RESEARCH PROTOCOL

Tight control dose reductions of biologics in psoriasis patients with low disease activity: a randomized pragmatic trial.

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PROTOCOL TITLE '*Tight control dose reductions of biologics in psoriasis patients with low disease activity: a randomized pragmatic trial.'*

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	The Netherlands
Multicenter research:	***Participating centers*:***
	ZGT Almelo, dept. of Dermatology
	ZGT Hengelo, dept. Of Dermatology
	St. Anna Hospital Geldrop, dept. Of Dermatology
	Slingeland Hospital Doetinchem, dept. of Dermatology
	Gelre Hospital, Apeldoorn, dept. Of Dermatology
	***see section I1 for additional information centers.**
Sponsor (in Dutch: verrichter/opdrachtgever)	***RadboudUMC, Nijmegen***
Subsidising party	***Zonmw, The Netherlands***
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Pharmacy	***Not applicable***

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
ANCOVA	**Analysis of covariance**
CV	**Curriculum Vitae**
DALY	**Disability-adjusted life year**
DCER	**Decremental cost-effectiveness ratio**
DLQI	**Dermatology Life Quality Index**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HRQoL	**Health-related quality of life**
Hs-CRP	**High-sensitivity c-reactive protein**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
iMTA	**Institute for Medical Technology Assessment**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NI	**Non-inferiority**
PASI	**Psoriasis Area and Severity Index**
RA	**Rheumatoid arthritis**
(S)AE	**(Serious) Adverse Event**
SF-36	**Short-form (36) health survey**
SmPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie 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**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
WTP	**Willingness to pay**

SUMMARY

Rationale/hypothesis: Moderate-to-severe psoriasis can be treated with biologics. These drugs have significantly improved the quality of life of psoriasis patients, but are very expensive drugs that should be used as efficiently as possible. In addition, the long-term safety profile can probably be improved if patients receive the lowest effective dose.

Objective To investigate whether the dose of biologics can be reduced in patients with psoriasis with stable disease: Is dose reduction non-inferior to the current practice regarding clinical effectiveness? Secondary aims are: to investigate what influence dose tapering has on quality of life, whether there are predictors for successful dose reduction, and to determine the cost-effectiveness of dose reduction.

Study design: A pragmatic, multicentre, randomized, controlled, non-inferiority study with cost-effectiveness analysis.

Study population: Patients who used a biologic for at least 6 months (etanercept, adalimumab, ustekinumab) can be included if they have long-term stable low disease activity. Low disease activity is defined as a PASI score (Psoriasis Area and Activity Score) <5 and a health-related quality of life score ≤5 (Dermatology Quality of life index: DLQI).

Intervention: 120 patients will be randomized into two groups: (1) dose reduction guided by PASI and DLQI (n=60, intervention) and (2) maintenance of normal dosage (n=60, usual care).

Main study parameters/endpoints: The primary outcome is clinical effectiveness. Secondary outcomes are: health-related quality of life (HRQoL), number and time to disease flares, costs, health status, anti-drug antibody formation and serious adverse events

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: As it is a daily practice study, in general, no extra visits are needed except for the regular visits every three months during one year. The general visits will be prolonged due to scoring disease activity, administering questionnaires and discussing drug changes. One or two extra vials of blood will be taken during regular blood collection every visit. Risks of dose decrease are deemed to be small. Exacerbation of psoriasis can be expected as well as antibody formation against the biologic. In general, we assume a lower risk of adverse events related to the drug itself due to the lower toxicity profile.

1. INTRODUCTION AND RATIONALE

Psoriasis is a chronic skin disease characterized by erythematous, scaly plaques and associated with important comorbidities such as cardiovascular disease and psoriatic arthritis. In Europe, psoriasis prevalence varies depending on the country of origin, with higher prevalence numbers in northern countries [range: 1.3-8.5%].[1] The disease burden is high. Worldwide, the mean number of disability-adjusted life years (DALYs) per 100.000 persons attributed to psoriasis was 15.6. (Goff BJD 2015, *in press*). Impairment of disease-related quality of life is comparable to that of patients with cancer and depression.[2] In the past years, effective targeted biological treatments have become available for psoriasis and are frequently prescribed by dermatologists at the moment. These biologics block specific cytokines (TNF-alpha, Il-12, Il-23) in the psoriasis pathogenesis pathway. In general, biologics are considered relatively safe. Important side effects mainly comprise immunosupression-related risks such as infections (including TBC), and non-melanoma skin cancer. However, the long-term effects are not known yet.

Biologics should be efficiently prescribed, as they involve high costs: approximately €15.000–30.000 per patient annually (€15.000 refers to the normal dose). For the Netherlands, the estimated total annual costs for psoriasis treatment with biologics reaches €56 million, placing a high burden on the national health care expenditures. [3] Another issue is that the risk of serious side-effects (malignancies) was found to be dose-dependent in a study of TNF-alpha inhibitors in RA.[4] Current opinion holds that thriving for the lowest possible, effective dose of biologics should be self-evident.[3] Of note, biologics dose-tapering studies in other diseases were referred to in the Dutch news (NOS) indicating the high impact of such studies on population level.[5] We aim to investigate whether we could taper the biologics dose in psoriasis as well. The primary research question for this proposal is: Is a biologics dose tapering strategy non-inferior to usual care with respect to disease activity? Secondary questions are: Is quality of life (DLQI) maintained during dose tapering? Are there factors that predict successful dose tapering? How cost-effective is dose tapering in this group? How does dose-tapering change the safety profile regarding side-effects or antibody formation?

The evidence for dose tapering in psoriasis is limited, with only one small prospective study reporting successful dose tapering of adalimumab in 10 patients.[6] The other evidence concerns small retrospective case descriptions [7-9] or early dose-reductions for etanercept which lie beyond the scope of the present study proposal.[10] Evidence is available that stopping biologic treatment leads to disease flare in a substantial part of patients and

reintroduction of the biologic can lead to lower effectiveness. [11-14] Moreover, disease related quality of life was shown to worsen disproportionately during flares.[13] In infliximab, intermittent therapy is associated with higher risk for infusion reactions and loss of efficacy and will therefore not be investigated.[15] For the abovementioned reasons, we propose to study dose tapering for etanercept, adalimumab and ustekinumab only, under tight control of disease *without* discontinuation of the drug due to the prementioned obstacles. Dose reduction will be achieved by increasing the time between injections. For instance, the original etanercept dose (50mg/week) will be decreased to 50mg/10 days first. If disease activity maintains low for 3 months, further decrease to 50mg/2 weeks will take place. Treating patients with etanercept 50mg/2 weeks instead of 50mg/ week would lead to an annual cost reduction of €7.500 in a single patient and would result in an estimated €5.4 million of savings *annually* for patients with psoriasis treated with biologics in the Netherlands

