STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

ICH Harmonised Tripartite Guideline
[EMEA Status as of December 1995]

1. TITLE PAGE

Dose reduction of the new generation biologics (IL17 and IL23 inhibitors) in psoriasis: A pragmatic, multicentre, randomized, controlled, non-inferiority study - *BeNeBio study*

Report date	Version 1.0 dd 31-07-2025 Version 1.1 dd. 06-01-2026
Protocol ID	80-85200-98-18562
Short title	Dose reduction of the new generation biologics (IL17 and IL23 inhibitors) in psoriasis
EudraCT number	2019-004230-42
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Sponsor (in Dutch: verrichter/opdrachtgever)	Radboud University Medical Center, department of Dermatology, Nijmegen, The Netherlands
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Laboratory sites	KU Leuven Laboratorium voor Therapeutische en Diagnostische Antilichamen O&N II Herestraat 49 - bus 820 3000 Leuven
Study initiation date	30-06-2020
First patient enrolled	20-08-2020
Last Patient Last Visit	30-01-2025

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2. SYNOPSIS

Biologics are effective agents for the treatment of psoriasis. The newest generation of biologics block interleukin 17 and 23. Physicians always prescribe these drugs in a fixed dose, but probably, not every patient needs this. Therefore, in patients with low disease activity under a normal dose, we examined if the dose can be reduced. A lower dose has advantages: it may lead to fewer side effects and lower healthcare costs. It is however important that the disease does not worsen due to dose reduction. We have investigated the best way to reduce the dose, and which patients are eligible for dose reduction. In 17 Belgian and Dutch hospitals, we have divided patients into 2 study groups: a group that gradually reduces the dose (DR) and a group that continues to use the normal dose (UC).

In the BeNeBio study, we investigated if the reduced dose did not lead to a worsening of psoriasis and if quality of life remained stable in patients with psoriasis who are treated with these biologics. We have also investigated side effects, costs and the blood levels of the medication at the 3-monthly study visits of the 18 months follow-up period (*Figure 1*).

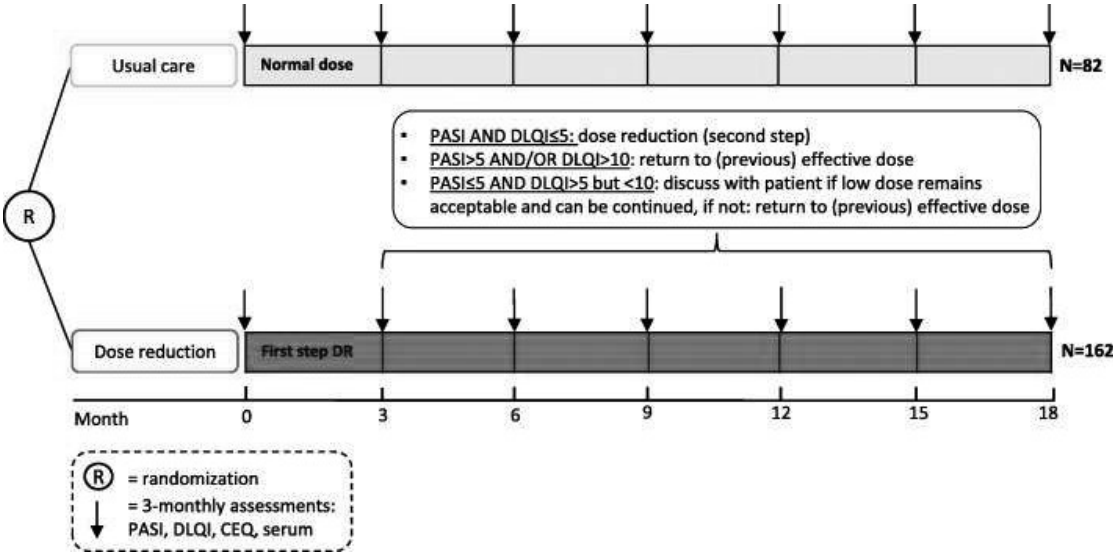


Figure 1: Study design of the BeNeBio trial.

Patients (n = 244) using secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab, or tildrakizumab were randomized to dose reduction or usual care. Control visits were scheduled every 3 months for assessment of PASI, DLQI, cost-effectiveness questionnaires (EQ-5D-5L, SF-36, iMTA MCQ, and PCQ), drug levels, and anti-drug antibodies. CEQ, Cost-Effectiveness Questionnaires; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index

The results showed that DR of IL-17 and IL-23 inhibitors by a two-step DR strategy of first 67% and second 50% of the standard dose, is non-inferior to UC. In addition, DR was cost-effective compared to UC.

More information on the BeNeBio trial:

- See ClinicalTrials.gov ID: NCT04340076
- See Annex 1

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
AEoSI	Adverse Event of Special Interest
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NCoor	National Coordinating Center (here: UZGent)
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
PD	Pharmacodyanmics
(S)AE	(Serious) Adverse Event
SPC	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. (here: Radboudumc). 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.

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Ethical approval for this study was obtained from the Medical Ethical Committee (Arnhem-Nijmegen) for the Dutch sites and from the competent authorities (FAMHP) and the Ethics Committee of University Hospital Ghent after consulting the Ethics Committees of each participating site in Belgium.

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Consent

The involved investigator in each centre or his/her representative explained the nature of the study to the subject and answered all questions regarding the study.

The patient was given sufficient time to think about whether or not to participate in this study. Before any study acts were performed, the patient gave his/her consent by signing the consent form.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

UZGent coordinated the Belgian BeNeBio sites and **Radboudumc Nijmegen** coordinated the Dutch BeNeBio sites. Radboud Technology Center Clinical Studies, team Integraal provided the monitor for the Dutch sites, HIRUZ monitored the Belgium sites.

According to the BeNeBio **monitoring plan** all participating centers were visited by the monitor for the first time 4 weeks after inclusion of the first patient. Monitoring took place at site and remote. More information can be found in the monitoring plan of the trial.

Investigator meetings were annually organized. All PI's, study staff, statisticians and patient participants were invited for these meetings.

The Steering committee had one meeting every six months. Invited to these meetings were: PI UZGent and Radboudumc, postdoc's, Phd's, statistician, monitors, funders, HTA expert, one external PI, Patient partners, independent expert.

Study team meetings with staff from the coordinating centres UZGent and Radboudumc were held every 2 weeks

Meetings KCE and ZonMw and study teams BE end NL were held monthly.

Risk classification of the study was negligible.

This study was considered a low risk trial because the medicinal products were already authorized for the market, the medicinal products were used in accordance with the conditions of the marketing authorization, the use of the medicinal products for research was evidence-based and additional diagnostics/monitoring within the framework of the study did not impose more than a minimal additional burden on the participants.

Blood samples collected during each study visit were processed and stored locally and then collected annually by a courier (IHCT) and taken to the laboratory in Belgium.

7. INTRODUCTION

Psoriasis is a chronic skin disease characterized by erythematous, scaly plaques and associated with important comorbidities such as cardiovascular disease and psoriatic arthritis. Psoriasis affects approximately 2-3% of the Western population (approximately 500.000 patients in the Netherlands, and 330.000 in Belgium). The disease burden is high, with reduced disease-related quality of life similar to that of cancer or depression patients. In the past years, effective targeted biological treatments have become available for patients with moderate-to-severe psoriasis, and frequently prescribed by dermatologists.

These biologics block specific cytokines (TNFα, interleukin (IL)-12, IL17, or IL23) in the psoriasis pathogenesis pathway. In general, biologics are considered relatively safe, but their very long-term safety profile has yet to be established. The new generation biologics entered the market in recent years: IL17 inhibitors since 2016 (secukinumab, ixekizumab, brodalumab and bimekizumab) and IL23 inhibitors since 2018 (guselkumab; risankizumab) and tildrakizumab followed in 2023). Trial data were promising, and effectiveness rates were often higher than in first generation biologics like TNFα-inhibitors or ustekinumab. The problem is that, like most biologics, the new agents are marketed in a fixed dose despite the fact that thriving for the lowest possible, effective dose of biologics should be self-evident.

The main research question of the BeNeBio trial was: is it possible to taper the dose of the new biologics (IL17 and IL23 inhibitors) in clinical practice?

8. STUDY OBJECTIVES

Primary Objective:

To assess if tightly controlled dose tapering is non-inferior to usual care with regards to the cumulative incidence of persistent disease flares (PASI> 5 for ≥ 3 months) after 18 months.

Secondary Objective(s):

1. To assess the proportion of patients with successful dose tapering after 12 and 18 months (successful dose tapering is defined as lower dose than the normal dose and PASI≤ 5).
2. To assess difference in PASI and DLQI course in patients with dose tapering vs. usual care.
3. To assess and compare PASI and DLQI at month 12 in patients with dose tapering vs. usual care.
4. To assess and compare PASI and DLQI at month 18 in patients with dose tapering vs. usual care.
5. To assess incidence of short disease flares (PASI> 5 at 1 time point) after 18 months in patients with dose tapering vs. usual care.
6. To identify predictors (clinical characteristics and biomarkers) for successful dose decrease
7. To count the number of Serious Adverse Events (SAE) related to the intervention in patients with dose tapering.
8. To count and compare the number of (all) Serious Adverse Events (SAE) and Adverse Events of Special Interest (AEoSI) in patients with dose tapering vs. usual care.
9. To assess the pharmacokinetic (PK) profile of tapered biologics vs. normal dose.
10. To assess if tightly controlled dose tapering is cost-effective compared with usual care.
11. To assess the proportion of patients with initiation of other anti-psoriatic medication during the study (intensive topical therapies, methotrexate, acitretin) in patients with dose tapering vs. usual care.

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15. To assess and compare PASI and DLQI at month 18 in patients with dose tapering vs. usual care.
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20. To assess the pharmacokinetic (PK) profile of tapered biologics vs. normal dose.
21. To assess if tightly controlled dose tapering is cost-effective compared with usual care.
22. To assess the proportion of patients with initiation of other anti-psoriatic medication during the study (intensive topical therapies, methotrexate, acitretin) in patients with dose tapering vs. usual care.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

Study design: A multicentre, pragmatic, randomized, controlled, non-inferiority trial.
Study population: Patients treated with new generation biologics (IL17 and IL23 inhibitors) could be included if they had proven long-term stable low disease activity (at least 6 months) with a normal biologic dose, and a PASI and DLQI ≤ 5 at start of study.

Patients were randomized 2:1 to dose reduction and usual care. (see supplemental file 1: Flow chart study inclusion)

Intervention: Tight controlled dose reduction by spacing of dose intervals of IL17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab) and IL23 inhibitors (guselkumab, risankizumab, tildrakizumab). Dose reduction was achieved by increasing the time between injections. The dose was decreased to 67% of the original dose. If disease activity maintained low for 3 months, further decrease to 50% of the original dose has taken place. In case of a PASI > 5, or unacceptable DLQI (see supplemental file 2) or when the patient is not willing to further prolong the lower dose, the previous dose was reinstalled.

Comparator: Standard of care
Sample size: Based on a non-inferiority margin of 15%, 244 patients were randomized (2:1) into two groups: dose reduction guided by PASI and DLQI (n=162, intervention) and maintenance of normal dosage (n=82, usual care).

Main study parameters/endpoints: The primary outcome is non-inferiority of (cumulative incidence of) persistent flares (PASI> 5 for ≥ 3 months). Secondary outcomes include percentage of patients with successful dose reductions after 12 and 18 months, disease activity (course of PASI score), incidence of short disease flares

(PASI>5 at 1 time point), health-related quality of life (HRQoL) as measured by dermatology life quality index (DLQI), candidate predictors for successful dose tapering, serious adverse events (SAE) related to the intervention, and SAEs and adverse events of interest (AEoSI) in general, pharmacokinetic analyses (drug trough and anti-drug antibody levels), and cost-effectiveness (health utilities measured with EQ5D, costs with iMTA and iPCQ questionnaires).

Study duration and visit schedule: The trial consisted of three-monthly visits, which converge with regular visits in most patients. A maximum deviation of 4 weeks before or after the ideal visit date was accepted. If a patient had a disease flare outside this window, an additional study visit was planned. The total follow-up duration in this study was 18 months.

9.2 Discussion of Study Design, including the Choice of Control Groups

Study design: A multicenter, pragmatic, randomized, controlled, non-inferiority trial.

Choice of control: As the biologics included in the BeNeBio trial were already used in daily clinical practice, standard-of-care was chosen as the control group.

9.3 Selection of Study Population

9.3.1 Inclusion criteria

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

- Diagnosis of plaque psoriasis (primarily)
- Treatment for 6 months at least with IL17 or IL23 inhibitor in a normal dose (dose advised by the label)
- PASI $\leq$ 5 at inclusion and in previous 6 months (in previous 6 months, it should be clear from the patient record that psoriasis was clear/almost clear if no PASI scores are available).
- DLQI $\leq$ 5 at inclusion

9.3.2 Exclusion criteria

A potential subject who met any of the following criteria was excluded from participation in this study:

- Another indication than plaque psoriasis as the main indication for biologic use (e.g. receives biologic for rheumatoid arthritis as the main indication).
- Concomitant use of systemic immunosuppressants other than methotrexate or acitretin (e.g. prednisone, ciclosporin etc).
- Severe comorbidities with short life-expectancy (e.g. metastasized tumor).
- Presumed inability to follow the study protocol.

9.3.3 Removal of patients from therapy or assessment

There were no predetermined reasons for removing patients from the trial. In case a patient has becoming ineligible during the trial e.g. switching to another biologic or

discontinuation of therapy due to pregnancy,…), these patients still have been followed up every 3 months until end of the trial (month 18).

9.4 Treatments

9.4.1 Treatments administered

The intervention in this study refers to the dose reduction strategy of regularly used drugs (biologics: secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab, tildrakizumab). These drugs are approved for the indication of moderate-to-severe psoriasis and are administered subcutaneously.

Secukinumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Secukinumab
Qualitative and quantitative composition	Interleukin-17A antagonist Cosentyx 150 mg solution for injection in pre-filled pen: Each pre-filled pen contains 150 mg secukinumab in 1 ml. Cosentyx 300 mg solution for injection in pre-filled pen: Each pre-filled pen contains 300 mg secukinumab in 2 ml. Secukinumab is a recombinant fully human monoclonal IgG1/κ antibody produced in Chinese Hamster Ovary (CHO) cells.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose is based on body weight (Table 1) and administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Each 75 mg dose is given as one subcutaneous

	injection of 75 mg. Each 150 mg dose is given as one subcutaneous injection of 150 mg. Each 300 mg dose is given as one subcutaneous injection of 300 mg or as two subcutaneous injections of 150 mg.
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	Novartis Europharm Limited

Ixekizumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Ixekizumab
Qualitative and quantitative composition	Interleukin-17A antagonist Taltz 80 mg solution for injection in pre-filled syringe. Each pre-filled syringe contains 80 mg ixekizumab in 1 ml. Taltz 80 mg solution for injection in pre-filled pen. Each pre-filled pen contains 80 mg ixekizumab in 1 ml. Ixekizumab is produced in CHO cells by recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by 80 mg (one injection) at weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks (Q4W).
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	Eli Lilly and Company (Ireland) Limited

Brodalumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Brodalumab
Qualitative and quantitative composition	Interleukin-17 receptor antagonist Each pre-filled syringe contains 210 mg brodalumab in 1.5 ml solution. 1 ml solution contains 140 mg brodalumab. Brodalumab is a human monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose is 210 mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	LEO Pharma A/S Industriparken 55 DK-2750 Ballerup Denmark

Bimekizumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Bimekizumab
Qualitative and quantitative composition	Bimzelx 160 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 160 mg of bimekizumab in 1 mL. Bimzelx 320 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 320 mg of bimekizumab in 2 mL. Bimzelx 160 mg solution for injection in pre-filled pen Each pre-filled pen contains 160 mg of bimekizumab in 1 mL. Bimzelx 320 mg solution for injection in pre-filled pen Each pre-filled pen contains 320 mg of bimekizumab in 2 mL Bimekizumab is a humanised IgG1monoclonal antibody produced in a genetically engineered Chinese hamster ovary (CHO) cell line by recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose for adult patients with plaque psoriasis is 320 mg (given as 2 subcutaneous injections of 160 mg or 1 subcutaneous injection of 320 mg) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter.
Authorised in the EU	Yes
Used within scope	Yes

Marketing authorisation holder	UCB Pharma S.A. Allée de la Recherche 60 B-1070 Bruxelles Belgium

Guselkumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Guselkumab
Qualitative and quantitative composition	Interleukin-23p19 antagonist Tremfya 100 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 100 mg of guselkumab in 1 mL solution. Tremfya 100 mg solution for injection in pre-filled pen Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution. Guselkumab is a fully human immunoglobulin G1 lamda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose is 100 mg by subcutaneous injection at Weeks 0 and 4,

	followed by a maintenance dose every 8 weeks (q8w)
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	Janssen-Cilag International NV

Risankizumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Risankizumab
Qualitative and quantitative composition	Interleukin-23p19 antagonist Skyrizi 150 mg solution for injection in pre-filled pen Skyrizi 150 mg solution for injection in pre-filled syringe Skyrizi 75 mg solution for injection in pre-filled syringe Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous

Standard dosing for the indication	The recommended dose is 150 mg administered as a subcutaneous injection at week 0, week 4, and every 12 weeks thereafter (either as two 75 mg pre-filled syringe injections or one 150 mg pre-filled pen or pre-filled syringe injection)
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen Germany

Tildrakizumab

Also refer to	Summary of Product Characteristics (SmPC)
Name of the IMP	Tildrakizumab
Qualitative and quantitative composition	Interleukin-23p19 antagonist Ilumetri 100 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 100 mg of tildrakizumab in 1 mL. Ilumetri 200 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 200 mg of tildrakizumab in 2 mL. Ilumetri 100 mg solution for injection in pre-filled pen

	Each pre-filled pen contains 100 mg of tildrakizumab in 1 mL. Ilumetri 200 mg solution for injection in pre-filled pen Each pre-filled pen contains 200 mg of tildrakizumab in 2 mL. Tildrakizumab is a humanised IgG1/k monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.
Pharmaceutical form	Solution for injection
Method of administration	Subcutaneous
Standard dosing for the indication	The recommended dose is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter. At the physician's discretion, in patients with high disease burden or in patients above 90 kg of body weight a dose of 200 mg may provide greater efficacy.
Authorised in the EU	Yes
Used within scope	Yes
Marketing authorisation holder	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona Spain

9.4.2 **Identity of investigational product(s)**

See 9.4.1.

