this T2T trial are registered for PsA and different combinations of these products are given in standard PsA care. The first treatment arm contains subjects who are given standard care, which is the same as care they would receive if they were to decline participation in this study. For this reason, chapter 13.1 is skipped/not applicable.

We expect subjects in the secukinumab (intervention) arm to be exposed to a medium risk. In our opinion the benefits of participation and the therapeutic effect we expect secukinumab to have outweighs the possible risks, like earlier mentioned side effects. In this study, the time point at which secukinumab will be administered is earlier than in standard care, which could be a potential risk for patients. So far, no studies have been conducted in which secukinumab is used as first line therapy in PsA. This makes it difficult to predict the precise risk subjects in this group will be exposed to. Since secukinumab is registered for PsA and patients and physicans/research nurses are instructed to pay careful attention to side effects and/or AEs, we believe that safety of subjects is sufficiently guaranteed.

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