Evidence for dose tapering in rheumatic diseases exists, however this evidence is not directly applicable to the psoriasis patient and separate studies are mandatory. Although psoriasis shares features of its inflammatory pathway with other diseases[16], important differences exist. An important discrepancy is that dose tapering in RA (and also in psoriatic arthritis) is almost always combined with continuation of other disease-modifying antirheumatic drugs, which influence effectiveness. In psoriasis, biologics are most often prescribed as monotherapy, conform the label. Furthermore, drug survival studies comparing RA and psoriasis revealed significantly higher survival rates for psoriasis over RA. This indicates differences between the diseases regarding drug related effectiveness, side-effects and behavioural factors. (BioCAPTURE and DREAM registry data, *in press JAAD 2015)* Moreover, safety studies showed differences between adverse events of biologics in RA as compared to psoriasis or psoriatic arthritis.[17, 18] The value of adalimumab antibodies and through levels at baseline for prediction of successful dose response has been studied in rheumatoid arthritis, but is contradictory.[19, 20]

To conclude, with this multicenter, pragmatic, randomized, controlled, non-inferiority study with cost-effectiveness analysis, we aim to assess whether clinical effectiveness (PASI) of dose tapering is not inferior to usual psoriasis care with a margin of 0.5 at 12 months of follow up. Also, influence of intervention on dermatology related quality of life (DLQI) will be assessed. Patient characteristics, immunologic and genetic factors that can be predictive for successful dose-reduction will be investigated as well to take note of diversity among patients. Moreover, the cost-effectiveness of the intervention will be assessed. Safety profiles will be established in both groups and trough drug concentrations will be compared.

Successful dose-tapering of biologics could lead to important cost-savings and probably to a better long-term safety profile.

2. OBJECTIVES

Primary Objective: We aim to investigate whether we could taper the biologics dose in psoriasis. The primary research question for this proposal is: Is a biologics dose tapering strategy non-inferior (NI) to usual care with respect to disease activity (PASI) at 12 months (NI margin=0.5).

Secondary Objective(s):

- Proportion of patients with successful dose tapering at 12 months. Successful dose tapering is defined as a lower dose than the regular dose (as defined by the label).
- To compare quality of life (DLQI) maintenance between dose-reduction and usual care.
- To compare disease activity (PASI) at all time points (3-6-9 months) between dose-reduction and usual care.
- To compare the proportion of patients with 1 or more persistent flare (persistent flare is defined as at least 3 months PASI increase >5 or DLQI >5) between dose-reduction and usual care.
- To identify factors that are associated with successful dose tapering (e.g. baseline variables such as patient and treatment characteristics, Hs-CRP, HLAcw6, anti-drug antibody and through levels).
- To compare development of serious adverse events (SAEs) between dose-reduction and usual care.
- To calculate cost-effectiveness of the intervention.

3. STUDY DESIGN

This study is a multicenter, pragmatic, randomized, controlled, non-inferiority trial.

Randomization will be web-based and stratified by center using variable permuted blocks with concealment of allocation. Patients will be randomized 1:1 to (1) dose-tapering or (2) drug continuation of the maintenance dose. We aim to include all 3 biologics to an equal extent. Appendix 1 contains a flow chart for inclusion and randomization of study population. Appendix 2 shows the study protocol per treatment arm.

1. Dose-tapering: patients receive daily practice care, but doses of etanercept, adalimumab or ustekinumab will be lowered: intervals of drug-administration will be prolonged stepwise with tight control of disease activity and DLQI. First, the dose will be decreased to 66-70% of the normal dose (by interval prolongation with a factor 1.5). If patients remain in a state of low disease activity, the dose will be further reduced to 50% (by doubling the original interval). Each step will be analyzed after three months, or when the patient visits earlier due to complaints. The disease is considered to flare when the PASI score increases 3 points as compared with baseline PASI and/or DLQI becomes >5 (decreased HRQoL). If a step-down leads to disease-flare, patients will return to the preceding step, and the dose will not be tapered again.
    - Etanercept maintenance dose is 50mg/week; the interval will be prolonged subsequently to 50mg/10 days (step 1) and to 50mg/14 days (step 2).
    - Adalimumab maintenance dose is 40mg/2 weeks; the interval will be prolonged subsequently to 40mg/3 weeks (step 1) and to 40mg/4 weeks (step 2).
    - Ustekinumab is given 90mg or 45mg /12 weeks (dose depends on weight); the interval will be prolonged subsequently to 90mg or 45 mg/18 weeks (step 1) and to 90mg/45mg per 24 weeks (step 2).
2. Continuation of maintenance dose: patients will continue treatment with the normal dose and treatment regimens will be based on usual daily practice care. Treatment decisions are made at the discretion of the treating physician. Dose tapering beyond the dose as advised by the label are not common in daily practice psoriasis care. All study parameters will be monitored in this group.
    - All patients included in this study were using a regular dose of the biologic as advised by the label (etanercept 50mg/week, adalimumab 40mg/2 weeks, ustekinumab 45mg/12 weeks or 90mg/12 weeks in patients with a body weight below or above 100kg respectively).

Allowed concomitant or topical (rescue) medication:

When patients receive conventional antipsoriatic systemic treatments concomitant to their original biologic regimen, this regimen will be described. As it is a pragmatic and randomized trial, we do not want to intervene and expect the use to be equal in both groups. Eventual differences in concomitant use will be described. The same accounts for topical therapy use during the study.

Baseline measures:

- HLA-C*06 allele - HLA-C*06 has been associated with good clinical response on ustekinumab, therefore, we want to investigate whether it is a predictor for successful response and for successful dose-tapering in all 3 biologics.[21]
- Patient and treatment characteristics: sex, age, previous conventional antipsoriatic drugs and/or biologics used, disease duration, and original PASI.

If available, baseline measures will be extracted from the existing BioCAPTURE database. Baseline measures will be used to identify predictors for successful dose tapering.

Outcome measures and assessments:

Primary outcome measure:

Every three months:

- Disease-activity (Psoriasis Area and Severity Index (PASI), effectiveness measure used in most psoriasis trials.)

Secondary outcome measures:

Every three months:

- HRQol (Dermatology Life Quality Index (DLQI)
- Number of patients with 1 or more persistent flares (persistent flare is defined as at least 3 months PASI increase >5 or DLQI >5)
- Treatment characteristics (dose of biologic, drug pauses, use of concomitant antipsoriatic systemic drugs (dose and duration of use), use of topical therapies during treatment (steroid class and duration of use))
- High-sensitivity CRP (marker disease-activity)
- Anti-drug antibody and through levels [x]
- Serious adverse events (SAE) and their causal relation with the biologic
- Costs (iMTA questionnaires)
- Health status (SF-36)

[X]trough levels of ustekinumab cannot be taken every 3 months but will be taken at their trough level moment.