9.4.3 Method of assigning patients to treatment groups

After obtaining written informed consent, the investigator entered participants in a web-based randomization program (Castor). Participants were allocated to each group (DR or UC) by this web-based randomization program (Castor) that generated block randomization (variable block size of 6, 9, 12) with a random (2:1) allocation sequence and stratified by biologic (Figure 2). A patient was randomized 2:1 to DR or continuation of the normal dose (UC). The ratio of 2:1 was chosen to be able to include more determinants in an analysis for successful DR.

Due to the pragmatic character of this trial, and due to the nature of the intervention (injections), patients and investigators will not be blinded.

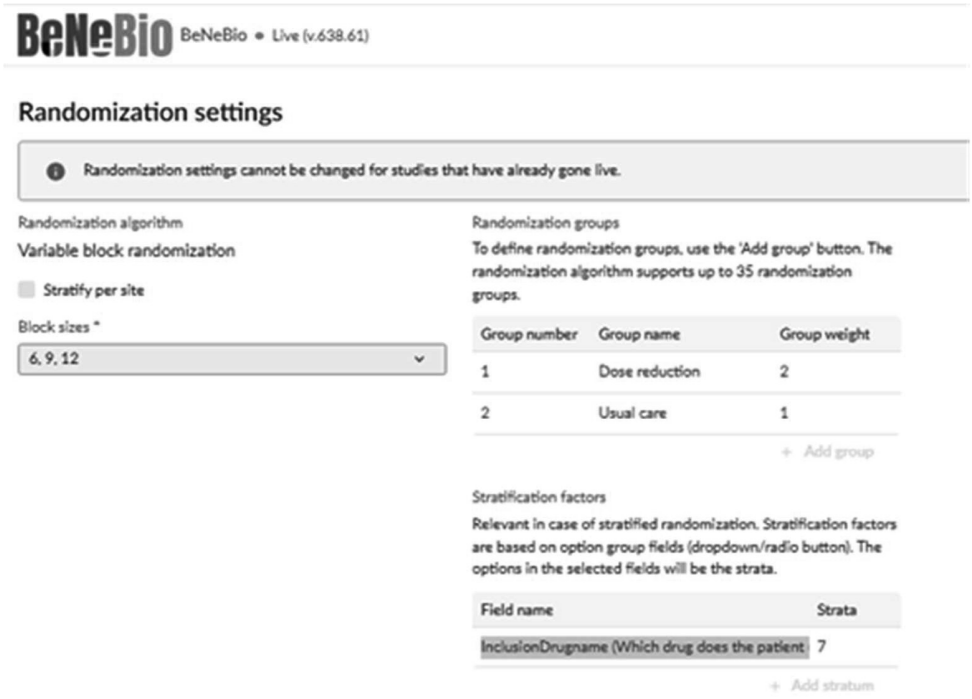


Figure 2: Randomization setting in CASTOR as applied in the BeNeBio trial.
Participants were allocated to each group (DR or UC) by this web-based randomization program (Castor) that generated block randomization (variable block size of 6, 9, 12) with a random (2:1) allocation sequence and stratified by biologic

9.4.4 Selection of doses in the study

Control group: standard of care = routine care with novel biologics, including empirical treatment modifications

Intervention group: stepwise dose tapering of the novel biologics by prolonging the dosing interval between two drug administrations, thereby achieving 67% (first step) and 50% (second step) of the original dose.

9.4.5 Selection and timing of dose for each patient

Patients in the UC group continued the standard biologic dose. Disease activity was monitored at every 3-montly study visit using PASI and DLQI, assessed by trained physicians and nurses. In the DR group, DR was continued when disease activity remained low (PASI $\leq$ 5 and DLQI $\leq$ 5). When flares (PASI > 5 and/or DLQI > 10) occurred, or when the patient was not willing to further use the lower dose, the previous effective dosing interval was reinstalled. When PASI $\leq$ 5 and DLQI > 5 but $\leq$ 10, it was discussed with the patient if the lowered dose could be continued. After DR failure, no new DR attempts were made.

9.4.6 Blinding

Due to the pragmatic character of this trial, and due to the nature of the intervention (injections), patients and investigators were not blinded.

9.4.7 Prior and concomitant therapy

Due to the pragmatic character of the trial, concomitant use of methotrexate or acitretin was accepted. Concomitant use of other systemic immunosuppressants (e.g. prednisone, ciclosporin etc.) was prohibited (i.e. exclusion criteria).

9.4.8 Treatment compliance

Medication dispensing records were collected for each participant from their pharmacies (in the Netherlands). Patients were asked to fill in patient diaries with information on medication use. In Belgium, participants were instructed to collect their medication dispensing records from their pharmacies and/or to report the batch numbers in the patient diaries.

In addition, the date of drug administration was collected in order to verify the dosing schedule.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and safety measurements assessed and flow chart

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	*M0*	*M0*	*M3*	*M6*	*M9*	*M12*	*M15*	*M18*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
Dose reduction		♦—	—	—	—	—	—	—♦
Usual care		♦—	—	—	—	—	—	—♦
ASSESSMENTS:								
Demographics	X							
Dosage schedules	X		X	X	X	X	X	X
Comedication	X		X	X	X	X	X	X
PASI	X		X	X	X	X	X	X
DLQI	X		X	X	X	X	X	X
EQ-5D-5L	X		X	X	X	X	X	X
SF-36	X		X	X	X	X	X	X
iMTA MCQ	X		X	X	X	X	X	X
iMTA PCQ	X		X	X	X	X	X	X
Adverse events			X	X	X	X	X	X
Serum	X		X	X	X	X	X	X

Table 1: Flowchart of trial interventions within the BeNeBio study

Abbreviations: M months, PASI Psoriasis Area and Severity Index, DLQI Dermatology Life Quality Index, EQ-5D-5L European Quality of Life-5 Dimensions-5 Level questionnaire, SF-36 Short Form-36 questionnaire, iMTA MCQ institute for Medical Technology Assessment Medical Consumption Questionnaire, PCQ Productivity Cost Questionnaire

Effectiveness: A PASI was scored at baseline and every 3 months thereafter. A window of -2 weeks was allowed for baseline PASI. PASI stands for Psoriasis Area and Severity Index which is a composite measure of erythema, scaling, induration and extensiveness of the psoriasis plaques. It results in a single score for psoriasis severity ranging from 0-72. It takes a physician around 3-5 minutes to assess this score, depending on his/her experience. This non-invasive scoring method was not burdensome for the patient and is assessed in daily clinical practice as well.

Quality of life: The DLQI, Dermatology Life Quality Index, is a simple practical questionnaire for routine clinical use. It was assessed every three months (in total, 7 times). It consist of 10 questions surveying the impact of skin disease on health-related quality of life. It takes approx. 2-5 minutes to complete and is also often done in daily practice.

Cost-effectiveness: Cost-effectiveness questionnaires were administered every three months (in total 7 times). The set consisted of: the EQ-5D-5L questionnaire, SF-36 questionnaire and adapted versions of the iMTA Medical Consumption Questionnaire (MCQ), and Productivity Cost Questionnaire (PCQ). Adaptations in the MCQ and PCQ were made in order to ask for more disease specific information and information regarding the intervention (dose reduction). Furthermore, the questionnaires were adapted to correspond more to the Belgian education and healthcare system.
The set of questionnaires were sent digitally to the patients via the electronic database CASTOR (https://www.castoredc.com/nl/waarom-Castor.html) or were administered on paper (hardcopy).

The EQ-5D-5L and SF-36 are health-related quality of life questionnaires which can be used to derive utilities from. It takes approx. 10-15 minutes to complete these questionnaires. The iMTA Medical Consumption questionnaire measures all relevant health care related costs like outpatient visits at any medical specialist, hospitalizations and imaging procedures. iMCQ and iPCA are instruments for measuring medical consumption and work productivity respectively. It takes approx. 10 minutes to complete. Cost-effectiveness questionnaires are not routinely taken in daily practice.

Outcomes such as AEs, SAEs were also assessed and documented in daily clinical care.

Extra vials of blood (one vial per visit for serum drug levels and anti-drug antibodies, maximum of 10 cc with a total of 7 vials) were drawn every 3 months.

9.5.2 **Appropriateness of measurements**

The efficacy and safety measures chosen in this trial were standard in the field. All are widely used and generally recognized as reliable, accurate, and relevant.

9.5.3 **Primary efficacy variable(s)**

Non-inferiority of the incidence proportion of persistent flares (Psoriasis Area and Severity Index (PASI) >5 for ≥ 3 months). [Time Frame: 18 months].

9.5.4 **Drug concentration measurements**

Two vials of blood were drawn every 3 months during the study visits. Within 24 hours, serum was prepared and aliquoted in 3 eppendorfs (volume 300 µl). The prepared serum

was stored in the laboratory of the specific hospital at minus 20 or minus 80 degrees Celsius. In case there were no facilities to prepare the serum, tubes were sent within 24 hours on room temperature to Dpt. of Dermatology UZGent (Belgium) through a single choice of courier service (Inter Healthcare Transport – blanket order UZGent). Vials were labeled with a code (pseudonimization) and stored at -80°C in the dermatology biobank (BIODIP, FAGG registration number B670201734415) of Prof Jo Lambert (medical responsibility), which was managed by the Bioresource Center Ghent at the Ghent University Hospital.

In case serum samples were stored on-site, samples were sent to UZGent after study finalization for storage in BIODIP. Once all samples were collected at the Ghent University Hospital, one vial per sample was sent to the laboratory of Therapeutic and Diagnostic Antibodies (KUL) on dry ice (Inter Healthcare Transport courier service). In this lab, serum samples from guselkumab, secukinumab and ixekizumab were analyzed through an *in-house* developed enzyme-linked immunosorbent assay (ELISA) for serum drug and anti-drug antibody levels(1–3). Serum samples of risankizumab were transferred to ApDia (company to whom *in-house* ELISA risankizumab assay was transfered) for analysis. Lab analysis data was linked to a code – KUL and ApDia did not have access to the datasheet for depseudonimization. Remaining vials in the dermato-biobank (BIODIP) of Prof Lambert will remain for 20 years as mentioned in the informed consent. No additional analyses will be performed without the patients' consent and a new application for ethical approval.

9.6 Data Quality Assurance

Data of all Dutch participating sites was monitored following the guidelines of the Radboudumc, as specified in the monitoring plan. Radboudumc worked with the integrated Clincial Research Center Nijmegen (CRCN) and Research Technology Center Clinical Studies (RTC-cs) (https://www.radboudumc.nl/research/radboud-technology-centres/clinical-studies) for this purpose.

In Belgium, monitoring at each participating site was performed according to sponsor's monitoring plan by qualified monitors from HIRUZ, the Clinical Trials Unit from Ghent University Hospital.

In addition, instruction manuals e.g. lab manual were provided to all participating sites as guidance.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans

The primary outcome is **non-inferiority of the incidence proportion of persistent flares (PASI > 5 for ≥ 3 months) in patients undergoing DR, with a non-inferiority margin of 15%.** If the 95% confidence interval from the difference in incidence of persistent flares in the DR group versus UC group exceeds the non-

inferiority margin at 18 months of follow-up, it can be concluded that non-inferiority could not be demonstrated for DR. This margin was based on previous literature and clinical grounds.(4–6) Extensive rationale can be found elsewhere. (7)
Baseline and treatment characteristics were summarized using descriptive statistics. The mean cumulative dose per patient for each biologic was calculated, along with the percentage of the dose used in the DR group compared to the UC group.

Per-protocol analyses were performed because this type of analysis is the preferred and most conservative analysis for noninferiority studies. Patients adhering to the DR protocol, including DR patients that returned to their normal dose according to the protocol, remain in their allocated group. Patients who should have returned to a higher dose are excluded from per-protocol analysis from the point of deviation onward, though they will complete all study procedures. Protocol deviations were summarized and reported. Patients lost to follow-up were analyzed until their lost to follow update, with relevant information documented.

For sensitivity and cost-effectiveness purposes (reported in separate paper**), an intention-to-treat (ITT) analysis** will also be conducted. Protocol deviators will be included, with missing data imputed using last observation carried forward (LOCF) and multiple imputation methods. The extent and nature of missing data were reported.

The primary outcome—incidence proportion of persistent flares—was calculated for both groups and reported as proportions with 95% confidence intervals using Fisher's exact test (Clopper-Pearson), analyzed via OpenEpi (V3.01). Non-inferiority will not be demonstrated if the difference in incidence proportion of persistent flares exceeds 15% at 18 months. Time to first persistent flare were visualized using Kaplan-Meier curves.

The proportion of patients with successful DR will be reported descriptively. PASI and DLQI over time will be compared between groups using mixed-model analysis. At each 3-month time point, PASI were compared directly using unpaired t-tests or non-parametric alternatives. PASI and DLQI at 12 and 18 months were analyzed via ANCOVA, adjusting for baseline values. Multivariable regression will identify predictors of successful DR at 12 and 18 months, testing the four most promising baseline variables, including drug trough levels. (ongoing research)

Serious adverse events (SAEs) and adverse events of special interest (AEoSI) were summarized as proportions and rate ratios with confidence intervals, and between-group differences tested using Fisher's exact test. Additionally, events deemed specifically related to DR itself, as assessed by two reviewers were analyzed. Subgroup analyses by drug class or individual drugs will be performed where numbers allow.

All statistical analyses were performed with SPSS software, version 293.0 (SPSS Inc) and SAS software, version 9.4 (SAS Institute Inc).

9.7.2 Determination of sample size

Based on clinical experience with a previous non-inferiority dose reduction study (CONDOR trial)(4,8–11), we estimated that approximately 7% of patients in usual care will experience a persistent disease flare (definition: PASI> 5 for ≥ 3 months). We estimated that 11% of patients has a persistent disease flare in the dose reduction arm, as this percentage will slightly increase due to the intervention. A difference of 4-5% (an extra 4 or 5% of patients will experience a persistent flare compared to the proportion of persistent flares in usual care) is acceptable, because a small increase in flares is inherent to dose reduction. We keep in mind that the difference in flares might slightly deviate from the previous dose reduction study, and some space in the margin is included. Therefore, a 15% non-inferiority margin represents a reasonable cutoff value in this context. Although somewhat arbitrary, a difference in long persistent flares of over 15% between usual care and dose reduction group would constitute a clinical relevant non-inferiority margin in this context. The underlying reason is that we expect that the majority of the persistent disease flares will resolve after reintroduction of a higher dose after >3 months. A small amount of 15% of the patients with a persistent flare would therefore experience a longer duration of their persistent flare (>3 months). In long persistent flares, multiple treatment alternatives are available as there are currently 11 biologics that can be prescribed for psoriasis. In our clinical view, this seems to balance with an expected chance of being able to reduce the dose, and thus the benefit-harm ratio seems well-balanced.

In our previous dose reduction study, persistent flares were easy to control in the end without residual damage for the patients. Also from our daily clinical practice, we notice that patients with flares will get a response after switching their biologic or after increasing the dose. Of note, a flare is not an exacerbation of psoriasis. With tight control of clinical effectiveness and monitoring of dermatology related quality of life we expect the risk of persistent flares (of over 3 months) to be low. With this margin, one-sided testing (α=0.025;1−β=0.8) and a randomisation ratio of 2:1 dose tapering versus usual care, we calculated that 222 patients need to be included to reject the null-hypothesis of inferiority. Taking a drop-out rate of 10% into account, 244 patients need to be included. In summary, 244 patients will be randomized (2:1) into two groups dose reduction guided by PASI (n=162, intervention) and maintenance of normal dosage (n=82, usual care).

9.8 Changes in the Conduct of the Study or Planned Analyses

During the trial, two protocol amendments were submitted:

1. **Prolongation of the inclusion period**

In consultation with the funders (KCE and ZonMW), the coordinating investigators submitted a non-substantial amendment on September 11, 2023 to prolong the inclusion period of the BeNeBio trial as the recruitment rate was strongly impacted by the

COVID-19 pandemic. The amendment was approved on October 3, 2023. This change had no implication on the interpretation of the study.

2. Adding a new biologic to the inclusion criteria

In 2021 the biologic 'bimekizumab', a dual inhibitor of IL-17A and IL-17F, entered the European market and was approved for the indication of moderate-to-severe psoriasis. As the biologic was reimbursed in the Netherlands from October 2024 (and not yet in Belgium), the coordinating investigators decided to add the biologic in the protocol. A substantial amendment was subsequently submitted and approved. As a consequence, the Dutch participating sites were able to include patients who were treated with this biologic as well.

As the sample size of the trial has not been adapted, this change resulted in a lower absolute number of inclusions of the other biologics. However, this has no direct impact on the interpretation of the study as the biologics are grouped as IL-17 and IL-23 inhibitors for the primary and secondary endpoints.

10. STUDY PATIENTS

10.1 Disposition of Patients

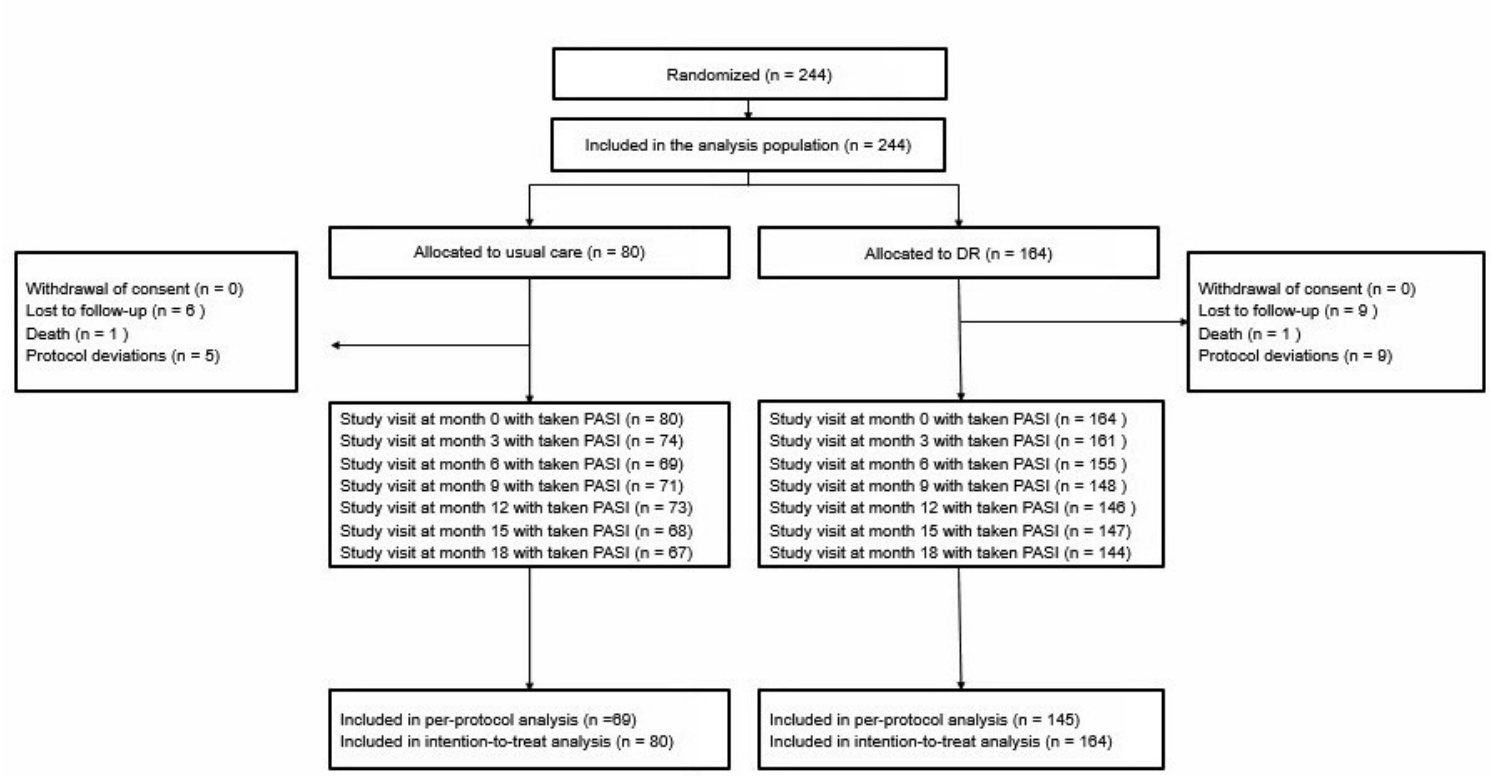


Figure 3: Flowchart of patient inclusion in the BeNeBio trial.