Data collection:

Database management: The collected data will be entered in CASTOR, an electronic database set up for clinical trials. https://www.castoredc.com/nl/waarom-Castor.html. This database is free of charge for studies with <200 patients. Data will be coded and kept based on the rules for good clinical practice (GCP) by BROK certified personnel (GCP: http://ichgcp.net/; codes of conduct: http://www.federa.org/code-goed-gedrag). Handling of personal data will comply with the Dutch Personal Data Protection Act (WBP, wet bescherming persoonsgegevens). As many patients that will be eligible for this study have already been registered in our BioCAPTURE registry, we can extract baseline data from the database. Data of all centers will be monitored following the guidelines of the Radboudumc. Samples send to the dermatology laboratory Radboudumc and Sanquin will be (coded) for the personnel taking care of the samples.

Laboratory measurements

A blood sample will be drawn for HLA-C*06 genetic analysis at baseline. All samples will be analyzed at the dermatology laboratory at the Radboudumc using PCR with sequence-specific primers for this gene. The method is described previously.[22]

For anti-drug antibodies and trough levels, a serum sample will be drawn at trough-level moments. All samples will be sent to the Laboratory for Monoclonal Therapeutics, Sanquin Diagnostic Services, Amsterdam, the Netherlands. The method for analysis is described elsewhere.[23]

4. STUDY POPULATION

4.1 Population (base)

This study will be carried out in 6 dermatology departments in the Netherlands: 1 academic center (Radboudumc, Nijmegen), and in 5 non-academic hospitals (St Anna Hospital, Geldrop; Ziekenhuisgroep Twente (ZGT), Almelo en ZGT Hengelo; Gelre Hospital, Apeldoorn; Slingeland Hospital, Doetinchem.) Patients already using biologics for at least 6 months (etanercept, adalimumab, ustekinumab) for moderate-to-severe plaque psoriasis with sustained low disease activity on biologics will be asked for participation in this study. They will receive oral and written information, and informed consent will be obtained before inclusion in this study.

We define sustained low disease activity by the following criteria:

(1) During the last 6 months, subsequent low disease activity scores (PASI (psoriasis area and severity index) <5) until the moment of inclusion. At least 2 PASI scores should be available.

(2) Good disease-related quality of life (DLQI (dermatology life quality index) ≤5) at the moment of inclusion in the study

The feasibility of inclusion of the patient sample is based on the following calculation: cross-sectionally, 45% of patients currently treated with biologics from our database fulfilled criteria of stable clinical remission. This refers to an absolute number of 90 patients that could participate directly. With regard to the remaining number of to be included patients: we start or switch patients on biologics continuously (approximately 1-2 per week), we therefore expect that we can include new patients who reached the inclusion criteria in time in the Radboudumc frequently. Moreover, 5 non-academic will participate in this study. If we notice that inclusion is problematic or a center cannot participate (anymore) for a reason, we can use our BioCAPTURE network to ask more hospitals to participate.

4.2 Inclusion criteria

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

- Sustained low disease activity as described above on *the dose as advised by the label.*
- Established diagnosis of plaque psoriasis.
- Receiving treatment with adalimumab, etanercept, or ustekinumab for at least 6 months.*

- Age ≥18 years.
- Ability to understand informed consent, read and answer questionnaires.

*Infliximab was excluded for analysis as intermittent therapy increases the risk for infusion reactions. Secukinumab was excluded as it has been introduced very recently and almost no patients can theoretically be stable for > 6 months at start of this study.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Psoriasis itself is not the *main* reason for biologic prescription (e.g. when a patient has RA and psoriasis, and RA is the main reason for the biologic).
- Concomitant use of immunosupressants other than methotrexate or acitretin for psoriasis.
- Severe comorbidities with short life-expectancy (e.g. metastasized tumour).
- Presumed inability to follow the study protocol.

4.4 Sample size calculation

Per arm, 54 patients need to be included to provide sufficient power for statistical analyses (P 80%, α 0.05, β 0.80, NI-margin 0.5). The non-inferiority (NI) margin of 0.5 is calculated based on our opinion of clinical meaningfulness. As patients in clinical remission in the BioCAPTURE cohort showed a PASI standard deviation (SD) of 1.4, this margin is 36% of the SD. This percentage approximates a rule of thumb for calculating the non-inferiority margin: ⅓ of SD. As we performed our analysis with correction for the baseline value of PASI, a formula that will increase power significantly is available taking into account the correlation between the baseline value and the follow-up measurements.[24] This correlation was found to be 0.67 in our existing cohort. When performing a t-test for sample size calculation, the sample size can be multiplied by $1-\rho^2$ if we add one extra subject per group, where ρ is the correlation between the baseline measure and the follow-up measure (here: 0.67). Thus when we perform a t-test with the non-inferiority margin set at 0.5, α set at 5% and a ρ of 0.67, we achieve 80% power when enrolling 54 patients per arm. Taking a possible drop-out rate of 10% into account, 60 patients need to be included in each arm. *(Appendix 3, patient inclusion schedule).*

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The intervention in this study refers to the dose-decrease of regularly used drugs (biologics).

5.2 Use of co-intervention (if applicable)

No other co-intervention is applied.

5.3 Escape medication

As it is a daily practice study, topical therapies and concomitant systemic therapy (methotrexate or acitretin) are allowed and can be used when a disease flare is noticed. Also, if disease activity rises, we will always propose the patient to return to the previously used dose of the biologic. In case of persistent flare, even after reinstallment of the original dose, switch to other biologics will be proposed according to daily practice guidelines.

The patients will be instructed to contact us in case of flare and will consequently be invited for an in-between visit to decide whether dose increase of the biologic and/or escape medication is indicated. This will also be clearly described in the patient leaflet and discussed with the patient before starting the study. The criteria for dose re-increase are based on PASI and DLQI ór if the patient strongly wishes a dose reinstallment of his/her biologic. The latter will be visible in DLQI measurements as well in most cases, as this reflects the patients feelings about his/her psoriasis. If this is not the case, the patient will be a drop out.

5.4 Treatment after study

When dose decrease has shown to be successful in this study and no safety concerns have become visible, we will advise patients who successfully responded to the lower dose in this study to remain on this dose. We will instruct patients to contact his/her physician as soon as a disease-flare develops. If we will find clinically important changes in antibody formation against biologics in case of dose-decrease, we will anticipate on that during follow up.

Currently, continuous monitoring of DLQI and PASI is adapted in the Radboudumc for all daily practice psoriasis care. Thus, patients will be followed using these parameters after the study is finished. In other centers it is expected that patient with successful dose-

decrease will continue the low dose, and will be followed as was done before study inclusion.

6. INVESTIGATIONAL PRODUCT

The biologics used are no strict investigational products. They are used in daily practice and will be produced and distributed as such. Only the frequency of administration will be lowered in the intervention group, and the usual dosage will be continued in the control group. Therefore, information on the products will be given in the 'non-investigational product section'.

6.1 Name and description of investigational product(s)

Not applicable (NA)

6.2 Summary of findings from non-clinical studies

NA

6.3 Summary of findings from clinical studies

NA

6.4 Summary of known and potential risks and benefits

NA

6.5 Description and justification of route of administration and dosage

NA

6.6 Dosages, dosage modifications and method of administration

NA

6.7 Preparation and labelling of Investigational Medicinal Product

NA

6.8 Drug accountability

NA

7. NON-INVESTIGATIONAL PRODUCT

The biologics used are no strict investigational products. They are used in daily practice and will be produced and distributed as such. Only the frequency of administration will be lowered in the intervention group, and the usual dosage will be continued in the control group. Therefore, information on the products will be given in the 'non-investigational product section'.

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

Adalimumab (Humira®) is a recombinant human monoclonal antibody that is expressed in Chinese hamster ovary cells. Farmacotherapeutic category: Immunosuppressive agents, Tumornecrosfactor-alfa (TNF-α) inhibitors. ATC-code: L04AB04.

Etanercept (Enbrel®) is a human tumornecrosisfactor-receptor-p75 Fc-fusion protein produced with recombinant DNA-technology in a mammalian expression system of Chinese hamster ovary cells (CHO). Farmacotherapeutic category: Immunosuppressive agents, Tumornecrosfactor-alfa (TNF-α) inhibitors. ATC-code: L04AB01.

Ustekinumab (Stelara®) is a fully human IgG1κ-monoklonal antibody against interleukin (IL)-12/23, produced in a mouse-myeloma cel line using recombinant DNA-technology. Farmacotherapeutic category: Immunosuppressive agents, interleukin-inhibitors. ATC-code: L04AC05.

7.2 Summary of findings from non-clinical studies

Adalimumab (Humira®) SmPC text, section D 2.1, page 114-115
Etanercept (Enbrel®) SmPC text, section D 2.2, page 30
Ustekinumab (Stelara®) SmPC text, section D 2.3, page 15

7.3 Summary of findings from clinical studies

Adalimumab (Humira®), SmPC text, section D 2.1, page 95-114
Etanercept (Enbrel®), SmPC text, section D 2.2, page 11-29
Ustekinumab (Stelara®), SmPC text, section D 2.3, page 2-15

7.4 Summary of known and potential risks and benefits

Adalimumab (Humira®), SmPC text, section D 2.1, page 82-94 (risks), 95-114 (benefits)
Etanercept (Enbrel®), SmPC text, section D 2.2, page 5-15
Ustekinumab (Stelara®), SmPC text, section D 2.3, page 3-8

7.5 Description and justification of route of administration and dosage

Adalimumab (Humira®), SmPC text, section D 2.1, 114-115.

Etanercept (Enbrel®), SmPC text, section D 2.2, page 28-29

Ustekinumab (Stelara®), SmPC text, section D 2.3, page 13-15

7.6 Dosages, dosage modifications and method of administration

Adalimumab (Humira®), SmPC text, section D 2.1, page 78-82, 237-239.

Etanercept (Enbrel®), SmPC text, section D 2.2, page 3-5

Ustekinumab (Stelara®), SmPC text, section D 2.3, page 2

Dosages in this study:

In the control group, patients will receive dosages by the label as can be read in the SmPC texts (section D 2.1-D 2.3). Dose-tapering patients will receive pragmatic daily practice care, but doses of etanercept, adalimumab or ustekinumab will be lowered: intervals of drug-administration will be prolonged stepwise. First, the dose will be decreased to 66-70% of the normal dose (by interval prolongation with a factor 1.5). If patients remain in a state of low disease activity, the dose will be further reduced to 50% (by doubling the original interval). Each step will be analyzed after three months, or when the patient visits earlier due to complaints. If a step-down leads to disease-flare, patients will return to the preceding step, and the dose will not be tapered again.

Absolute dosages in the dose tapering group:

Etanercept maintenance dose is 50mg/week; the interval will be prolonged subsequently to 50mg/10 days (step 1) and to 50mg/ 14 days (step 2).

Adalimumab maintenance dose is 40mg/2 weeks; the interval will be prolonged subsequently to 40mg/3 weeks (step 1) and to 40mg/4 weeks (step 2).

Ustekinumab is given 90mg or 45mg /12 weeks (dose depends on weight); the interval will be prolonged subsequently to 90mg or 45 mg/18 weeks (step 1) and to 90mg/45mg per 24 weeks (step 2).

7.7 Preparation and labelling of Non Investigational Medicinal Product

No special preparation or labelling will be performed. All patients receive their drug as they used to receive from the regular pharmacy. Batch numbers will be registered in the CRF.

7.8 Drug accountability

The investigator must maintain an accurate record of the used medication batch numbers. Monitoring of drug accountability will be performed by the designed monitor.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Disease-activity (PASI) at 12 months.

8.1.2 Secondary study parameters/endpoints (if applicable)

- HR-QoL (DLQI) at each time point (month 3/6/9/12)
- Disease-activity scores (PASI) at each time point (month 3/6/9/12)
- Persistent flare (yes/no)
- Number and relatedness of SAEs
- Extent of trough level antidrug antibodies and serum drug levels at each time point
- Predictors related to successful dose-tapering (baseline patient and treatment characteristics, HLA-C*06, baseline trough drug concentration and anti-drug antibodies, high-sensitivity CRP)

8.1.3 Other study parameters

Not applicable due to the randomized and pragmatic design. If there still is suspicion for confounding effects of a variable, this will be described.

8.2 Randomisation, blinding and treatment allocation

Randomization will be web-based and stratified by center using variable permuted blocks with concealment of allocation. Patients will be randomized 1:1 to (1) dose-tapering or (2) drug continuation of the maintenance dose. We aim to include all 3 biologics to an equal extent.

8.3 Study procedures

See appendix 2 for flow chart of study procedures per drug. A PASI score will be done every 3 months. PASI stands for Psoriasis Area and Severity Index[25] which is a composite measure of erythema, scaling, induration and extensiveness of the psoriasis plaques.[26] It results in a single score for psoriasis severity ranging from 0-72. It takes a physician around 2-3 minutes to assess this score, depending on his/her experience. The non-invasive scoring method will not be a burden for the patient and is assessed in daily clinical practice often as well.