10.2 Protocol Deviations

One patient was included while one of the inclusion criteria was not met. Patient was randomized to the usual care group and dropped out from visit month 15. The collected data of this patient until visit month 15 was left out of the per protocol analysis.

The way of handling other protocol deviations during the study is described in chapter 11.1.

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

In total, **4 different analyses** have been conducted:

- Per protocol 1 with last observation carried forward (PP1_LOCF)
- Per protocol 2 with last observation carried forward (PP2_LOCF)
- Intention-to-treat with last observation carried forward (ITT_LOCF)
- Intention-to-treat with multiple imputation (ITT_MI)

We performed two different per protocol analyses. In the first per protocol analysis (PP1), patients were excluded if they deviated from the protocol independent of the treatment arm (dose reduction (DR) or usual care (UC). In the second per protocol analysis (PP2), patients with DR were excluded if they deviated from the DR protocol but patients with UC were allowed to start DR, to switch biologic, to withdraw from/stop their biologic or to use longer/shorter intervals than protocol without medical reason. The PP2 analysis was performed in light of the pragmatic character of this trial, also, no clear statement in the protocol was provided for the UC arm at start of the trial. Imputation by last observation carried forward (LOCF) was performed for missing visits until the moment a patient was excluded. Secondary objectives analyzed by the intention-to-treat (ITT) with multiple imputation (MI) analysis, are upcoming. Figure 4 shows per analysis which patients were included and excluded.

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Case	PP1_LOCF		PP2_LOCF		ITT_LOCF		ITT_MI	
	DR	UC	DR	UC	DR	UC	DR	UC
Deviation from DR protocol: PASI >5 and/or DLQI >10 and patient remained on DR	Excluded	*n/a*	Excluded	*n/a*	**Included**	*n/a*	Included	*n/a*
Start DR while randomized to UC	*n/a*	Excluded	*n/a*	Included	*n/a*	Included	*n/a*	Included
Dropout (lost to follow-up)	Excluded	Excluded	Excluded	Excluded	Included	Included	Included	Included
Switch of biologic	Excluded	Excluded	Included *(only if protocol was followed prior to switch)*	Included	Included	Included	Included	Included
Withdrawal from/stop of biologic	Excluded	Excluded	Excluded	Included	Included	Included	Included	Included
Systematically longer / shorter injection interval than protocol without medical reason	Excluded	Excluded	Excluded	Included	Included	Included	Included	Included

Figure 4: overview of in-/excluded patients per analysis.

PP: per protocol, LOCF: last observation carried forward, ITT: intention-to-treat, MI: multiple imputation, DR: dose reduction, UC: usual care, PASI: Psoriasis Area and Severity Index, DLQI: Dermatology Life Quality Index.

11.2 Demographic and Other Baseline Characteristics

A total of 164 patients was randomized to DR and 80 patients to UC. In the total study population, the mean age was 51 years with a standard deviation (±SD) of 15 years and the majority was male (67%). The median body mass index (BMI) of the total study population was 27.1 (interquartile range [IQR] 5.8) (Table 1). At baseline, the median PASI score was 0.0 [1.1] and median DLQI score was 0.0 [1.0] in the total study population. Included patients had most frequently a PASI and DLQI score ≤1 at baseline (Figure 5). Table 2 also shows that both in the DR and UC group, the baseline characteristics were comparable.

Table 2: Baseline characteristics of the total BeNeBio study population and split for DR and UC group.

Results are presented as mean with the standard deviation (±SD), percentage (%) with the absolute number of patients (N), and median with the interquartile range [IQR]. NB: the two non-melanoma skin cancers were both basal cell carcinomas. BMI = Body Mass Index. PASI: Psoriasis Area and Severity Index. DLQI: Dermatology Life Quality Index. SMI: small molecule inhibitor. PsA: psoriatic arthritis. UVB: ultraviolet B. PUVA: psoralen with ultraviolet A.

Baseline characteristics	**Study population (N=244)**	**Dose reduction group (N=164)**	**Usual care group (N=80)**
Age (years)	51 ±15	49 ±15	54 ±15
Male	67% (163)	65% (106)	71% (57)
BMI	27.1 [5.8]	26.9 [5.5]	27.6 [6.7]

Age at onset of psoriasis	27 ±16	26 ±16	30 ±16
Disease duration (years)	21 [20]	21 [21]	22 [19]
PASI	0.0 [1.1]	0.0 [0.9]	0.05 [1.2]
DLQI	0.0 [1.0]	0.0 [1.0]	0.0 [1.0]
Biologic naivety	47% (114)	50% (82)	40% (32)
Concomitant use of conventional systemic therapy			
- Methotrexate	1.6% (4)	1.2% (2)	2.5% (2)
- Acitretin	0.4% (1)	0% (0)	1.3% (1)
Number of previously used treatments per patient			
- Conventional systemic	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]
- Biologic/SMI	1.0 [1.0]	0.5 [1.0]	1.0 [1.75]
Comorbidities of interest			
- Cardiovascular disease	34% (84)	33% (54)	37.5% (30)
- Depression/anxiety	15% (36)	18% (29)	9% (7)
- Rheumatologic condition			
o Concomitant PsA	14% (34)	13% (21)	16% (13)
o not PsA	7% (18)	7% (11)	9% (7)
- Diabetes mellitus (type 1 or 2)	11% (27)	12% (19)	10% (8)
- Inflammatory bowel disease	2% (5)	2% (3)	2.5% (2)
- Malignancy	3% (8)	2% (4)	5% (4)
- Non-melanoma skin cancer	0.8% (2)	1% (2)	0% (0)

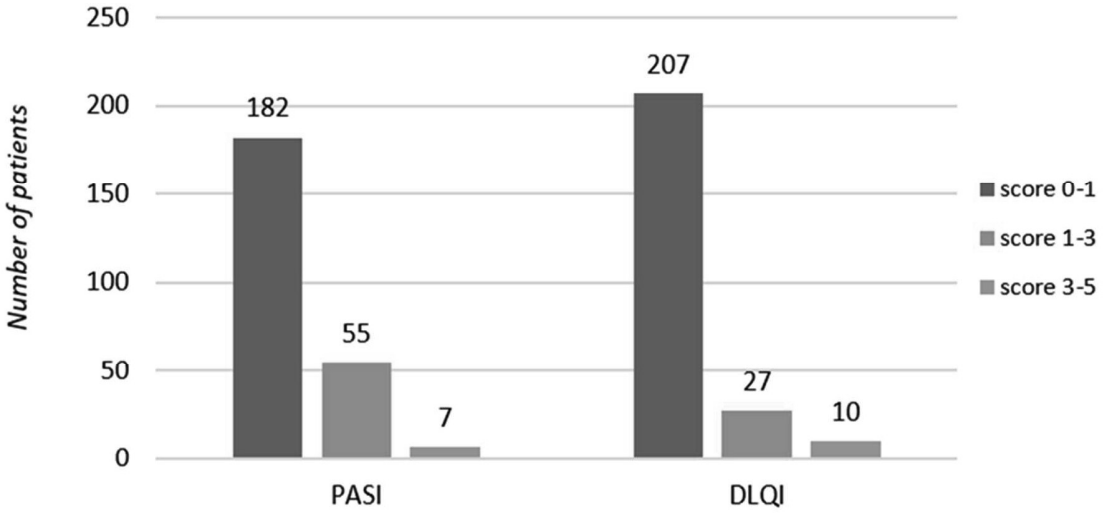


Figure 5: Number of patients with a PASI score 0-1, score 1-3 or score 3-5, and number of patients with a DLQI score 0-1, score 1-3 or score 3-5 at baseline.

PASI: Psoriasis Area and Severity Index. DLQI: Dermatology Life Quality Index.

Almost half of the total study population (N=114; 47%) was biologic naive at baseline (Table 3). A median of 2.0 [1.0] conventional systemic treatments and a median of 1.0 [1.0] biologic/small molecule inhibitor (SMI) was previously used per patient in the total study population. Adalimumab was the most frequent previously used biologic (N=65, 27%), followed by etanercept (N=46, 19%) and ustekinumab (N=42, 17%) (Table 3). Topical corticosteroids and methotrexate were the most frequent previously used non-biologic treatments with both 87% (N=211) of the patients of the total study population, followed by ultraviolet therapy (ultraviolet B (UVB)/psoralen with ultraviolet A (PUVA)) with 84% (N=206) of the patients (Table 3). At baseline, the four most frequently used biologics were guselkumab (N=72, 30%), ixekizumab (N=62, 25%), risankizumab (N=51, 21%) and secukinumab (N=35, 14%). The three least frequently used biologics were brodalumab (N=15, 6%), tildrakizumab (N=6, 3%) and bimekizumab (N=3, 1%) (Figure 6). A total of 239 patients (98%) did not use concomitant conventional systemic therapy (methotrexate or acitretine) at baseline. Only two patients in both DR and UC group (1.2% and 2.5% respectively) used methotrexate and one patient in the UC group used acitretin (1.3%) at start study (Table 3). At baseline, different comorbidities of interest were recorded (Table 2). The most frequent comorbidity was cardiovascular disease (N=84, 34%), followed by depression/anxiety (N=36, 15%), concomitant PsA (N=34, 14%) and diabetes mellitus (N=27, 11%). Almost half of the total study population (N=129, 53%) had none of these comorbidities at baseline.

Table 3: previously used treatments in the total study population and the dose reduction and usual care group at baseline. *Results are presented as percentage (%) with the absolute number of patients (N). UVB: ultraviolet B. PUVA: psoralen with ultraviolet A.*

Baseline characteristic	**Study population (N=244)**	**Dose reduction group (N=164)**	**Usual care group (N=80)**
Previously used treatments			
Non-biologic			
Conventional topical			
- Topical corticosteroids	87% (211)	88% (144)	84% (67)
- UVB/PUVA	84% (206)	83% (136)	88% (70)
- Topical vitamin D	37% (89)	38% (62)	34% (27)
- Dithranol	8% (19)	8% (13)	7.5% (6)
Conventional systemic			
- Methotrexate	87% (211)	85% (139)	90% (72)
- Ciclosporin	49% (119)	48% (78)	51% (41)
- Fumaric acid esters	28% (68)	29% (48)	25% (20)
- Acitretin	16% (39)	13% (22)	21% (17)
Biologic			
TNFα inhibitors			
- adalimumab	27% (65)	25% (41)	30% (24)
- etanercept	19% (46)	18% (30)	20% (16)
- infliximab	5% (13)	5% (8)	6% (5)
- certolizumab pegol	0.4% (1)	1% (1)	0% (0)
IL-12/23 inhibitor			
- ustekinumab	17% (42)	15% (25)	21% (17)

IL-17 inhibitors			
- secukinumab	9% (22)	9% (15)	8.8% (7)
- ixekizumab	6% (15)	7% (11)	5% (4)
- brodalumab	3% (6)	2% (4)	3% (2)
IL-23 inhibitors			
- guselkumab	2% (5)	3% (5)	0% (0)
- risankizumab	0.4% (1)	1% (1)	0% (0)
- tildrakizumab	0.4% (1)	0% (0)	1% (1)
Small molecule inhibitor			
PDE-4 inhibitor			
- apremilast	10% (25)	12% (20)	6% (5)

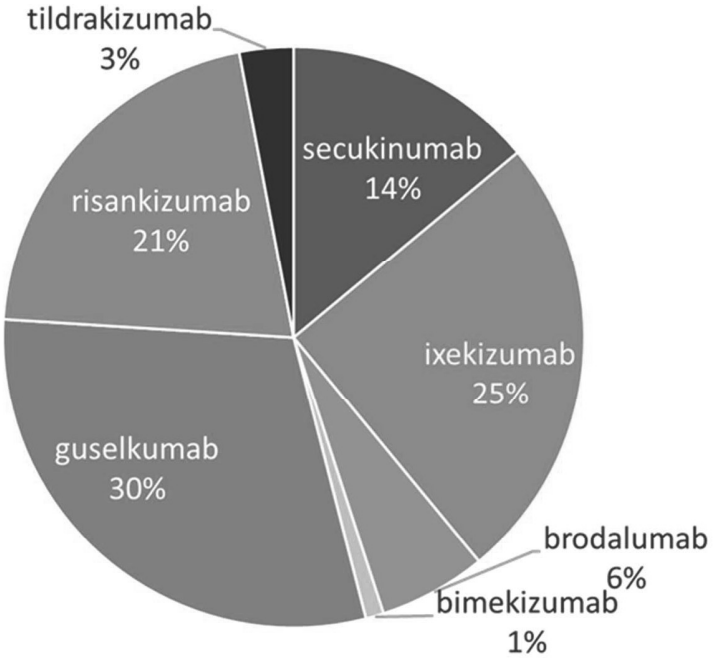


Figure 6: Biologic distribution of the total study population (N=244) at baseline.

11.3 Measurements of Treatment Compliance

Assessment of compliance was performed by collecting the dates of drug administration to verify if the dosing interval was respected.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of efficacy

The primary endpoint of the BeNeBio trial is the difference in cumulative incidence of persistent flares (PASI >5 for ≥3 months) between DR and UC with a non-inferiority margin of 15%. Secondary outcomes include the proportion of patients with successful DR (patients on DR with PASI ≤5), course of PASI and DLQI, serious adverse events, health related quality of life, costs, and pharmacokinetic profile. Results were analyzed in a per protocol (PP) and intention-to-treat (ITT) analysis.

PRIMARY OUTCOME:

The primary outcome is the difference in cumulative incidence of persistent flares between DR and UC with a non-inferiority margin of 15%. This means that the upper limit of the 95% confidence interval (CI) of the difference in proportions has to be <15%.

Conclusion: The primary outcome is reached in all analyses, as shown in all the analyses below (PP1 LOCF, PP2 LOCF, ITT LOCF and ITT MI).

PP1_LOCF

A total of 214 patients completed the study in the PP1_LOCF analysis

In total, 4/214 patients (1.87%) had a persistent flare over 18 months follow-up.
In the DR group, 3/145 patients (2.07%) had a persistent flare and 1/69 patients (1.45%) in the UC group.

Proportion of persistent flares in DR and UC:

- DR: 3/145 = 0.0207
- UC: 1/69 = 0.0145
- Difference in proportions DR-UC: 0.0062 = 0.62%

95% CI of the difference in proportions (calculated with Confidence Interval for the Difference Between Two Independent Proportions): 0.62% [-5.84%; **4.64%**]

The upper limit of the 95% CI is <15%, thereby DR is non-inferior to UC.

PP2_LOCF

A total of 221 patients completed the study in the PP2_LOCF analysis
In total, 5/221 patients (2.26%) had a persistent flare over 18 months follow-up.
In the DR group, 3/148 patients (2.03%) had a persistent flare and 2/73 patients (2.74%) in the UC group.

Proportion of persistent flares in DR and UC:

- DR: 3/148 = 0.0203
- UC: 2/73 = 0.0274
- Difference in proportions DR-UC: -0.0071 = -0.71%

95% CI of the difference in proportions (calculated with Confidence Interval for the Difference Between Two Independent Proportions): -0.71% [-3.54%; **7.55%**]

The upper limit of the 95% CI is <15%, thereby DR is non-inferior to UC.

ITT_LOCF
A total of 244 patients completed the study in the ITT_LOCF analysis
In total, 8/244 patients (3.28%) had a persistent flare over 18 months follow-up.
In the DR group, 6/164 patients (3.66%) had a persistent flare and 2/80 patients (2.5%) in the UC group.

Proportion of persistent flares in DR and UC:

- DR: 6/164 = 0.0366
- UC: 2/80 = 0.025
- Difference in proportions DR-UC: 0.0116 = 1.16%

95% CI of the difference in proportions (calculated with *Confidence Interval for the Difference Between Two Independent Proportions):* 1.16% [-5.31%; **5.63%**]

The upper limit of the 95% CI is <15%, thereby DR is non-inferior to UC.

ITT_MI
A total of 244 patients completed the study in the ITT_MI analysis.

The difference in proportions of persistent flares between DR and UC: 0.0191 = 1.91%

95% CI of the difference in proportions (calculated with 'R' statistics):

1.91% [-2.86%; **6.69%**]
The upper limit of the 95% CI is <15%, thereby DR is non-inferior to UC.

SECONDARY OBJECTIVE 1: Successful dose reduction
For all three analyses (PP1_LOCF, PP2_LOCF, ITT_LOCF), the proportion of patients with successful DR after 12 and 18 months was analyzed (Tables 4 to 6). Successful DR was defined as using a lower dose than standard dose with PASI ≤ 5.

After 12 months, 77% of patients had a successful DR in the PP1- and PP2_LOCF analysis, and 76% in the ITT_LOCF analysis. After 18 months, 75% of patients had a successful DR in the PP1_LOCF analysis, and 73% in the PP2- and ITT_LOCF analysis.