The DLQI, Dermatology Life Qualtiy Index[27], is a simple practical questionnaire for routine clinical use (section F 1.3). It will be assessed every three months. It consist of 10 questions

surveying the impact of skin disease on health-related quality of life. It takes aprox. 2-5 minutes to complete and is also often done in daily practice.

Cost-effectiveness questionnaires will be administered four times (3/6/9/12 months). The set consists of: SF-36 questionnaire[28], iMTA Medical Consumption Questionnaire[29] and Productivity Cost Questionnaire (section F 1.1-2).[29] (www.imta.nl)
The SF-36 is a health-related quality of life questionnaire which can be used to derive utilities from (section F 1.4). It takes aprox. 10 minutes to complete. The iMTA Medical Consumption questionnaire measures all relevant health care related costs like outpatient visits at any medical specialist, hospitalizations and imaging procedures. Loss of productivity due to illness or recovery in patients below the age of 65 will be estimated based on patient reported absences from paid (or unpaid) labor measured with the Productivity Cost Questionnaire. iMTA and iPCA take aprox. 10 minutes to complete. Cost-effectveness questionnaires are not routinely taken in daily practice. Outcomes such as AEs, SAEs are also assessed and documented in daily clinical care.

Extra vials of blood (1x for genetics, 5x for antibodies/through levels) will be drawn at times when blood is taken for routine measurements. Also, high sensitivity CRP will be assessed together with the routine blood measurements and no extra blood is needed for that.

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.

8.5 Replacement of individual subjects after withdrawal

When subjects are withdrawn from the study, they will not be replaced. When missings are random, imputation of missing data will be carried out. Patients that are lost to follow up will be incorporated until their lost to follow up date only, as it is a per protocol approach. Missings and lost to follow up patients will be described. For the primary research question and questionnaires, we will carry out linear interpolation between measures, or a last observation carried forward when the last measure is missing.

For the predictor analysis, we will carry out a multiple imputation procedure for predictors. In this analysis, we will implement the outcome of this analysis for the prediction of missing values.

8.6 Follow-up of subjects withdrawn from treatment

Reason for withdrawal will be documented in the medical file and CRF. If the subject only withdraws from treatment, but not from the study itself, he/she will be followed until end of study and data will be handled as stated in the design section (per protocol approach for most analyses, except for the intention to treat approach for the cost-effectiveness analysis).

8.7 Premature termination of the study

The principle investigator, after appropriate consultation between the relevant parties, reserves the right to discontinue the study at any time and to remove all study materials if they becomes aware of conditions or events that suggest a possible hazards to patients if the study continues. Possible reasons for termination of the study include, but are not limited to:

- Safety concerns based on reported data.
- Failure to enrol patients at an acceptable rate.
- Unsatisfactory enrolment with respect to quantity or quality.
- Inaccurate or incomplete data collection
- Falsification of records.
- Failure to adhere to the protocol

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal.[30] The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. 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 or not considered related to etanercept, adalimumab or ustekinumab dose-decrease. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

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

- 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;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All adverse events, whether reported spontaneously by the participants or observed by the researcher or any other staff involved in the research, occurring during or shortly (2 months) after the study, will be recorded.

The patients included in this study are already using biologics, and keep using biologics. These patients experience adverse events related to immunosuppressive effects of these drugs and are closely monitored in daily practice. We will only report SAEs related to the intervention (dose-reduction) to the METC. All other SAEs will be monitored and described in the studies but not reported to the METC. Participating centers will notify the sponsor of this

study immediately in case of SAE(s) (at least within 7 days if death or life-threatening events took place). The sponsor (principal investigator or coordinating investigator) will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events. The subsiding party will be notified using the regular updates.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

The risk for SUSARs is deemed to be very low, especially SUSARs related to the intervention. Though, if a SUSAR occurs, the principal or coordinating investigator will report this to the METC in 7 days through the *Toetsingonline* webportal. Participating centers will notify the principal or coördinating investigator of this study immediately in case of SUSARs (at least within 7 days if death or life-threatening events took place) and they will notify the METC as described above.

9.3 Annual safety report

NA

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 end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

A DSMB will not be installed if this study is judged as a non-investigational product study.

However, we will perform safety reviews every year or interim safety reviews when this is deemed necessary by one of the research staff members.

The annual safety review will be performed by a research committee. This committee includes the sponsor (principal and coordinating investigator), head of the department of Dermatology (Radboudumc) and a rheumatologist (dr. A den Broeder, St Maartenskliniek)

who is experienced in dose-reduction studies in rheumatology but who does not work at one of the dermatology departments involved in this study and does not treat the patients himself. The main reason to establish the committee is to evaluate the occurrence of side-effects related to the interventions (e.g. psoriasis exacerbations) and monitor whether these (S)AEs occur more frequently than expected. If so, the research committee will discuss this with the METC. All (S)AEs will be discussed during the annual review.

10. STATISTICAL ANALYSIS

Patient and treatment characteristics will be summarized as means or medians and percentages, depending on the type of measurement. All analysis will be done according to a per protocol analysis, as this is the preferred and most conservative analysis for non-inferiority studies.[31] For the cost-effectiveness analysis however, results derived from intention to treat analyses are needed and will be done as well.

When missings are random, imputation of missing data will be carried out. Patients that are lost to follow up will be incorporated until their lost to follow up date only, as it is a per protocol approach. Extent and nature of missing data and information about lost to follow up patients will be described.

10.1 Primary study parameter(s)

- The primary outcome (PASI) at 12 months will be analyzed with ANCOVA in which the baseline PASI will be included as covariate (to gain efficiency). If the PASI score in the intervention group exceeds the non-inferiority margin (0.5) at 12 months of follow up, the intervention will be regarded as inferior to usual practice.

10.2 Secondary study parameter(s)

- Proportion of patients with successful dose reduction will be assessed. ‘Successful dose reduction’ is defined as using a lower dose than the regular dose at 12 months.
- DLQI at 12 months will be analyzed with ANCOVA in which the baseline values will be included as covariate (to gain efficiency).
- DLQI and PASI scores will be directly compared at other time points (month 3/6/9) between the two groups using an unpaired t-test or a non-parametric alternative.
- We will carry out a logistic regression analysis in order to identify predictors (baseline patient and treatment characteristics, HLA-C*06, baseline trough drug concentration and anti-drug antibodies, high-sensitivity CRP) that are related to the absence of flare. Based on group size, we will test the 4 most promising variables.
- Number of patients with a persistent flare will be analyzed for both groups and presented as rate ratios and relative rate ratios with corresponding confidence intervals. Time until flare for the dose tapering group will be graphically presented by Kaplan-Meier curve.
- The extent of trough level antidrug antibodies and serum drug levels will be directly compared at each time point between the two groups using an unpaired t-test or a non-parametric alternative.

- Correlation between marker of disease activity (high-sensitivity CRP) and PASI at different time points will be assessed.
- All SAEs will be described per group in a frequency table. Causal relation with the biologic will be assessed and described by two physicians using an ordinal scale (unrelated, possibly unrelated, possibly related etc). The number of patients with a (probably) related SAE will be analyzed as rate ratios and relative rate ratios with corresponding confidence intervals.
- Cost-effectiveness The impact of dose reduction on the quality of life of patients will be assessed by the SF-36 at 6 months and 1 year after randomization and the SF-6D utility will be used to derive a QALY estimate for each patient according to the trapezium rule.[28] The SF-6D was chosen as principal generic health related quality of life instrument because it contains domains that are relevant for psoriasis patients. The cost analysis exists of two main parts. First, on patient level, volumes of care related to the psoriasis care and biologic treatment will be measured by means of the iMTA Medical Consumption Questionnaire.[29] This questionnaire measures all relevant health care related costs like outpatient visits at any medical specialist, hospitalizations and imaging procedures. In addition, the medication use will be derived from the electronic patient records. Loss of productivity due to illness or recovery in patients below the age of 65 will be estimated based on patient reported absences from paid (or unpaid) labor measured with the Productivity Cost Questionnaire.[29] The second part of the cost-analysis consists of determining the cost prices for each volume of consumption. The standard cost prices from the 'Dutch Guidelines for Cost Analyses' and www.medicijnkosten.nl will be used. For units of care where no standard prices are available real costs prices will be determined on the basis of full cost pricing. Productivity losses will be valued by means of the friction cost method. In the end, volumes of care will be multiplied with the cost prices for each volume of care to calculate costs. Because we anticipate non-inferiority of the dose reduction strategy we will primarily analyze cost-savings: direct medical cost as well as total costs (medical and non-medical costs) will be compared between intervention and usual care group. A possible small but acceptable loss of effect can be incorporated in the analyses by determining a decremental cost-effectiveness ratio (DCER) by dividing the difference in costs by the difference in QALYs between the groups. The DCER expresses with how much money a loss of 1 QALY is compensated. If this amount is high the decision makers are willing to accept a loss of effect. Uncertainty in the DCER will be non-parametrically determined using bootstrap techniques (1000 replications). Results from this analysis will be presented in a scatter plot and willingness to pay (or accept) curve. Furthermore. the Net

Monetary Benefit (NMB) per patient will be calculated for different levels of willingness to pay (WTP) in dollars per QALY, using the formula: WTP * effect (difference in QALY) - costs. This results in the net amount of money saved, when the possible loss of QALY is corrected for, using different WTP levels per QALY. (Model approach and discounting are not applicable to this study).

10.3 Other study parameters

Not applicable due to the randomized and pragmatic design. If there still is suspicion for confounding effects of a variable, this will be described.

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be performed in accordance with the ICH GCP guidelines. The study will be conducted in full accordance with the principles of the "Declaration of Helsinki". (http://www.wma.net/en/30publications/10policies/b3).

Although randomisation and medication changes will be applied, we deem the risk for (related) SUSARs very low. Moreover, we use registered products in patients with an indication who used the biologic for at least 6 months before entering this study. Also, we think the long and short-term safety profile will be improved with the intervention. We do not focus on the "working mechanism, the safety or effectiveness of the drug itself", the main reasons why a study should be defined as interventional, but we focus on strategy.[30, 32] The strategy of interest has been adapted in studies, also outside the field of dermatology, without any reports of major adverse events.[6-9, 33-35] We ask for extra blood assessments during normal blood-taking moments, which is debated whether it should count as an interventional study due to the unproportionally high administrative burden,[36] For the above mentioned reasons, we hereby would like to ask the CMO to judge this as a non-interventional study.

As we further discuss in chapter 11.4, the main risk is disease flare due to dose reduction, but with the tight control strategy this risk is kept low and will be reversed soon. Another risk could theoretically be increased antibody formation against the biologic, however, this may only regard one of the biologics (adalimumab). A recent study suggest that (anti)drug levels in adalimumab and etanercept were not predictive for successful dose reduction.[19]

Because we only look at specific candidate-genes (SNPs) related to the disease or drug response itself, there will be no risk for incidental findings. We will not perform research on whole genes or genome sequencing.

11.2 Recruitment and consent

All dermatologists in the participating centers will be informed on the study. The involved investigator in each center or his/her representative will explain the nature of the study to the subject and will answer all questions regarding the study. Other dermatologists in the

Netherlands will be made aware of the study and requested to recruit and refer eligible patients to centers involved in the study.

It is the responsibility of the local investigator to obtain written informed consent (according to local legal requirements and regulations). The information is intended to give each participant a thorough understanding of the purpose and nature of the trial, the cooperation required, anticipated benefits and potential hazards of the study.

The following basic elements are included in the written information for the patient (section E1):

- A statement that the study involves research.
- A full and fair explanation of the procedures to be followed, identifying which of them are experimental.
- A full explanation of the nature, expected duration, and purpose of the study.
- A description of any reasonable foreseeable risks or discomfort to the patient.
- A description of any benefits which may reasonably be expected.
- A statement indicating that the patient agrees to allow authorized personnel of the Coordinating Centre, who are bound to secrecy, to review the patient's records if required.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care.
- A consent form to be signed by the patient or his/her's relative will be made available. This form must first be approved by the responsible Ethics Committee.

11.3 Objection by minors or incapacitated subjects (if applicable)

NA

11.4 Benefits and risks assessment, group relatedness

In general, we think the study is of negligible risk. The rationale is described below:
The main risk in this study is the risk for disease flare. We keep this risk as low as possible using small steps of dose-reduction with tight control of clinical effectiveness and monitoring HRQoL using DLQI. Patients are free to withdraw from this study at any time point and will be further treated according to usual care principles. Trough drug concentrations and anti-drug antibodies will be tested frequently for all biologics. In infliximab, longer dosing intervals

were associated with more immunogenicity, resulting in lower trough drug concentrations and consequently, in lower effectiveness.[15] However, in a study where adalimumab was discontinued, only a small percentage developed antibodies after discontinuation.[37] Some patients that developed antibodies were still able to regain response.[37] In a dose-tapering study in rheumatoid arthritis, only 5% of patients developed anti-drug antibodies.[20] High antibody levels have been associated with tromboembolic processes in a small study, however, the causal relation is under debate and the study was too small to draw valid conclusions.[38, 39]

With a lower biologic dose, we expect the patient to benefit to from a milder short- and long-term safety profile due to lower exposure to a potentially toxic agent. In literature, although limited evidence exists, no safety problems were reported in dose-tapering studies.[6-9]

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.[30]

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 24th of November, 2014). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance company provides a maximum coverage of € 650.000,-- per research subject and € 5.000.000,-- for the complete study. € 7.500.000,-- per year for all studies of the same sponsor (“opdrachtgever”). More information: www.ccmo.nl.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. The damage is deemed to have manifested itself when it is reported to the insurer.