Table 4: proportion of patients with successful dose reduction after 12 and 18 months in the per protocol 1 analysis with last observation carried forward (PP1_LOCF). *M12: visit month 12, M18: visit month 18, N: number of patients, DR: dose reduction, PASI: Psoriasis Area and Severity Index*

PP1_LOCF after 12 months	
M12	*N in DR-group*
M12 completed	150
M12 completed + still DR step 1 or 2	117
M12 completed + successful DR (step 1 or 2 and PASI ≤ 5)	116

Proportion of patients with successful dose tapering after 12 months: 116/150 = 0.7733 = 77.3%	
PP1_LOCF after 18 months	
M18	*N in DR-group*
M18 completed	145
M18 completed + still DR step 1 or 2	109
M18 completed + successful DR (step 1 or 2 and PASI ≤ 5)	108
Proportion of patients with successful dose tapering after 18 months: 108/145 = 0.7448 = 74.5%	

Table 5: proportion of patients with successful dose reduction after 12 and 18 months in the per protocol 2 analysis with last observation carried forward (PP2_LOCF). *M12: visit month 12, M18: visit month 18, N: number of patients, DR: dose reduction, PASI: Psoriasis Area and Severity Index*

PP2_LOCF after 12 months	
M12	*N in DR-group*
M12 completed	151
M12 completed + still DR step 1 or 2	117
M12 completed + successful DR (step 1 or 2 and PASI ≤ 5)	116
Proportion of patients with successful dose tapering after 12 months: 116/151 = 0.7682 = 76.8%	
PP2_LOCF after 18 months	
M18	*N in DR-group*
M18 completed	148
M18 completed + still DR step 1 or 2	109
M18 completed + successful DR (step 1 or 2 and PASI ≤ 5)	108
Proportion of patients with successful dose tapering after 18 months: 108/148 = 0.7297 = 73%	

Table 6: proportion of patients with successful dose reduction after 12 and 18 months in the intention-to-treat analysis with last observation carried forward (ITT_LOCF). *M12: visit month 12, M18: visit month 18, N: number of patients, DR: dose reduction, PASI: Psoriasis Area and Severity Index*

ITT_LOCF after 12 months	
M12	*N in DR-group*
M12 completed	164
M12 completed + still DR step 1 or 2	128
M12 completed + successful DR (step 1 or 2 and PASI ≤ 5)	125
Proportion of patients with successful dose tapering after 12 months is: 125/164 = 0.7622 = 76.2%	
ITT_LOCF after 18 months	
M18	*N in DR-group*

M18 completed	164
M18 completed + still DR step 1 or 2	123
M18 completed + successful DR (step 1 or 2 and PASI ≤ 5)	120
Proportion of patients with successful dose tapering after 18 months is: 120/164 = 0.7317 = 73.2%	

SECONDARY OBJECTIVE 2: Course of mean PASI and DLQI

Per visit, the mean PASI and DLQI scores for both the DR and UC group were analyzed for the PP1-, PP2- and ITT_LOCF analyses. All analyses showed low mean PASI and DLQI scores for both groups, ranging from 0 to a maximum of 1.3 over the course of 18 months. Figures 7 to 12 show the course of mean PASI and DLQI scores per analysis.

- **PP1_LOCF analysis**

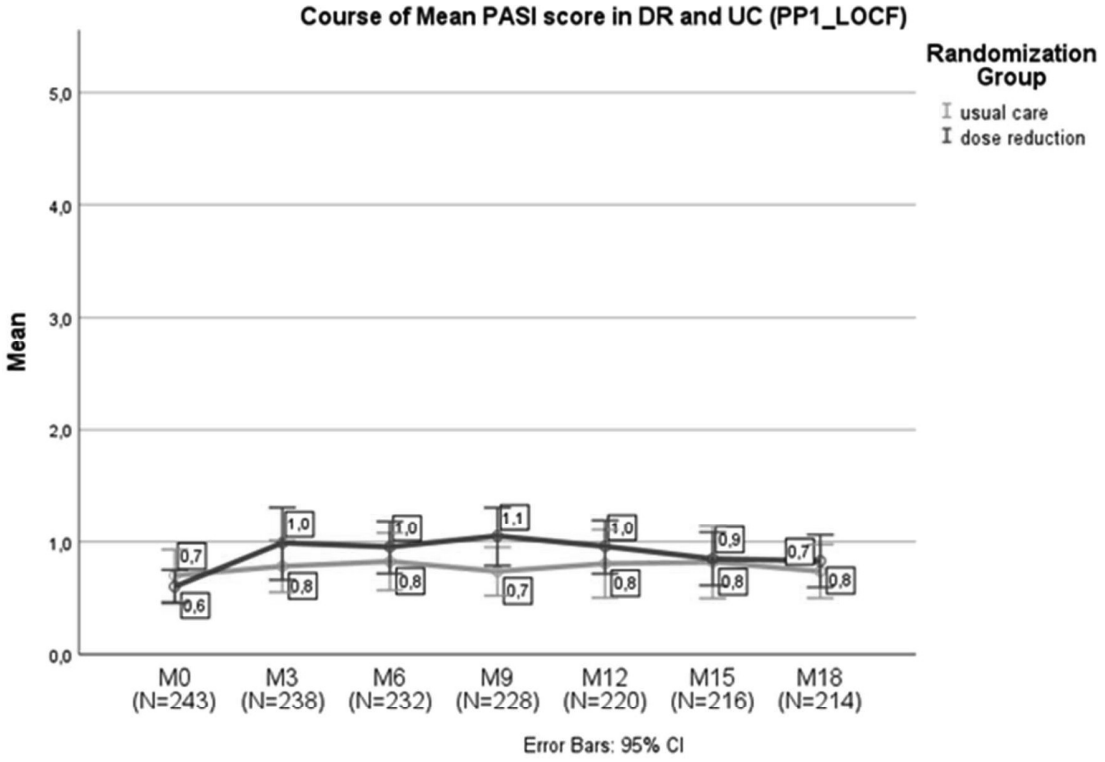


Figure 7: Course of mean PASI score over 18 months follow-up in the per protocol 1 analysis with last observation carried forward (PP1_LOCF). *The mean PASI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, PASI: Psoriasis Area and Severity Index.*

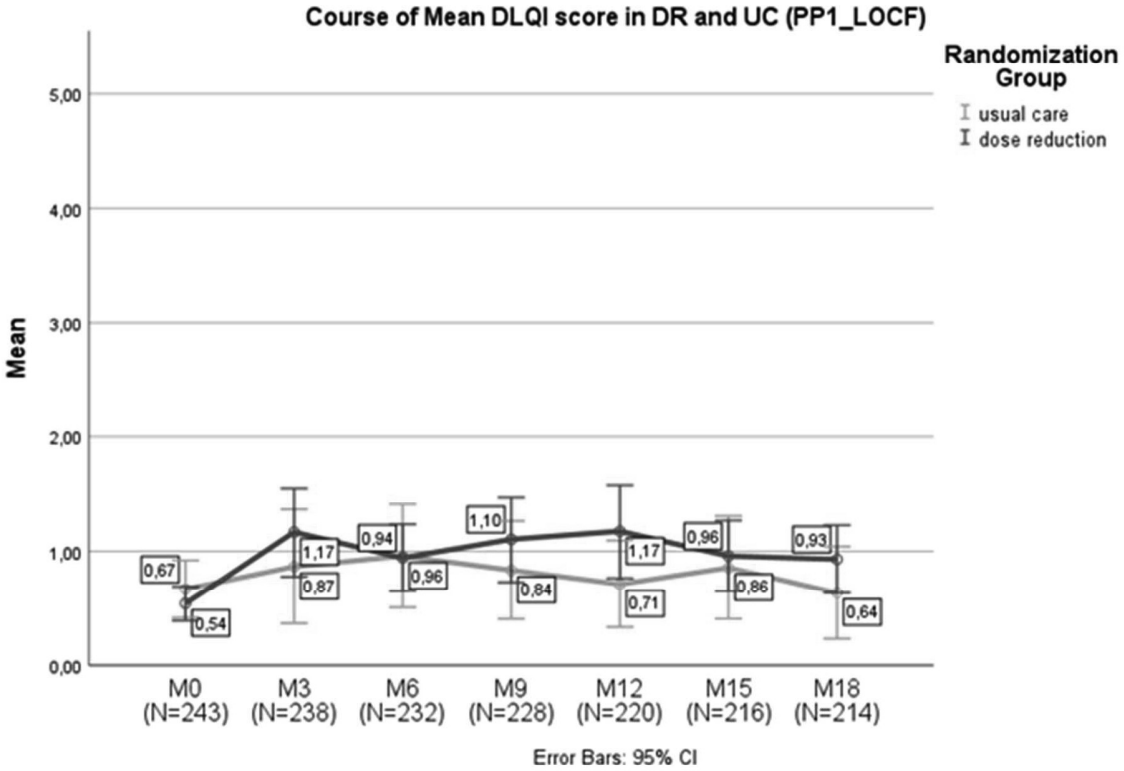


Figure 8: Course of mean DLQI score over 18 months follow-up in the per protocol 1 analysis with last observation carried forward (PP1_LOCF). *The mean DLQI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, DLQI: Dermatology Life Quality Index.*

- **PP2_LOCF analysis**

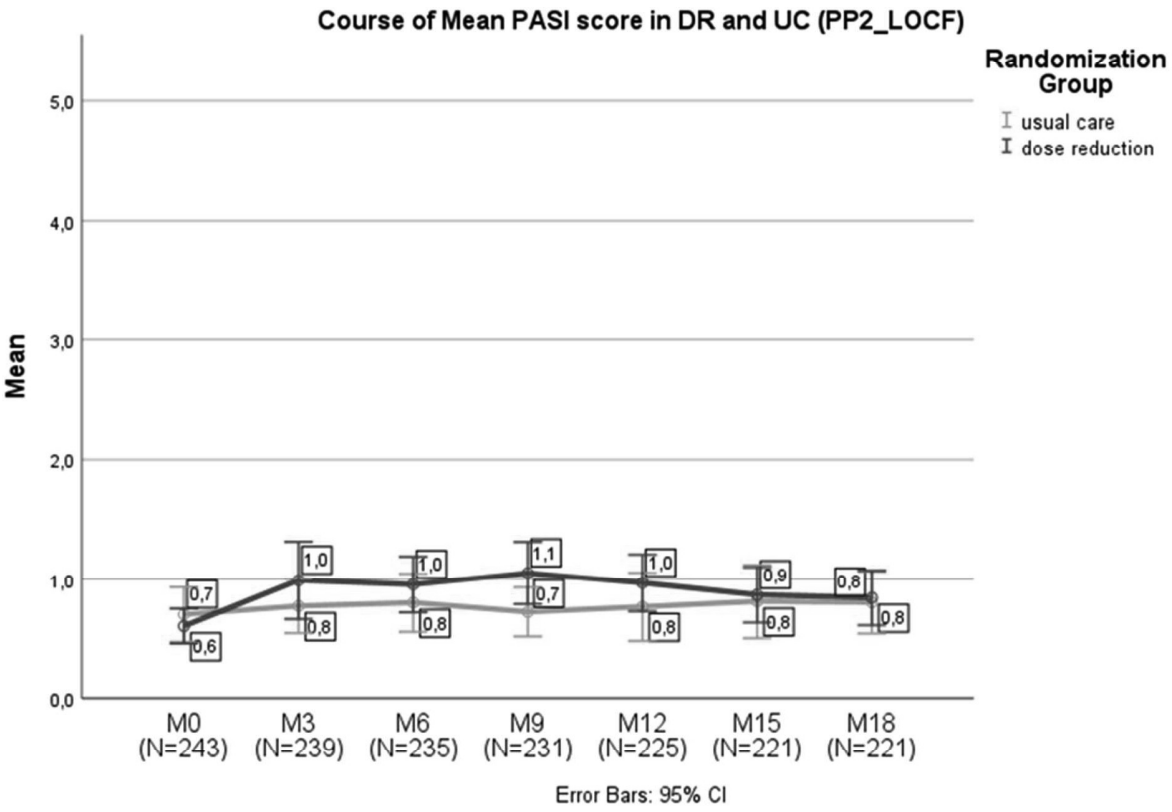


Figure 9: Course of mean PASI score over 18 months follow-up in the per protocol 2 analysis with last observation carried forward (PP2_LOCF). *The mean PASI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, PASI: Psoriasis Area and Severity Index.*

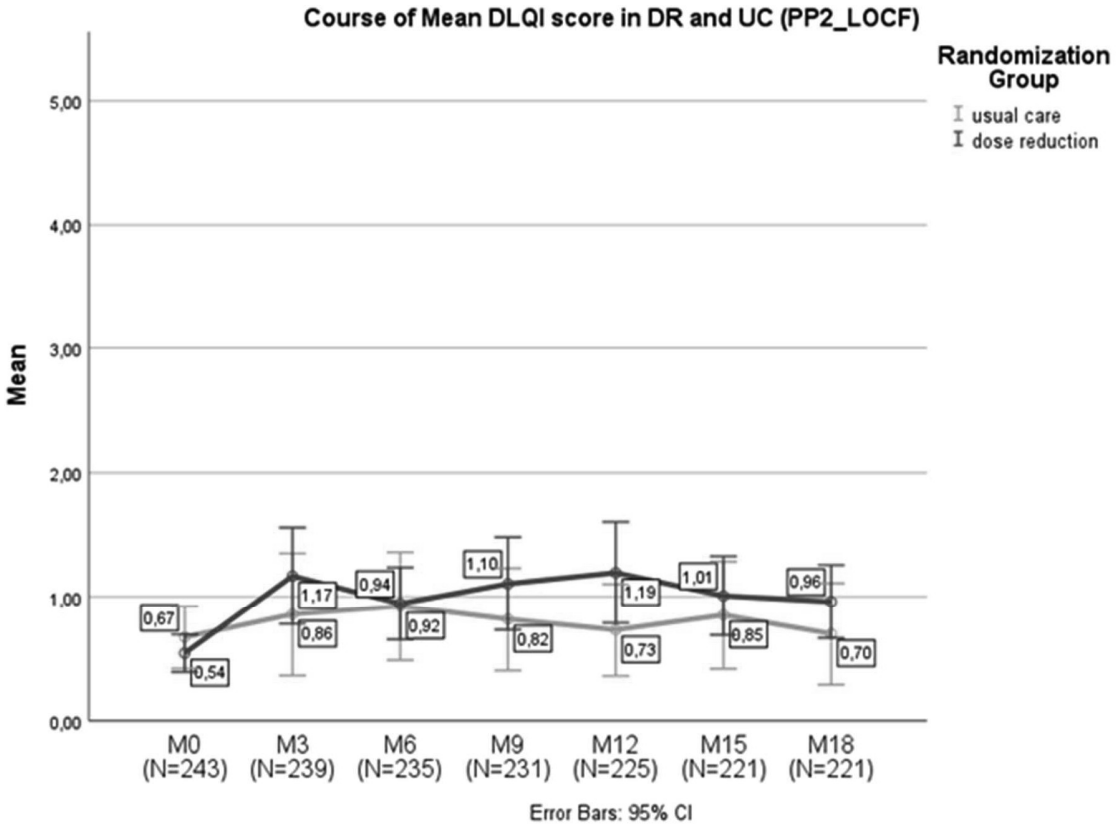


Figure 10: Course of mean DLQI score over 18 months follow-up in the per protocol 2 analysis with last observation carried forward (PP2_LOCF). *The mean DLQI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, DLQI: Dermatology Life Quality Index.*

- **ITT_LOCF analysis**

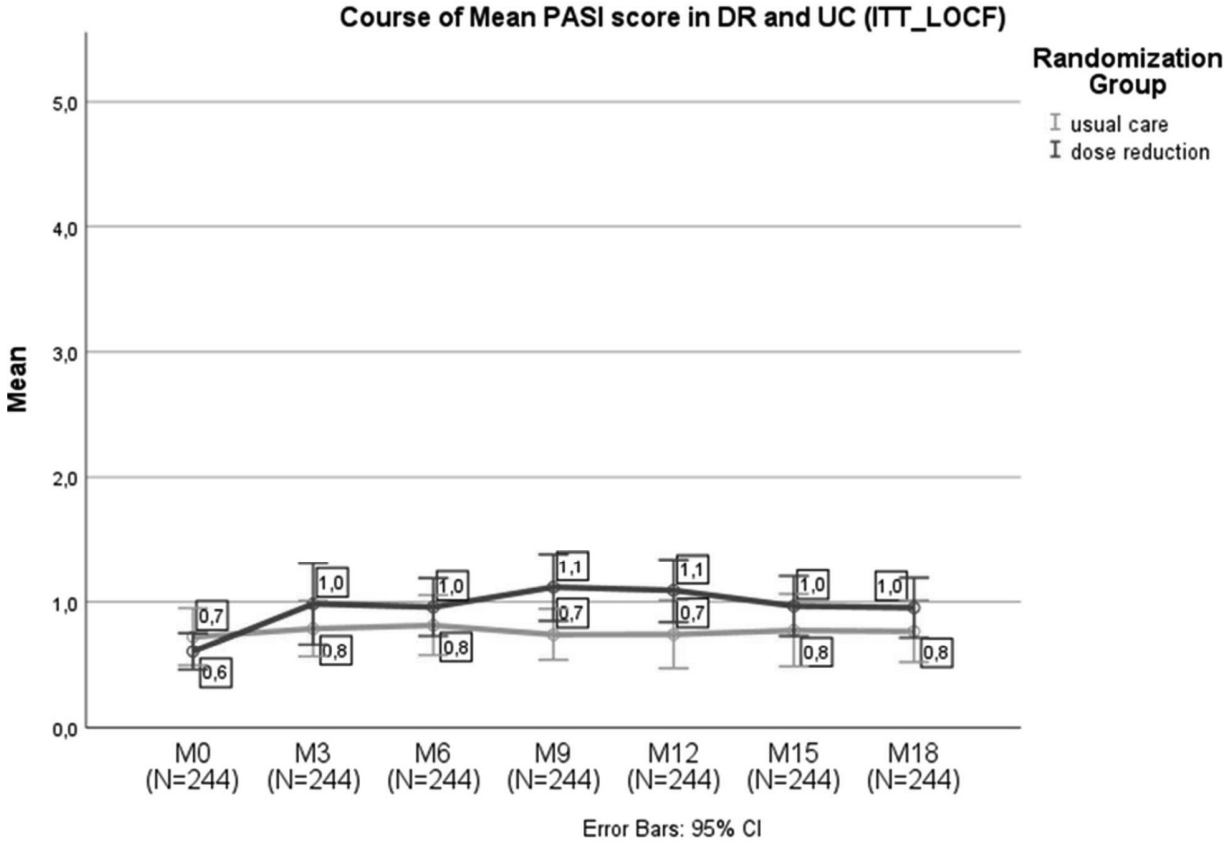


Figure 11: Course of mean PASI score over 18 months follow-up in the intention-to-treat analysis with last observation carried forward (ITT_LOCF). The mean PASI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, PASI: Psoriasis Area and Severity Index.