The study subject can contact the Insurance company directly:
Onderlinge Waarborgmaatschappij Centramed B.A.
Postbus 191
2270 AD Voorburg
Tel. 070 3017070
Email: Schade@centramed.nl

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The collected data will be entered CASTOR, an electronic database set up for clinical trials. https://www.castoredc.com/nl/waarom-Castor.html. Data will be coded and kept based on the rules for good clinical practice (GCP) by BROK certified personnel (GCP: http://ichgcp.net/; codes of conduct: http://www.federa.org/code-goed-gedrag). Handling of personal data will comply with the Dutch Personal Data Protection Act (WBP, wet bescherming persoonsgegevens). As many patients that will be eligible for this study have already been registered in our BioCAPTURE registry, we can extract baseline data from the database. Samples send to the dermatology laboratory Radboudumc and Sanquin will be anonymized (coded) for the personnel taking care of the samples.

Serum for antibodies will be fully used in Sanquin and cannot be stored, the duplos will be kept and stored in the dermatology laboratory of the Radboudumc. The same accounts for DNA. The projectleader will guard these materials.These sera and DNA will be stored for 15 years after the study. If it is planned to use these materials for other study purposes, we will ask the CMO for permission first as well as permission of the patient (in case the patient gave consent to be asked for permission for new study purposes).

For further information, see Datamanagement plan, appendix 4.

12.2 Monitoring and Quality Assurance

Data of all centers will be monitored following the guidelines of the Radboudumc. The research nurse from the Radboudumc (M Kooijmans) will monitor all centers.

For further information, see Monitoring plan, appendix 5.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion to the primary study protocol.

12.4 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited METC 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 adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC 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.

12.6 Public disclosure and publication policy

The research is currently being registered at the Dutch Trial Register (NTR5301 - http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5301) and will be registered at ClinicalTrials.gov.

Core publication(s) will be authored by investigator(s) of the Department of Dermatology from the Radboudumc, Nijmegen and all participating centers who contributed significantly to the implementation and conduct of the study and non-site personnel who contributed substantially to the design, interpretation or analysis of the study. Scientists making significant contributions to the study will be included in the list of authors.

Development of the core publication will be coordinated by a publication committee whose membership will include investigators who provided significant input into study design, implementation, conduct and interpretation, in addition to the scientific personnel responsible for study conduct. Results will be published regardless the nature of the outcomes.

Zonmw will be mentioned as subsiding party in all publications. Publication on, and results of the project will be presented to ZonMw using Projectnet until 4 years after finishing the study.

Also, during this period, we will inform Zonmw about the use of results of our study. For further information on ZonMw legislation regarding publications, see General funding provisions: http://www.zonmw.nl/fileadmin/documenten/Corporate/Algemene-subsidiebepalingen-ZonMw_per_1_juli_2013.pdf, Article 18 on publications.

We aim to publish in open access journals and we will present our results for international and national colleagues and the Dutch Patient board (PVN).

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

See 13.2 for rationale of omitting this chapter.

13.2 Synthesis

Step 13.1 is skipped because we think this is a non-interventional study with registered products (etanercept, adalimumab, ustekinumab) in patients with an indication for use only. All patients have been using the drug at least 6 months before entering this study. Moreover, data on working mechanism and risks are presented in chapter 7 with referring to SmPC texts, and are not the focus of the current study. In daily practice, sometimes methotrexate or acitretin is given next to the biologic. This will not be intervened upon as it is a pragmatic daily practice study. Addition of this medication is allowed, but it is not the focus of this study and is therefore not discussed above.

The overall risks of biologics are expected to decrease with this study, as the patients receive a lower dose of which we strongly expect that it will be accompanied by a milder toxicity profile. Especially the immunosuppressive effects of the included drugs will be lower and we therefore expect less short and long term side-effects related to these effects.

As evidence is limited on the amount of antibody formation and its consequences in the context of dose reduction, we will investigate this in the present study. Moreover, debate is still going on about the clinical significance of antibodies in the fields of dermatology and rheumatology.[40] Some literature exist on antibody formation after withdrawal or during a normal dose of a biologic. In a study where adalimumab was discontinued, only a small percentage (6%) developed antibodies after discontinuation; after retreatment only 1-2% still had antibodies.[37] With regard to etanercept, antibody formation is limited to non-neutralizing antibodies with limited or no effect on the drug effectiveness.[41] In a recent study on ustekinumab, only 7% developed antibodies on a normal dose and this percentage was too small to draw conclusions from regarding clinical effects.[42]

A logical consequence of dose-decrease is a higher number of patients with exacerbation of psoriasis. To prevent severe exacerbations and treat patients with exacerbations as soon as possible, we will see the patients every three months and measure disease severity and quality of life. Significant detoriation of these parameters (see design) will lead to our advice of returning to the original dose, or start escape medication. In the patient leaflet and face-to-

face, we will strongly advice the patients to call for an in-between visit when they have complaints of a worsening of their psoriasis.

To conclude, we think the expected risks of dose decrease may outweigh the risks of the original dosages by far. The expected risks will be anticipated on as much as possible and can be treated. We have other medication options available in case of antibody development leading to unresponsiveness of the agent under study, such as infliximab or secukinumab.