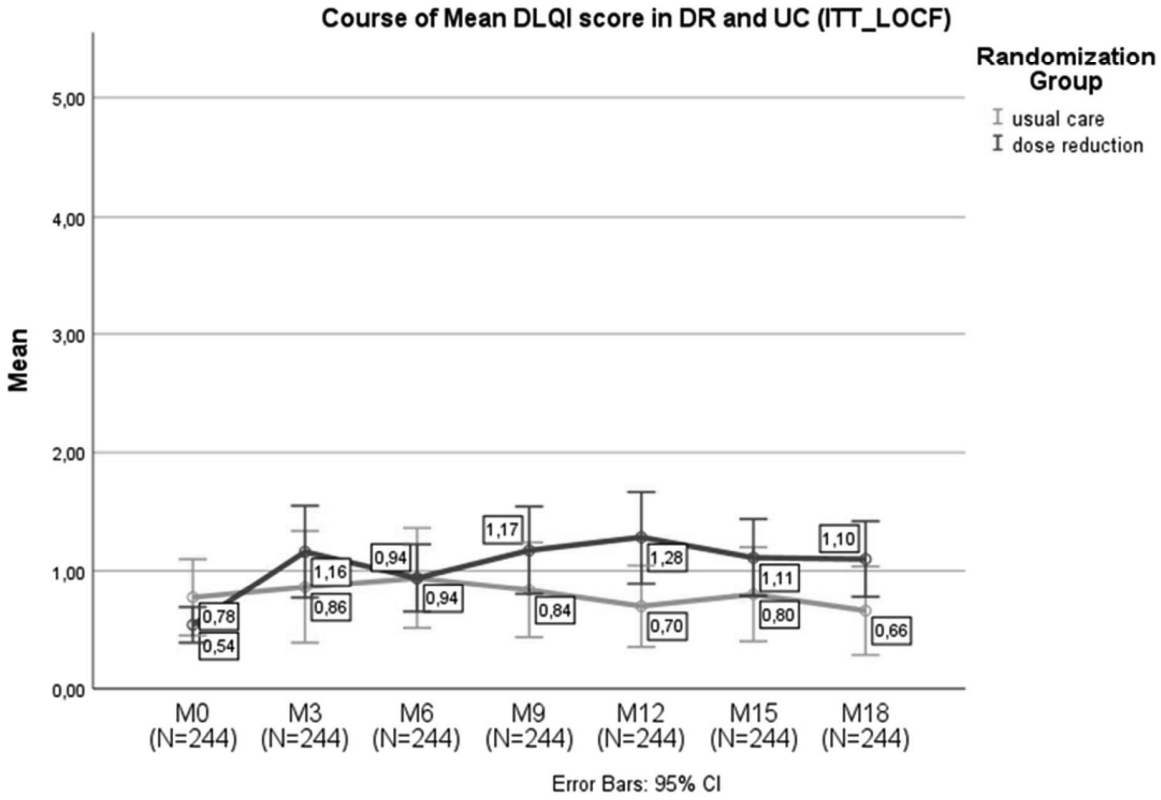


Figure 12: Course of mean DLQI score over 18 months follow-up in the intention-to-treat analysis with last observation carried forward (ITT_LOCF). *The mean DLQI score with 95% confidence interval (CI), for both DR and UC group, is shown per visit. M: visit month, DR: dose reduction, UC: usual care, DLQI: Dermatology Life Quality Index.*

SECONDARY OBJECTIVE 3: Incidence of short disease flares after 18 months

The incidence of short disease flares after 18 months was analyzed for both DR and UC group in all three analyses (PP1-, PP2- and ITT_LOCF). A short disease flare was defined as PASI > 5 at one time point. In the PP1_LOCF analysis, in the DR group, a total of 20 short disease flares occurred among 145 patients (14%) after 18 months. The incidence in the DR group of the PP1_LOCF analysis is comparable to the PP2_LOCF analysis (14%) and the ITT_LOCF analysis (16%). In the UC group, the incidence was 6%, 7%, and 6% for respectively the PP1-, PP2- and ITT_LOCF analysis. Tables 7 to 9 show the incidence of short disease flares per analysis.

Table 7: incidence of short disease flares (PASI >5 at one time point) after 18 months in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

DR: dose reduction, UC: usual care, M: visit month

PP1_LOCF	Number of short disease flares (PASI>5) in DR	Number of short disease flares (PASI>5) in UC	Total
M0	0	0	0
M3	3	0	3
M6	4	1	5
M9	7	0	7
M12	2	1	3
M15	2	2	4
M18	2	0	2
Total	20	4	24
Incidence short disease flares after 18 months in DR: 20/145 = 0.1379 = 13.8%			
Incidence short disease flares after 18 months in UC: 4/69 = 0.0579 = 5.8%			

Table 8: incidence of short disease flares (PASI >5 at one time point) after 18 months in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

DR: dose reduction, UC: usual care, M: visit month

PP2_LOCF	Number of short disease flares (PASI>5) in DR	Number of short disease flares (PASI>5) in UC	Total
M0	0	0	0
M3	3	0	3
M6	4	1	5
M9	7	0	7
M12	2	1	3
M15	2	2	4
M18	2	1	3
Total	20	5	25
Incidence short disease flares after 18 months in DR: 20/148 = 0.1351 = 13.5%			
Incidence short disease flares after 18 months in UC: 5/73 = 0.0685 = 6.9%			

Table 9: incidence of short disease flares (PASI >5 at one time point) after 18 months in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).
DR: dose reduction, UC: usual care, M: visit month

ITT_LOCF	Number of short disease flares (PASI>5) in DR	Number of short disease flares (PASI>5) in UC	Total
M0	0	0	0
M3	3	0	3
M6	4	1	5
M9	8	0	8
M12	4	1	5
M15	3	2	5
M18	4	1	5
Total	26	5	31
Incidence short disease flares after 18 months in DR: 26/164 = 0.1585 = 15.9%			
Incidence short disease flares after 18 months in UC: 5/80 = 0.0625 = 6.3%			

SECONDARY OBJECTIVE 4: Difference in PASI between DR and UC (every 3 months)

An unpaired t-test was performed to test if there is a significant difference in PASI at each time point (every 3 months) between DR and UC. This was performed for all three analyses. In PP1- and PP2_LOCF, at none of the time points there was a statistically significant difference in PASI between DR and UC. In ITT_LOCF, there was only at month 9 a statistically significant difference in PASI score between DR and UC with a difference in mean PASI score of 0.38 (p=0.028). Tables 10 to 12 show the results of the t-test per analysis, per time point.

Table 10: per time point, the mean PASI score was tested for a significant difference between DR and UC by an unpaired t-test in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).
PASI: Psoriasis Area and Severity Index, DR: dose reduction, UC: usual care, M: visit month, SD: standard deviation, df: degree of freedom.

Time point	PASI Mean (SD)		t (df)	p-value
	UC	DR		
M0	0.71 (1.01)	0.61 (0.94)	0.73 (241)	p = 0.466
M3	0.79 (0.99)	0.99 (2.08)	-0.81 (236)	p = 0.420
M6	0.83 (1.08)	0.96 (1.48)	-0.74 (187)	p = 0.461
M9	0.74 (0.91)	1.05 (1.64)	-1.83 (220)	p = 0.069
M12	0.81 (1.25)	0.96 (1.48)	-0.74 (218)	p = 0.460
M15	0.82 (1.33)	0.85 (1.42)	-0.15 (214)	p = 0.882
M18	0.74 (0.97)	0.83 (1.40)	-0.480 (212)	p = 0.632

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Table 11: per time point, the mean PASI score was tested for a significant difference between DR and UC by an unpaired t-test in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

PASI: Psoriasis Area and Severity Index, DR: dose reduction, UC: usual care, M: visit month, SD: standard deviation, df: degree of freedom.

Time point	PASI Mean (SD)		t (df)	p-value
	UC	DR		
M0	0.71 (1.01)	0.61 (0.94)	0.73 (241)	p = 0.466
M3	0.78 (0.98)	0.99 (2.08)	-0.85 (237)	p = 0.394
M6	0.80 (1.06)	0.96 (1.48)	-0.90 (198)	p = 0.370
M9	0.73 (0.89)	1.05 (1.64)	-1.94 (226)	p = 0.053
M12	0.77 (1.23)	0.97 (1.47)	-1.00 (223)	p = 0.318
M15	0.81 (1.31)	0.87 (1.42)	-0.28 (219)	p = 0.783
M18	0.81 (1.11)	0.85 (1.41)	-0.21 (219)	p = 0.836

Table 12: per time point, the mean PASI score was tested for a significant difference between DR and UC by an unpaired t-test in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

PASI: Psoriasis Area and Severity Index, DR: dose reduction, UC: usual care, M: visit month, SD: standard deviation, df: degree of freedom.

Time point	PASI Mean (SD)		t (df)	p-value
	UC	DR		
M0	0.72 (1.02)	0.61 (0.94)	0.87 (242)	p = 0.384
M3	0.79 (0.99)	0.98 (2.08)	-0.80 (242)	p = 0.428
M6	0.82 (1.07)	0.96 (1.47)	-0.87 (207)	p = 0.387
M9	0.74 (0.91)	1.12 (1.72)	-2.21 (240)	**p = 0.028**
M12	0.74 (1.21)	1.09 (1.62)	-1.87 (202)	p = 0.063
M15	0.78 (1.29)	0.97 (1.53)	-0.96 (242)	p = 0.336
M18	0.77 (1.10)	0.95 (1.53)	-0.98 (242)	p = 0.331

SECONDARY OBJECTIVE 5: ANCOVA PASI and DLQI at 12 and 18 months

To test if there was a difference in PASI and DLQI between DR and UC at month 12 and month 18, analysis of covariance (ANCOVA) was performed. The baseline variables used as covariate included gender, body mass index (BMI), disease duration, concomitant psoriatic arthritis (PsA), and number of previously used biologics (biologic naivity). For both PASI and DLQI, the results are shown per time point (month 12 and month 18) and per analysis (PP1-, PP2-, ITT_LOCF).

Month 12 – PASI score

PP1_LOCF

Figure 13 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI between DR and UC at month 12.

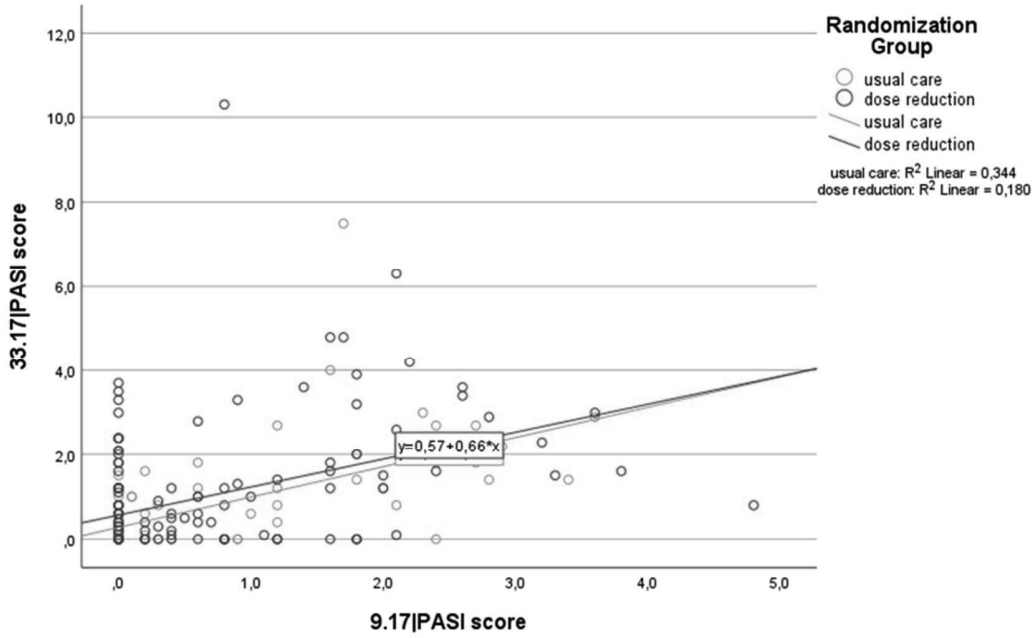


Figure 13: Regression slopes of PASI score at baseline and month 12 for both treatment groups in the per protocol 1 analysis with last observation carried forward (PP1_LOCF). *PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 33.17 PASI score = M12 (=post-test)).*

The main effects model showed no significant difference in PASI score between DR and UC at month 12 (p=0.300). Table 13 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 13: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI at month 12 in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (PASI M0)			After treatment (PASI M12) (unadjusted)		After treatment (PASI M12) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	150	0.59	0.08	0.96	0.12	0.98	0.11
Usual care	70	0.74	0.12	0.81	0.15	0.77	0.17

PP2_LOCF

Figure 11 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI scores between DR and UC at month 12.

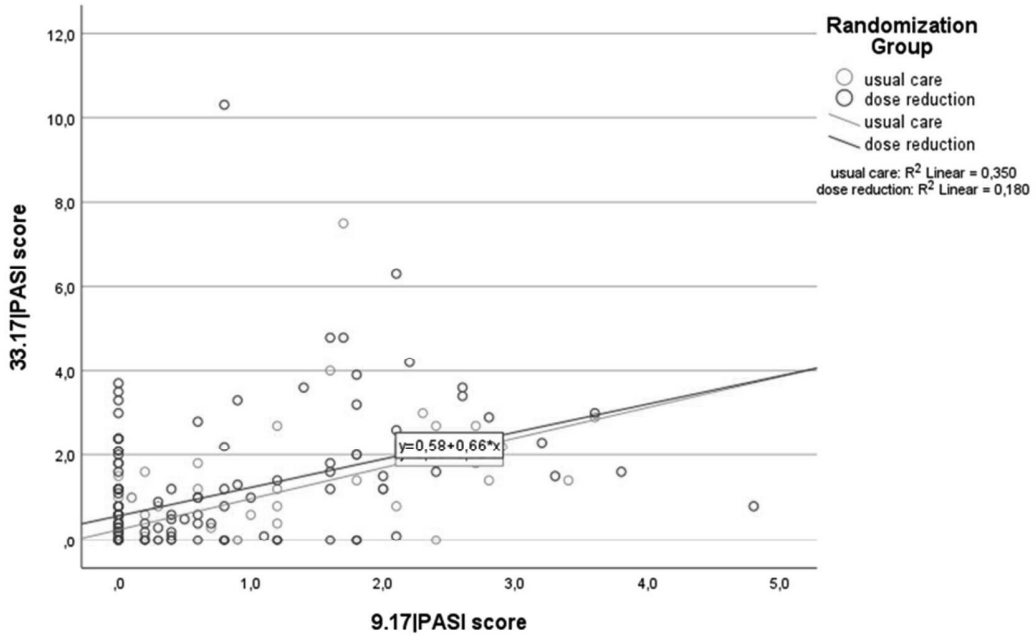


Figure 14: Regression slopes of PASI score at baseline and month 12 for both treatment groups in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 33.17 PASI score = M12 (=post-test)).

The main effects model showed no significant difference in PASI score between DR and UC at month 12 (p=0.196). Table 14 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 14: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI scores at month 12 in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (PASI M0)			After treatment (PASI M12) (unadjusted)		After treatment (PASI M12) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	151	0.60	0.08	0.97	0.12	0.99	0.11
Usual care	74	0.72	0.12	0.77	0.14	0.73	0.16

ITT_LOCF

Figure 15 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI scores between DR and UC at month 12.

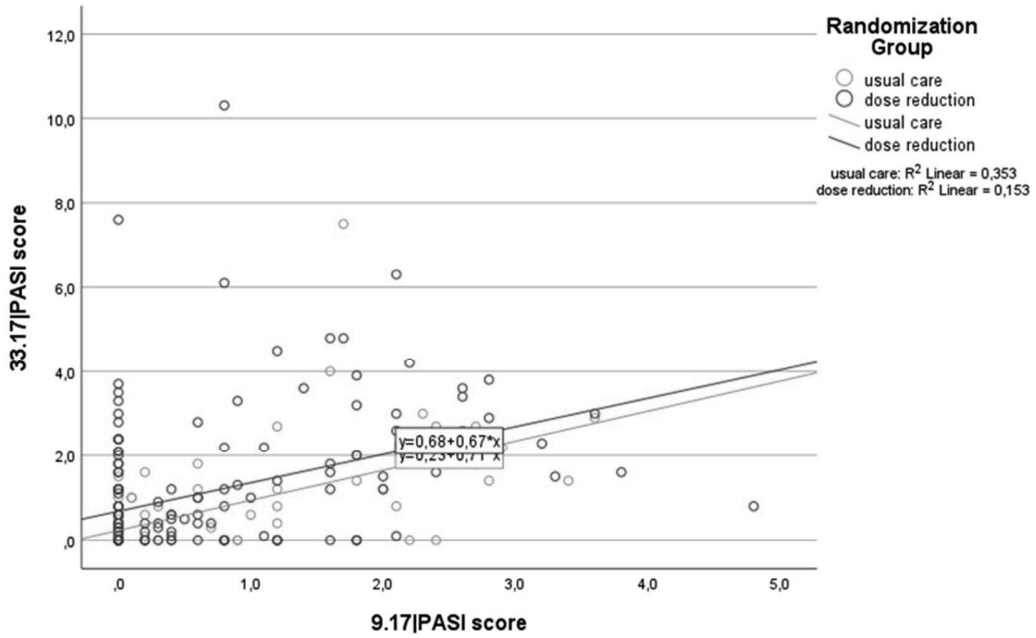


Figure 15: Regression slopes of PASI at baseline and month 12 for both treatment groups in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 33.17 PASI score = M12 (=post-test)).

The main effects model showed no significant difference in PASI score between DR and UC at month 12 (p=0.051). Table 15 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 15: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI scores at month 12 in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (PASI M0)			After treatment (PASI M12) (unadjusted)		After treatment (PASI M12) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	164	0.61	0.07	0.83	0.12	1.11	0.12
Usual care	80	0.72	0.11	0.74	0.12	0.71	0.17

Month 18 – PASI score

PP1_LOCF

Figure 16 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI between DR and UC at month 18.

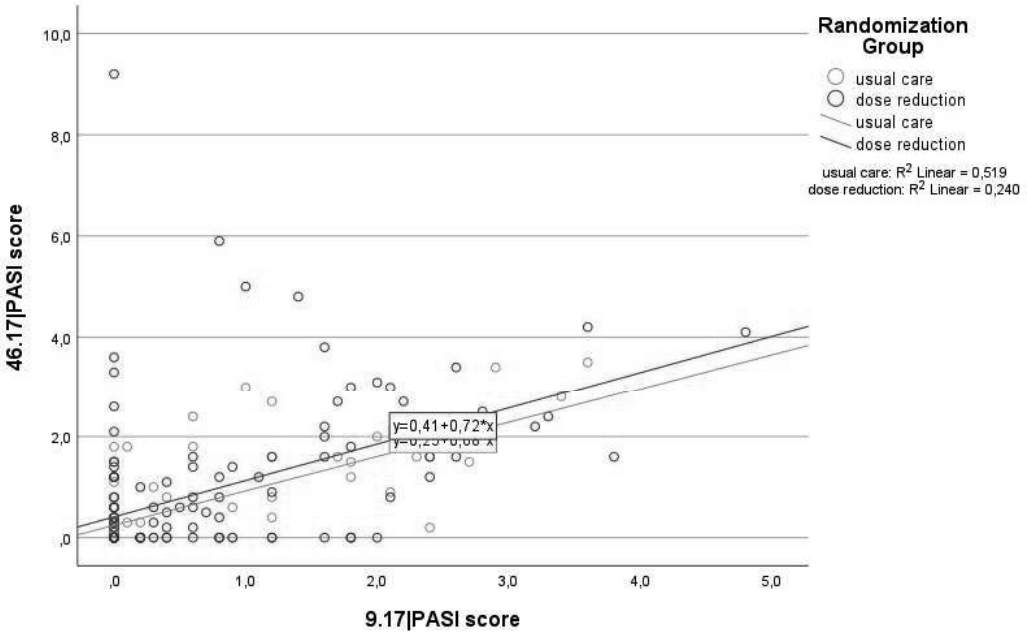


Figure 16: Regression slopes of PASI at baseline and month 18 for both treatment groups in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 46.17 PASI score = M18 (=post-test)).

The main effects model showed no significant difference in PASI between DR and UC at month 18 (p=0.460). Table 16 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 16: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI scores at month 18 in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	**Before treatment (PASI M0)**			**After treatment (PASI M18) (unadjusted)**		**After treatment (PASI M18) (adjusted)**	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	145	0.59	0.08	0.83	0.12	0.85	0.11
Usual care	69	0.73	0.12	0.74	0.12	0.71	0.16

PP2_LOCF

Figure 17 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI scores between DR and UC at month 18.

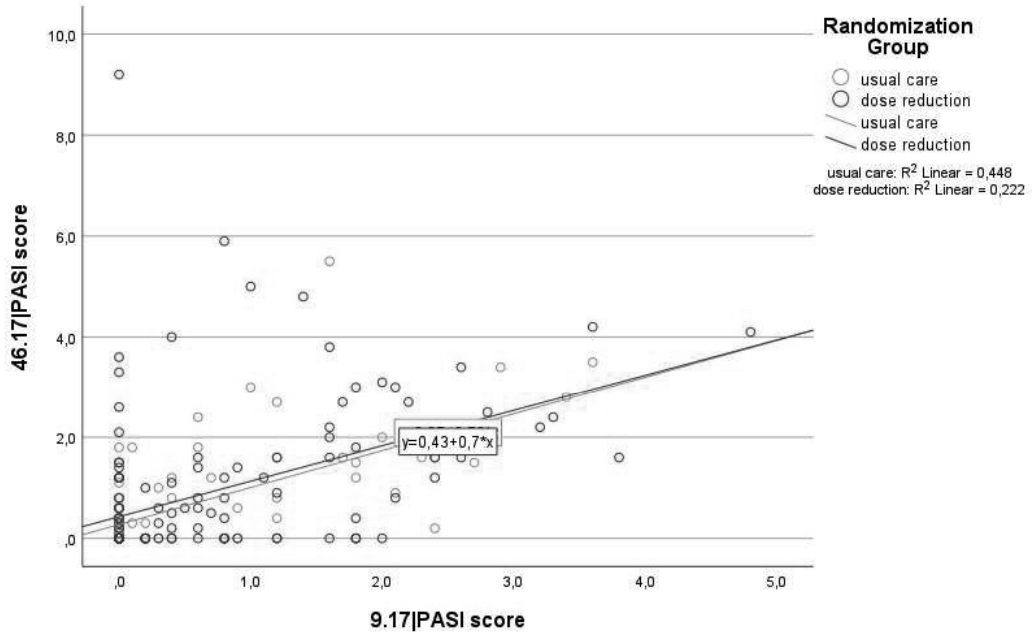


Figure 17: Regression slopes of PASI score at baseline and month 18 for both treatment groups in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 46.17 PASI score = M18 (=post-test)).

The main effects model showed no significant difference in PASI score between DR and UC at month 18 (p=0.615). Table 17 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 17: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI scores at month 18 in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (PASI M0)			After treatment (PASI M18) (unadjusted)		After treatment (PASI M18) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	148	0.59	0.08	0.85	0.12	0.86	0.11
Usual care	73	0.73	0.12	0.81	0.13	0.78	0.16

ITT_LOCF

Figure 18 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different PASI scores between DR and UC at month 18.

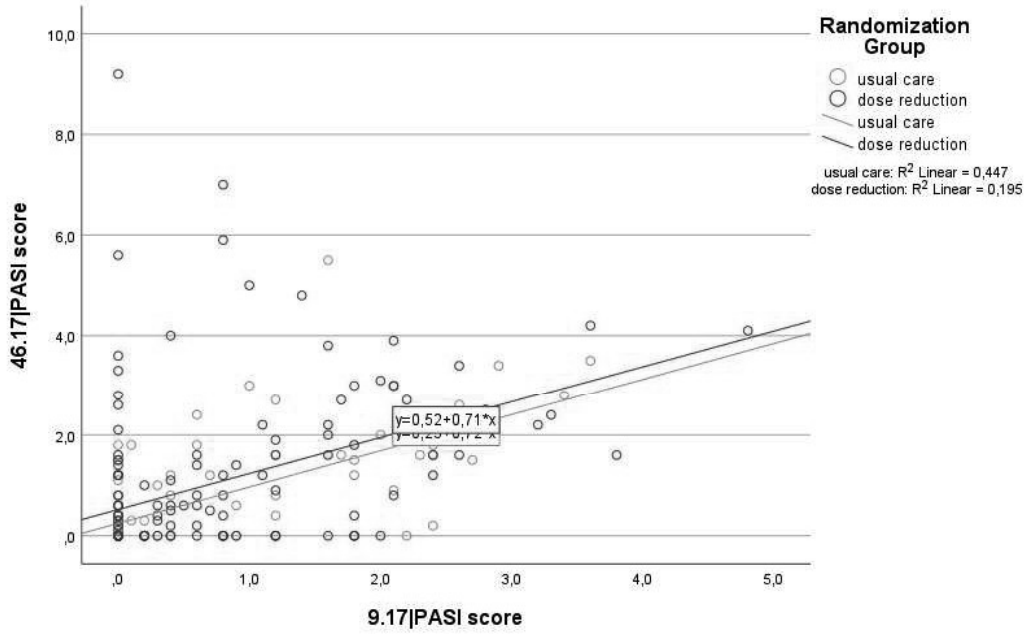


Figure 18: Regression slopes of PASI score at baseline and month 18 for both treatment groups in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

PASI: Psoriasis Area and Severity Index, 9.17 PASI score = M0 (=pre-test), 46.17 PASI score = M18 (=post-test)).

The main effects model showed no significant difference in PASI score between DR and UC at month 18 (p=0.189). Table 18 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 18: for DR and UC the mean PASI scores at baseline (M0) and the unadjusted and adjusted mean PASI scores at month 18 in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

PASI: Psoriasis Area and Severity Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (PASI M0)			After treatment (PASI M18) (unadjusted)		After treatment (PASI M18) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	164	0.61	0.07	0.95	0.12	0.97	0.11
Usual care	80	0.72	0.11	0.77	0.12	0.74	0.16

Month 12 – DLQI score

PP1_LOCF

Figure 19 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI scores between DR and UC at month 12.

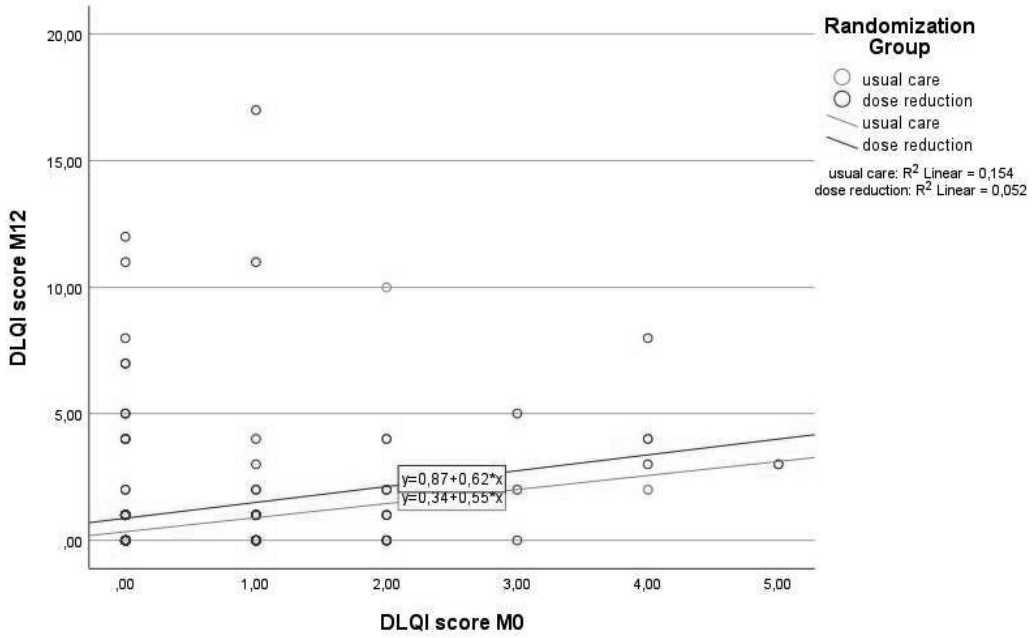


Figure 18: Regression slopes of DLQI score at baseline and month 12 for both treatment groups in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M12 =post-test.

The main effects model showed no significant difference in DLQI score between DR and UC at month 12 (p=0.168). Table 18 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 18: for DR and UC the mean DLQI scores at baseline (M0) and the unadjusted and adjusted mean DLQI scores at month 12 in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	**Before treatment (DLQI M0)**			**After treatment (DLQI M12) (unadjusted)**		**After treatment (DLQI M12) (adjusted)**	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	150	0.48	0.08	1.17	0.21	1.17	0.19
Usual care	70	0.67	0.13	0.71	0.19	0.72	0.27

PP2_LOCF

Figure 19 shows that the regression lines of DR and UC are parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI scores between DR and UC at month 12.

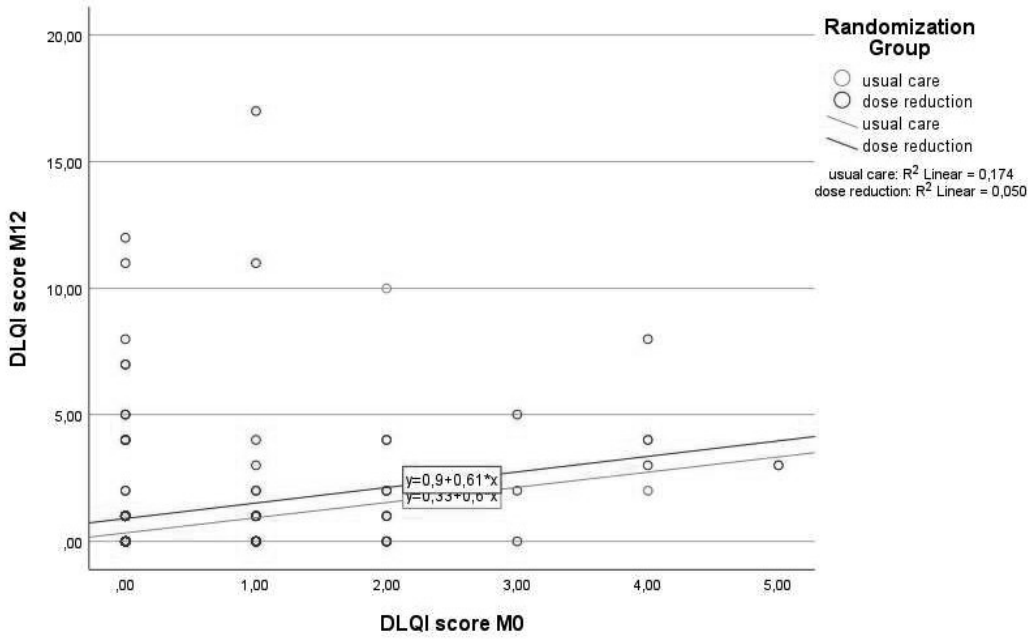


Figure 19: Regression slopes of DLQI score at baseline and month 12 for both treatment groups in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M12 =post-test.

The main effects model showed no significant difference in DLQI score between DR and UC at month 12 (p=0.143). Table 19 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 19: for DR and UC the mean DLQI scores at baseline (M0) and the unadjusted and adjusted mean DLQI scores at month 12 in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (DLQI M0)			After treatment (DLQI M12) (unadjusted)		After treatment (DLQI M12) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	151	0.48	0.08	1.19	0.21	1.20	0.18
Usual care	74	0.66	0.13	0.73	0.19	0.72	0.27

ITT_LOCF

Figure 20 shows that the regression lines of DR and UC are somewhat parallel to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI scores between DR and UC at month 12.

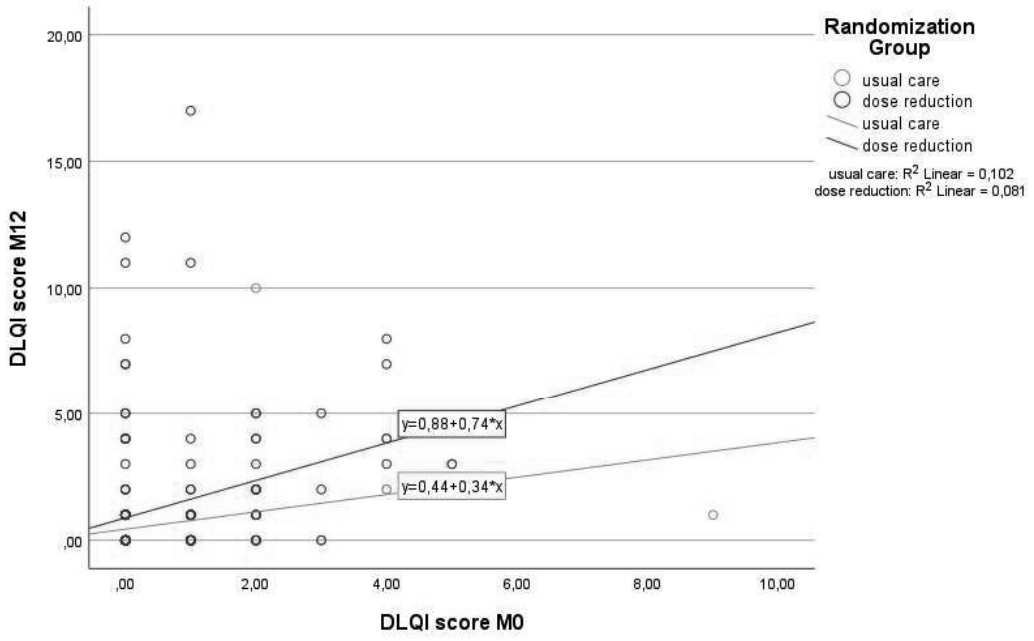


Figure 20: Regression slopes of DLQI at baseline and month 12 for both treatment groups in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M12 =post-test.

The main effects model showed no significant difference in DLQI score between DR and UC at month 12 (p=0.056). Table 20 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 20: for DR and UC the mean DLQI at baseline (M0) and the unadjusted and adjusted mean DLQI at month 12 in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M12: visit month 12, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (DLQI M0)			After treatment (DLQI M12) (unadjusted)		After treatment (DLQI M12) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	164	0.54	0.08	1.28	0.20	1.29	0.18
Usual care	80	0.78	0.16	0.70	0.17	0.69	0.25

Month 18 – DLQI score

PP1_LOCF

Figure 21 shows that the regression lines of DR and UC are close to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI scores between DR and UC at month 18.

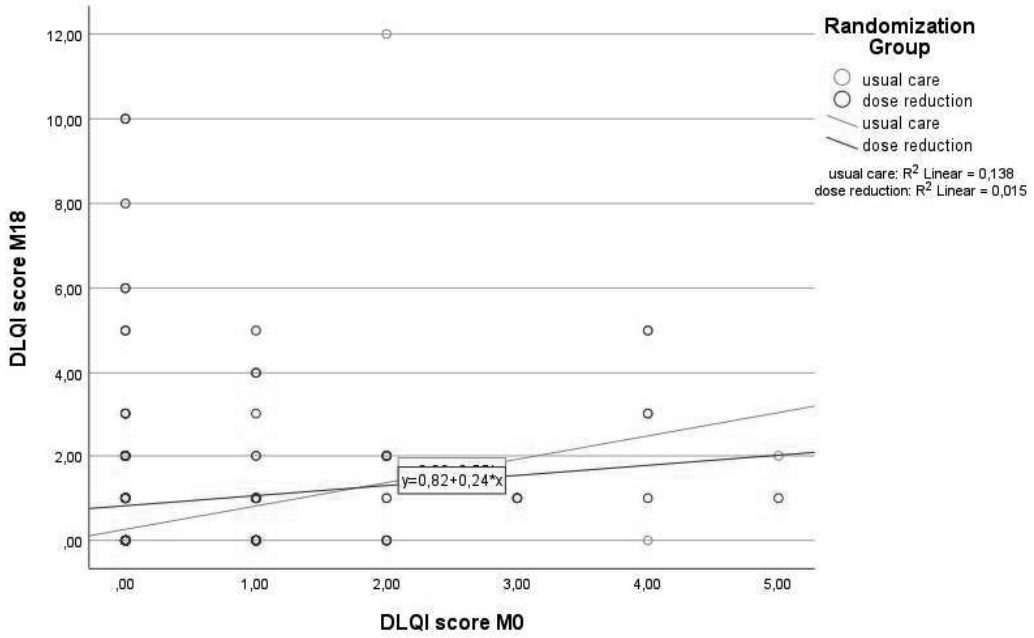


Figure 21: Regression slopes of DLQI score at baseline and month 18 for both treatment groups in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M18 =post-test.