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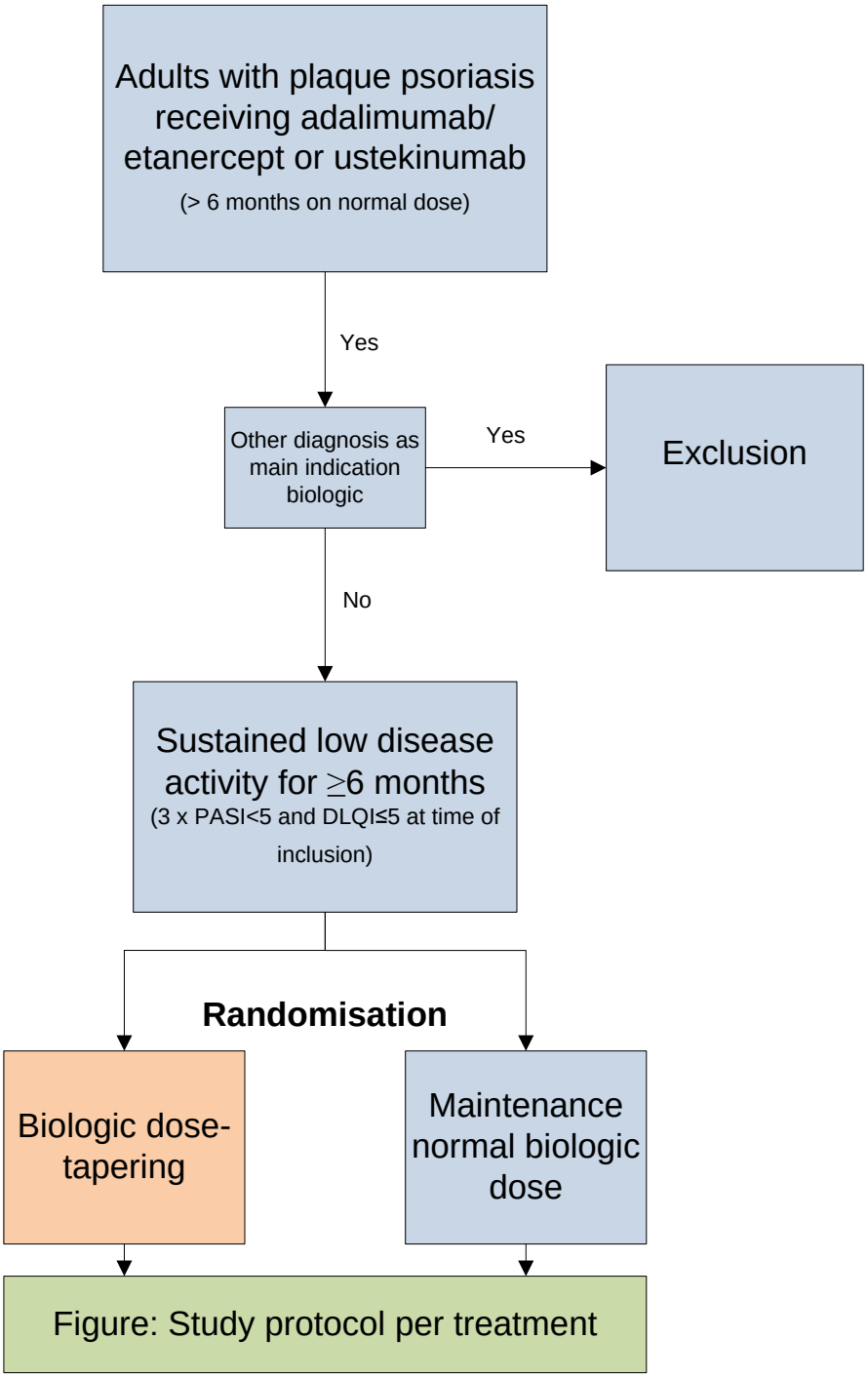
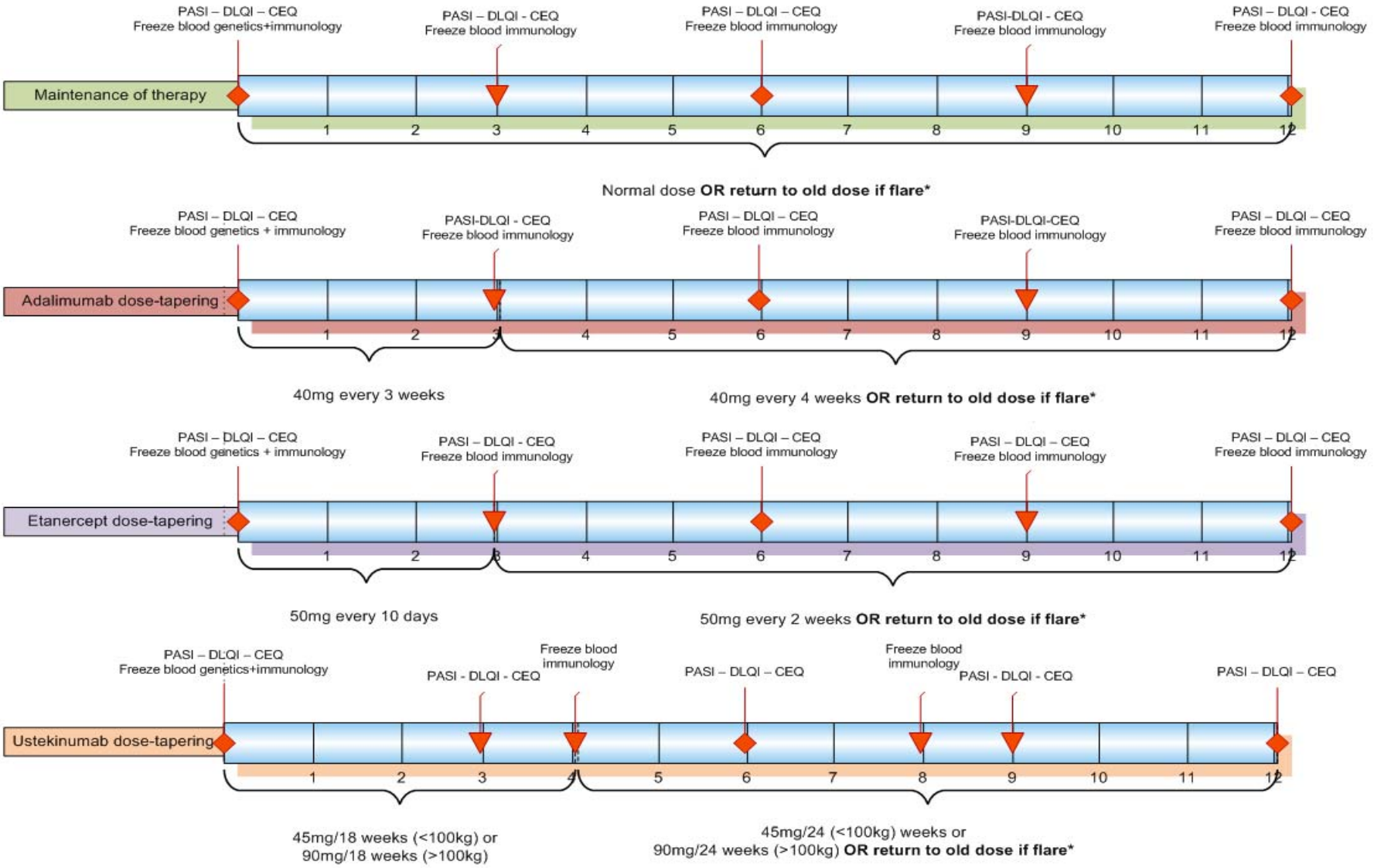
Figure: Flow chart study inclusion



Appendix 2: Study protocol per treatment



CEQ=Cost-effectiveness questionnaires (SF-36, iMTA Medical Consumption Questionnaire and productivity cost questionnaire). Ustekinumab blood samples for immunologic analyses are taken at deviating time points (trough moments) due to the low frequency of injections.