The main effects model showed no significant difference in DLQI score between DR and UC at month 18 (p=0.234). Table 21 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 21: for DR and UC the mean DLQI scores at baseline (M0) and the unadjusted and adjusted mean DLQI scores at month 18 in the per protocol 1 analysis with last observation carried forward (PP1_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	**Before treatment (DLQI M0)**			**After treatment (DLQI M18) (unadjusted)**		**After treatment (DLQI M18) (adjusted)**	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	145	0.47	0.08	0.93	0.15	0.94	0.15
Usual care	69	0.68	0.14	0.64	0.20	0.63	0.21

PP2_LOCF

Figure 22 shows that the regression lines of DR and UC are close to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI scores between DR and UC at month 18.

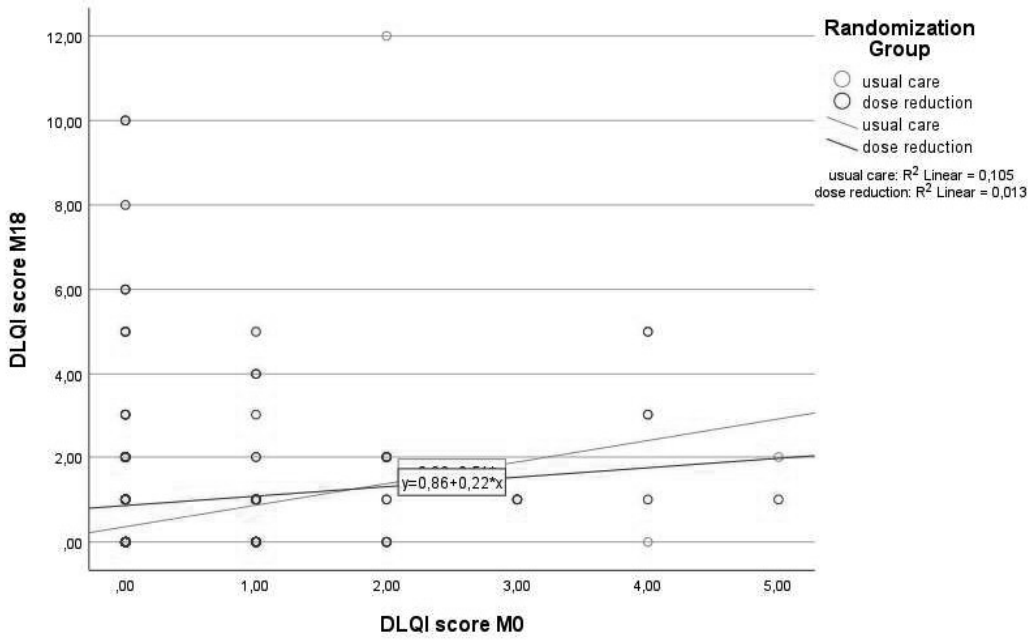


Figure 22: Regression slopes of DLQI score at baseline and month 18 for both treatment groups in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M18 =post-test.

The main effects model showed no significant difference in DLQI between DR and UC at month 18 (p=0.255). Table 22 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 22: for DR and UC the mean DLQI scores at baseline (M0) and the unadjusted and adjusted mean DLQI scores at month 18 in the per protocol 2 analysis with last observation carried forward (PP2_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (DLQI M0)			After treatment (DLQI M18) (unadjusted)		After treatment (DLQI M18) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	148	0.46	0.08	0.96	0.15	0.97	0.15
Usual care	73	0.67	0.13	0.70	0.21	0.68	0.21

ITT_LOCF

Figure 23 shows that the regression lines of DR and UC are close to each other, therefore the assumption of homogeneity of regression slopes is met. The interaction effects model also showed no significant interactions between DR/UC and the baseline covariates meaning that the covariates do not interact with the type of treatment and do not result in different DLQI between DR and UC at month 18.

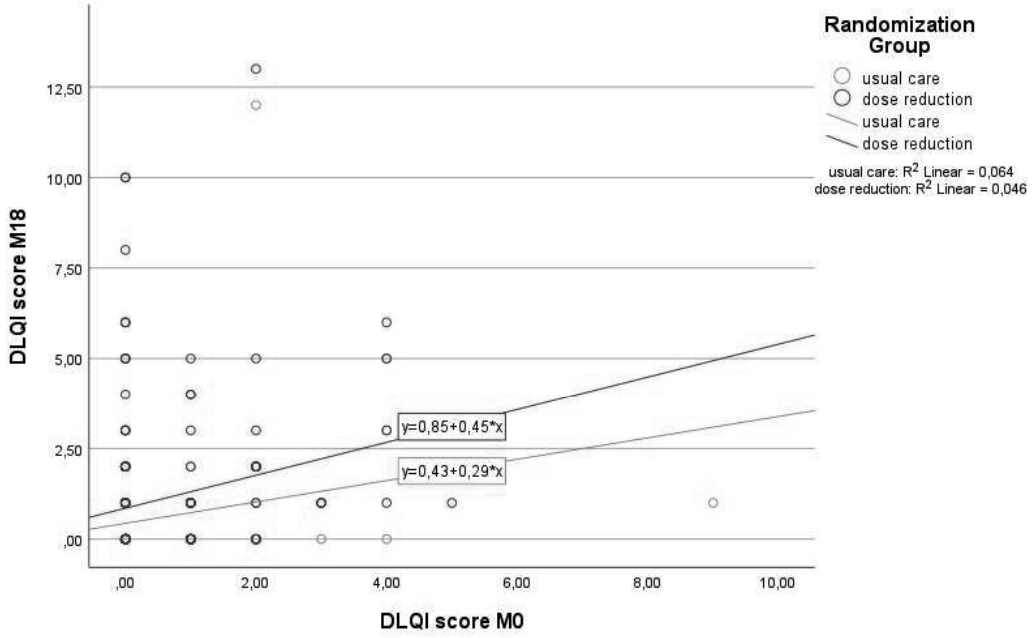


Figure 23: Regression slopes of DLQI score at baseline and month 18 for both treatment groups in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

DLQI: Dermatology Life Quality Index, DLQI score M0 =pre-test, DLQI score M18 =post-test.

The main effects model showed no significant difference in DLQI score between DR and UC at month 18 (p=0.070). Table 23 also shows a small difference between the unadjusted and adjusted means and standard error of the means, indicating a non-significant difference.

Table 23: for DR and UC the mean DLQI scores at baseline (M0) and the unadjusted and adjusted mean DLQI scores at month 18 in the intention-to-treat analysis with last observation carried forward (ITT_LOCF).

DLQI: Dermatology Life Quality Index, M0: visit month 0 (baseline), M18: visit month 18, N: number of patients, SEmean: standard error of mean.

Treatment	Before treatment (DLQI M0)			After treatment (DLQI M18) (unadjusted)		After treatment (DLQI M18) (adjusted)	
	N	Mean	SEmean	Mean	SEmean	Mean	SEmean
Dose reduction	164	0.54	0.08	1.10	0.16	1.12	0.15
Usual care	80	0.78	0.16	0.66	0.19	0.63	0.22

SECONDARY OBJECTIVE 6: Number of Serious Adverse Events (SAE) related to the intervention in patients with dose tapering.

The number of serious adverse events (SAE) was analyzed by descriptive statistics in the PP1_LOCF analysis (PP2_LOCF and ITT_LOCF will follow). In total, 15 SAE were reported in 13 patients. In the DR group, 11 SAE were reported in 9 patients. In the UC group, 4 SAE were reported in 3 patients. None of the 11 reported SAE in the DR group were related to DR (as for the SAE in the UC group).

The distribution of all SAE between the two randomization groups is acceptable considering the 2:1 randomization ratio. The rate ratio of the total number of SAE between DR and UC (RR 1,275 [0.406 - 4.006]) also shows that there was no statistically significant difference in the number of total SAE between DR and UC (Table 24).

SECONDARY OBJECTIVE 7: Number of Adverse Events of Special Interest (AEoSI) in patients with dose tapering vs. usual care.

The number of adverse events of special interest (AEoSI) was analyzed in the PP1_LOCF analysis (PP2_LOCF and ITT_LOCF will follow). In total, 259 AEoSI were reported, of which 167 were reported in the DR group and 92 in the UC group. The following adverse events were AEoSI: muscoluskeletal complaints (excl psoriatic arthritis (PsA) or trauma), worsening pre-existent PsA, PsA (new diagnosis), malignancy, infection, psychologic complaints, autoimmune disease (excl PsA), cerebrovascular event (CVA), myocardial infarction, pustular psoriasis. Additional categories of AEoSI were other, gynecological-urological, gastrointestinal (incl hepatologic), hypersensitivity reaction to biologic (incl injection site reaction), neurologic event (without musculoskeletal or CVA), unexpected reaction to vaccine. Table 24 shows that there was no statistically significant difference in number of AEoSI between DR and UC. However, it is remarkable that there were a few cases of new diagnosis of PsA in the DR group and none in the UC group. At the same time, there

were more cases of worsening of pre-existent PsA in the UC group compared to the DR group, but this difference was not statistically significant.

Table 24: number of serious adverse events (SAE), adverse events (AE) and adverse events of special interest (AEoSI) in the dose reduction (DR) and usual care (UC) group.
The difference between DR and UC was statistically tested on significancy by calculating the ate ratio (RR) with the 95% confidence interval (95% CI).

	DR			UC			Rate ratio		
	Event rate	95% BI		Event rate	95% BI		RR	95% BI	
Total SAE	4,805	[2,399 -	8,034]	3,768	[1,027 -	8,258]	1,275	[0,406 -	4,006]
SAE related to Dose Reduction (intervention)	0,000	[0,000 -	0,000]	NA	NA	NA	NA	NA	NA
Total AE	113,144	[99,783 -	127,332]	129,042	[108,339 -	151,528]	0,877	[0,713 -	1,079]
AEoSI	72,954	[62,308 -	84,426]	86,656	[69,857 -	105,238]	0,842	[0,653 -	1,086]
Muscoluskeletal complaints (excl PsA or trauma)	15,727	[11,015 -	21,264]	15,071	[8,614 -	23,303]	1,044	[0,579 -	1,880]
Worsening pre-existent PsA	1,311	[0,270 -	3,156]	3,768	[1,027 -	8,258]	0,348	[0,078 -	1,554]
PsA (new diagnosis)	1,747	[0,476 -	3,830]	NA	NA	NA	NA	NA	NA
Malignancy	1,747	[0,476 -	3,830]	NA	NA	NA	NA	NA	NA
Infection	48,053	[39,494 -	57,440]	63,108	[48,908 -	79,091]	0,761	[0,562 -	1,032]
Psychologic complaints	0,437	[0,011 -	1,611]	0,942	[0,024 -	3,475]	0,464	[0,029 -	7,415]
Autoimmune disease (excl PsA)	0,437	[0,011 -	1,611]	NA	NA	NA	NA	NA	NA
Cerebrovascular event	0,874	[0,106 -	2,434]	1,884	[0,228 -	5,248]	0,464	[0,065 -	3,293]
Myocardial infarction	0,874	[0,106 -	2,434]	0,942	[0,024 -	3,475]	0,928	[0,084 -	10,230]
Pustular psoriasis	0,437	[0,011 -	1,611]	NA	NA	NA	NA	NA	NA
Other	30,579	[23,838 -	38,147]	35,793	[25,329 -	48,037]	0,854	[0,576 -	1,268]
Gyn-urological	3,058	[1,229 -	5,705]		[-	]		[-	]
gastrointestinal incl hepatologic	3,495	[1,509 -	6,301]	4,710	[1,529 -	9,647]	0,742	[0,243 -	2,268]
Hypersensitivity reaction to biologic incl injection site reaction	1,311	[0,270 -	3,156]	0,942	[0,024 -	3,475]	1,391	[0,145 -	13,377]
Neurologic event without musculoskeletal or CVA	2,621	[0,962 -	5,097]	1,884	[0,228 -	5,248]	1,391	[0,281 -	6,894]
Unexpected reaction to vaccine	0,437	[0,011 -	1,611]		[-	]		[-	]

SAE=Serious Adverse Event, AE=Adverse Event, AEoSI=Adverse event of special interest. Event rate=events per 100 observation years, NA=not applicable. PsA=psoriatic artritis.

SECONDARY OBJECTIVE 8: Cost-effectiveness of dose reduction vs. usual care

A cost-utility analysis (CUA) was performed to analyze the cost-effectiveness of dose reduction *vs* usual care. This first (preliminary) CUA involved Quality Adjusted Life Years (QALYs) based on utility scores from the EuroQol-5 Dimensions – 5 Levels questionnaire (EQ-5D) calculated with the Dutch tariffs, and total costs (based on total biologic drug costs from the Dutch website 'medicijnkosten.nl', and total costs of outpatient visits and telephone consultations based on reference cost prices from the Dutch Manual for Economic Health Evaluations (2024)) per patient over a period of 18 months. To show cost-effectiveness, a cost-utility plane was conducted and a decremental cost-effectiveness ratio (DCER) was calculated by dividing the difference in mean costs between DR and UC by the difference in mean QALYs between DR and UC. The following results are preliminary with missing data being linearly interpolated. In the final analysis, missing data will be imputed. The final analysis will follow.

The cost-utility plane is the result of bootstrapping the data (QALYs and total costs on individual patient level) with 1,000 replications (Figure 24). All datapoints of the replications

are within the lower quadrants showing that DR results in cost savings of approximately €8,000 euros compared to UC. Also, most of the datapoints are within the southwest quadrant showing that in most cases DR results in a minimal decrease of –0.02 QALY. These results are also shown in table 25.

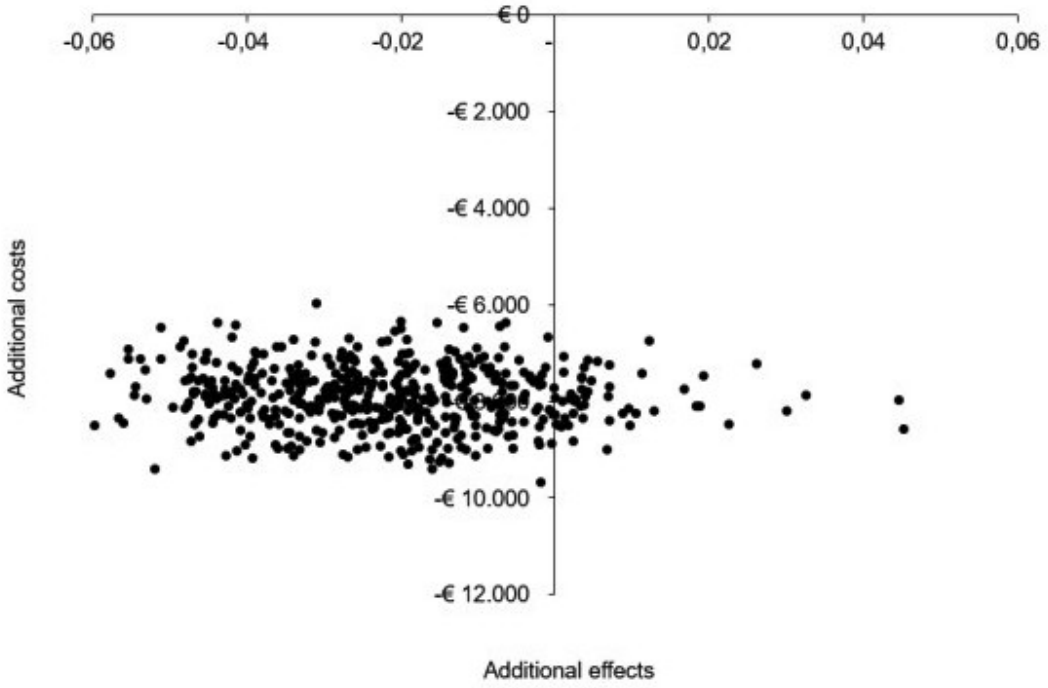


Figure 24: Cost-utility plane after bootstrapping with 1,000 replications.
X-axis represents the QALYs. The west quadrant represents loss of QALY and the east quadrant represents gain of QALY. Y-axis represents the total costs with the southern quadrants representing cost savings.

Table 25: Mean QALY and costs with 95% confidence interval for usual care and dose reduction, and the difference between the two randomization groups, after bootstrapping with 1,000 replications.
QALY: Quality Adjusted Life Years; CI: confidence interval.

	QALY (mean [95% CI])	**Difference in QALY (mean [95% CI])**	**Costs (mean [95% CI])**	**Difference in costs (mean [95% CI])**
Usual care (N=77)	0.89 [0.87;0.92]		€22,250 [21,199; 23,292]	
Dose reduction (N=160)	0.87 [0.85;0.89]	-0.02 [-0.05;0.01]	€14,331 [13,701; 15,048]	-€7,919 [-9,123; -6,547]

Calculating the DCER based on the results in table 25, results in:

DCER = (€14,331 -€22,250)/ (0.87 -0.89) = (-7,919)/ (-0.02) = €395,950 / QALY

The DCER is high at €395,950/QALY, indicating that dose reduction could result in significant cost savings while having a relatively modest impact on quality of life with a loss of –0.02 QALY, as was also shown in figure 22.

SECONDARY OBJECTIVE 9: The pharmacokinetic and pharmacodynamic profile of DR vs. UC

At each 3-monthly study visit, blood was taken from the participants, resulting in a maximum of 7 blood samples per individual patient. At 18 visits, no blood was drawn resulting in availability of 1.568 serum samples for analysis.

Table 26 gives an overview of the number of samples available at each timepoint. All samples, with the exception of the risankizumab samples, were analyzed by the Laboratory of Therapeutic and Diagnostics Antibodies of KU Leuven within a service level agreement.

	M0	M3	M6	M9	M12	M15	M18	Total
IL-17 inhibitors								
Secukinumab	35	33	33	33	32	34	33	**233**
Ixekizumab	62	60	57	58	54	54	49	**394**
Brodalumab	15	15	15	15	14	13	11	**98**
Bimekizumab*	3	3	3	3	3	3	3	**21**
IL-23 inhibitors								
Guselkumab	72	67	64	61	61	62	60	**447**
Risankizumab	51	48	45	47	48	48	47	**334**
Tildrakizumab	6	6	6	5	6	6	6	**41**
Total	**244**	**232**	**223**	**222**	**218**	**220**	**209**	**1.568**

Table 26 Number of blood samples collected in the BeNeBio per timepoint
IL: interleukine; M : month

Secukinumab concentrations were determined in **233** serum samples of **35** patients by using an in-house secukinumab immunoassay consisting of a combination of MA-SEC66A2 as capture antibody and MA-SEC67A9, conjugated to horseradish peroxidase, as detecting antibody.

Ixekizumab concentrations were determined in **394** serum samples of **62** patients by using an in-house ixekizumab immunoassay consisting of a combination of MA-IXE117E12 as capture antibody and MA-IXE100F5-biotin, as detecting antibody.

Guselkumab concentrations were determined in **447** serum samples of **72** patients by using an in-house guselkumab immunoassay consisting of a combination of MA-GUS9F6 as capture antibody and MA-GUS12G12, as detecting antibody.

Risankizumab concentrations were determined in **334**serum samples from **51** patients by using the commercial available kit of ApDia.

Brodalumab, tildrakizumab and bimekizumab concentrations are not (yet) measured due to the unavailability of validated assays. These samples will be stored at -80°C in the BIODIP biobank of the University Hospital Gent until analysis is possible.

Fifty of the measured drug concentration fell below the limit of quantification of the assay, meaning that these concentration of the measured biologic is too low to be reliably quantified by the ELISA used.

Next, to analyze the pharmacokinetics (PK) and pharmacodynamics (PD) of each biologic, Bayesian PK-PD models are being developed. The first Bayesian model for secukinumab has nearly been finalised. Comparable models for guselkumab, ixekizumab and risankizumab will follow. For the other included biologics no adequately validated drug level assays have been found to be available to determine the serum drug levels. Once these become available, serum levels will be determined and if there are sufficient samples, a similar Bayesian model can be developed. Serum secukinumab concentrations were measured every three months at random time points within the injection interval over an 18-month follow-up period. Population PK modelling was performed using non-linear mixed-effects modelling with the nlmixr2 package (v3.0.2) in R. Several structural models, statistical models, and covariate relationships were explored. Of the 35 patients initially enrolled on secukinumab, 5 were excluded due to missing or implausible data. The final PK dataset consisted of 180 serum drug concentration measurements from 30 patients (median weight: 81 kg; median age: 59.5 years; 53% female). A one-compartment model with first-order absorption and elimination processes provided the best fit. Interindividual variability was estimated for clearance, volume of distribution, and absorption rate constant, with body weight included as an allometric covariate on clearance and volume. A PD turnover model is currently under development to link the PK model to 199 PASI (Psoriasis Area and Severity Index) observations from the same cohort.

The developed PK model produced parameter estimates consistent with those reported in the literature. Once the PK-PD model is finalised, it will be externally validated on the BIOLOPTIM dataset. It can then be used to accurately predict the serum trough levels of the BeNeBio patients at baseline, we will then analyse if there is a correlation between low or high serum trough levels at baseline and successful dose reduction.

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13. DISCUSSION AND OVERALL CONCLUSIONS

This pragmatic, multicenter, randomized controlled trial showed that **DR of IL-17 and IL-23 inhibitors by a two-step DR strategy of first 67% and second 50% of the standard dose, is non-inferior to UC.** The difference in proportion of persistent flares between DR and UC did not exceed the non-inferiority margin of 15%. In addition, mean PASI and DLQI remained stable low in both DR and UC group over the period of 18 months and showed no statistically significant differences at 12 and 18 months. Finally, DR results in significant cost savings with a marginal decrease in QALY compared to UC indicating that DR of IL-17 and IL-23 inhibitors is also cost-effective.

Efficacy Results:

PRIMARY OUTCOME:
Non-inferiority of DR was shown in all the analyses (PP1 LOCF, PP2 LOCF, ITT LOCF and ITT MI), thereby the primary outcome is reached.

SECONDARY OBJECTIVE 1: Successful dose reduction
After 12 months, 77% of patients had a successful DR in the PP1- and PP2_LOCF analysis, and 76% in the ITT_LOCF analysis. After 18 months, 75% of patients had a successful DR in the PP1_LOCF analysis, and 73% in the PP2- and ITT_LOCF analysis.

SECONDARY OBJECTIVE 2: Course of mean PASI and DLQI
All analyses showed low mean PASI and DLQI scores for both groups, ranging from 0 to a maximum of 1.3 over the course of 18 months.

SECONDARY OBJECTIVE 3: Incidence of short disease flares after 18 months
In the PP1_LOCF analysis, in the DR group, a total of 20 short disease flares occurred among 145 patients (14%) after 18 months. The incidence in the DR group of the PP1_LOCF analysis is comparable to the PP2_LOCF analysis (14%) and the ITT_LOCF analysis (16%). In the UC group, the incidence was 6%, 7%, and 6% for respectively the PP1-, PP2- and ITT_LOCF analysis.

SECONDARY OBJECTIVE 4: Difference in PASI score between DR and UC (every 3 months)
In PP1- and PP2_LOCF, at none of the time points there was a statistically significant difference in PASI score between DR and UC. In ITT_LOCF, there was only at month 9 a statistically significant difference in PASI score between DR and UC with a difference in mean PASI score of 0.38 (p=0.028).

SECONDARY OBJECTIVE 5: ANCOVA PASI and DLQI at 12 and 18 months
Both at 12 and 18 months, for both PASI and DLQI, there was no significant difference between DR and UC.

	DR mean (SEmean)	**UC mean (SEmean)**	**p-value**
PASI at month 12			
PP1_LOCF	0.98 (0.11)	0.77 (0.17)	0.300

PP2_LOCF	0.99 (0.11)	0.73 (0.16)	0.196
ITT_LOCF	1.11 (0.12)	0.71 (0.17)	0.051
PASI at month 18			
PP1_LOCF	0.85 (0.11)	0.71 (0.16)	0.460
PP2_LOCF	0.86 (0.11)	0.78 (0.16)	0.615
ITT_LOCF	0.97 (0.11)	0.74 (0.16)	0.189
DLQI at month 12			
PP1_LOCF	1.17 (0.19)	0.72 (0.27)	0.168
PP2_LOCF	1.20 (0.18)	0.72 (0.27)	0.143
ITT_LOCF	1.29 (0.18)	0.69 (0.25)	0.056
DLQI at month 18			
PP1_LOCF	0.94 (0.15)	0.63 (0.21)	0.234
PP2_LOCF	0.97 (0.15)	0.68 (0.21)	0.255
ITT_LOCF	1.12 (0.15)	0.63 (0.22)	0.070

SECONDARY OBJECTIVE 6: Number of Serious Adverse Events (SAE) related to the intervention in patients with dose tapering.

In total, 15 SAE were reported in 13 patients. In the DR group, 11 SAE were reported in 9 patients. In the UC group, 4 SAE were reported in 3 patients. None of the 11 reported SAE in the DR group were related to DR (as for the SAE in the UC group). The rate ratio of the total number of SAE between DR and UC (RR 1,275 [0.406 - 4.006]) also shows that there was no statistically significant difference in the number of total SAE between DR and UC.

SECONDARY OBJECTIVE 7: Number of Adverse Events of Special Interest (AEoSI) in patients with dose tapering vs. usual care.

In total, 259 AEoSI were reported, of which 167 were reported in the DR group and 92 in the UC group. There was no statistically significant difference in number of AEoSI between DR and UC.

SECONDARY OBJECTIVE 8: Cost-effectiveness of dose reduction vs. usual care

The cost-utility analysis showed that DR resulted in cost savings of approximately €8,000 euros compared to UC with a minimal decrease of –0.02 QALY. The DCER is high at €395,950/QALY, indicating that DR could result in significant cost savings while having a relatively modest impact on quality of life with a loss of –0.02 QALY.

SECONDARY OBJECTIVE 9: The pharmacokinetic and pharmacodynamic profile of DR vs. UC

In total, 1.568 blood samples were collected and drug concentration for secukinumab, ixekizumab, guselkumab and risankizumab were measured with an in-house ELISA. The samples of patients treated with brodalumab, tildrakizumab and bimekizumab are awaiting analysis as there is currently no clinically validated ELISA available. Meanwhile, these samples will remain stored at -80°C in the BIODIP biobank of Ghent University Hospital.

The PK-PD models which will allow further analysis of the relationship between drug exposure, response and dose reduction are currently under development with secukinumab as the first example.

Conclusion
In conclusion, DR of IL-17 and IL-23 inhibitors by a two-step DR strategy of first 67% and second 50% of the standard dose, is non-inferior to UC. In addition, DR showed to be cost-effective compared to UC.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Not applicable.

15. REFERENCE LIST

A list of articles from the literature pertinent to the evaluation of the study should be provided. Copies of important publications should be attached in an appendix (16.1.11 and 16.1.12). References should be given in accordance with the internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".

16. APPENDICES

16.1 Study Information

16.1.1 **Protocol and protocol amendments**

16.1.2 **Sample case report form (unique pages only)**

16.1.3 **List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms**

16.1.4 **List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study**

16.1.5 **Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.**

16.1.6 **Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used**

Not applicable.

16.1.7 **Randomisation scheme and codes (patient identification and treatment assigned)**

16.1.8 **Audit certificates (if available)**

Not applicable.

16.1.9 **Documentation of statistical methods**

16.1.10 **Documentation of inter-laboratory standardisation methods and quality assurance procedures if used**

Assay validation Guselkumab

Assay validation Ixekizumab

Assay validation Secukinumab

16.1.11 Publications based on the study

Van der Schoot LS, van den Reek JMPA, Grine L, Schots L, Kievit W, Lambert JLW, de Jong EMGJ. Dose reduction of the new generation biologics (IL-17 and IL-23 inhibitors) in psoriasis: study protocol for an international, pragmatic, multicenter, randomized, controlled, non-inferiority study-the BeNeBio study. Trials. 2021 Oct 16;22(1):707. doi: 10.1186/s13063-021-05681-z. PMID: 34656148; PMCID: PMC8520290.

16.1.12 Important publications referenced in the report

1. Soenen R, Wang Z, Grine L, Dreesen E, Schots L, Brouwers E, et al. Therapeutic drug monitoring in dermatology: the way towards dose optimization of secukinumab in chronic plaque psoriasis. Clin Exp Dermatol [Internet]. 2022 Jul 25;47(7):1324–36. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ced.15157
2. Van den Berghe N, Truffot A, Peeters M, Compernolle G, Brouwers E, Soenen R, et al. Development and validation of immunoassays for monitoring of guselkumab and anti-guselkumab antibodies in patients with moderate-to-severe psoriasis. J Pharm Biomed Anal. 2020;189:1–9.
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4. Atalay S, Van Den Reek JMPA, Otero ME, Njoo MD, Mommers JM, Ossenkoppele PM, et al. Health economic consequences of a tightly controlled dose reduction strategy for adalimumab, etanercept and ustekinumab compared with standard psoriasis care: A cost-utility analysis of the condor study. Acta Derm Venereol

[Internet]. 2020 [cited 2021 Jun 21];100(19):1–7. Available from: https://pubmed.ncbi.nlm.nih.gov/33196101/
5. Atalay S, Berends SE, Groenewoud HMM, Mathot RAA, Njoo DM, Mommers JM, et al. Serum drug levels and anti-drug antibodies in the context of dose tapering by interval prolongation of adalimumab, etanercept and ustekinumab in psoriasis patients: results of the CONDOR trial. Journal of Dermatological Treatment [Internet]. 2022 [cited 2022 Aug 4];33(5):2680–4. Available from: https://www.tandfonline.com/doi/abs/10.1080/09546634.2022.2043546
6. Van Herwaarden N, Van Maas A Der, Minten MJM, Van Den Hoogen FHJ, Kievit W, Van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis:Open label, randomised controlled, non-inferiority trial. BMJ (Online). 2015 Apr 9;350.
7. van der Schoot LS, van den Reek JMPA, Grine L, Schots L, Kievit W, Lambert JLW, et al. Dose reduction of the new generation biologics (IL-17 and IL-23 inhibitors) in psoriasis: study protocol for an international, pragmatic, multicenter, randomized, controlled, non-inferiority study—the BeNeBio study. Trials. 2021;22(1):1–12.
8. Atalay S, Berends SE, Groenewoud HMM, Mathot RAA, Njoo DM, Mommers JM, et al. Serum drug levels and anti-drug antibodies in the context of dose tapering by interval prolongation of adalimumab, etanercept and ustekinumab in psoriasis patients: results of the CONDOR trial. Journal of Dermatological Treatment. 2022;33(5):2680–4.
9. Atalay S, van den Reek JMPA, Groenewoud JMM, van de Kerkhof PCM, Kievit W, de Jong EMGJ. Two-year follow-up of a dose reduction strategy trial of biologics adalimumab, etanercept, and ustekinumab in psoriasis patients in daily practice. J Dermatolog Treat [Internet]. 2022 [cited 2024 Jun 11];33(3):1591–7. Available from: https://pubmed.ncbi.nlm.nih.gov/33356686/
10. Atalay S, VAN DER SCHOOT LS, Vandermaesen L, VAN VUGT LJ, Eilander M, VAN DEN REEK JMPA, et al. Evaluation of a one-step dose reduction strategy of adalimumab, etanercept and ustekinumab in patients with psoriasis in daily practice. Acta Derm Venereol. 2021;101(5).
11. Atalay S, van den Reek JMPA, van Vugt LJ, Otero ME, van de Kerkhof PCM, den Broeder AA, et al. Tight controlled dose reduction of biologics in psoriasis patients with low disease activity: A randomized pragmatic non-inferiority trial. BMC Dermatol. 2017 May 8;17(1).
12. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998 Apr 30;17(8):873–90.

16.2. Patient Data Listings

16.2.1 Discontinued patients

16.2.2 Protocol deviations

16.2.3 Patients excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or Drug Concentration Data (if available)

16.2.6 Individual Efficacy Response data

16.2.7 Adverse event listings (each patient)

16.2.8. Listing of individual laboratory measurements by patient, when required by regulatory authorities

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ANNEX

I SYNOPSIS

Name of Sponsor/Company: Radboudumc	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use only)*
Name of Finished Product: NA	Page:	
Name of Active Ingredient: NA		

Title of Study:

Dose reduction of the new generation biologics (IL17 and IL23 inhibitors) in psoriasis: A pragmatic, multicentre, randomized, controlled, non-inferiority study - *BeNeBio study*

Investigators:

Coordinating investigator: Dr. J.M.P.A. van den Reek, MD (BeNeFIT role: projectleider/penvoerder, Center: Sponsor)

Principal investigators:

Prof. E.M.G.J. de Jong, dermatologist, head of department (BeNeFIT role: Hoofdaanvrager, Center: Sponsor)
Prof. J. Lambert (BeNeFIT role: co-projectleader (national coordinating center)

Study centre(s):

The Netherlands:
Radboudumc, Nijmegen
ErasmusMC Rotterdam
Catharina hospital, Eindhoven
Bravis Hospital, Bergen op Zoom
ZGT Almelo, Almelo
University medical center Utrecht
UMC Groningen
Maastricht UMC
Slingeland Ziekenhuis, Doetinchem
Amphia Ziekenhuis, Breda
Máxima Medisch Centrum, Veldhoven

Belgium:
UZGent, Ghent
UCL Saint Luc, Sint-Lambrechts-Woluwe
CHU Liège, Luik
AZ Maria Middelares, Ghent
Dermatologie Maldegem
ULB Erasme, Brussels
UZ Leuven, Leuven
AZ St Lucas, Ghent

Publication (reference)

Van der Schoot LS, van den Reek JMPA, Grine L, Schots L, Kievit W, Lambert JLW, de Jong EMGJ. Dose reduction of the new generation biologics (IL-17 and IL-23 inhibitors) in psoriasis: study protocol for an

international, pragmatic, multicenter, randomized, controlled, non-inferiority study-the BeNeBio study. Trials. 2021 Oct 16;22(1):707. doi: 10.1186/s13063-021-05681-z. PMID: 34656148; PMCID: PMC8520290.

Studied period (years): 2020-2025 (date of first enrolment): 20-08-2020 (date of last completed): 30-01-2025	**Phase of development:** Phase IV (post-marketing)

Objectives:

Primary Objective:

- To assess if tightly controlled dose tapering is non-inferior to usual care with regards to the cumulative incidence of persistent disease flares (PASI> 5 for ≥ 3 months) after 18 months.

Secondary Objective(s):

- To assess the proportion of patients with successful dose tapering after 12 and 18 months (successful dose tapering is defined as lower dose than the normal dose and PASI≤ 5).
- To assess difference in PASI and DLQI course in patients with dose tapering vs. usual care.
- To assess and compare PASI and DLQI at month 12 in patients with dose tapering vs. usual care.
- To assess and compare PASI and DLQI at month 18 in patients with dose tapering vs. usual care.
- To assess incidence of short disease flares (PASI> 5 at 1 time point) after 18 months in patients with dose tapering vs. usual care.
- To identify predictors (clinical characteristics and biomarkers) for successful dose decrease
- To count the number of Serious Adverse Events (SAE) *related to the intervention* in patients with dose tapering.
- To count and compare the number of (all) Serious Adverse Events (SAE) and Adverse Events of Special Interest (AEoSI) in patients with dose tapering vs. usual care.
- To assess the pharmacokinetic (PK) profile of tapered biologics vs. normal dose.
- To assess if tightly controlled dose tapering is cost-effective compared with usual care.
- To assess the proportion of patients with initiation of other anti-psoriatic medication during the study (intensive topical therapies, methotrexate, acitretin) in patients with dose tapering vs. usual care.
- A sub-analysis will be done for all outcomes above separately for IL23, IL17a inhibitors and IL17a receptor antagonist, and on drug level (if appropriate).

Methodology:

Main study parameter/endpoint

- The primary outcome is non-inferiority of (cumulative incidence of) persistent flares (PASI> 5 for ≥ 3 months).

Secondary study parameters/endpoints (if applicable)

- Numbers and proportions patients with a successful* dose decrease after 12 and after 18 months *(*Definition of successful dose tapering: lower dose than the normal dose and PASI≤ 5).*
- Correlation with time and PASI (disease severity) in both groups in patients with dose tapering vs. usual care.
- Correlation with time and DLQI (quality of life) in both groups in patients with dose tapering vs. usual care.
- Absolute PASI and DLQI at month 12 in patients with dose tapering vs. usual care.
- Absolute PASI and DLQI at month 18 in patients with dose tapering vs. usual care.

- Incidence of short disease flares** after 18 months in patients with dose tapering vs. usual care. *(**Definition of short flare: PASI>5 at 1 time point)*
- Proportion of patients with initiation of other antipsoriatic medication during the study (e.g. intensive topical therapies, methotrexate, acitretin) in patients with dose tapering vs. usual care.
- Predictors for successful* dose decrease. Candidate predictors include general patient and treatment characteristics.
  *(*Definition of successful dose tapering: lower dose than the normal dose and PASI≤ 5).*
- Absolute numbers and proportions of serious adverse events (SAE) and adverse events of interest (AEoSI) in patients with dose tapering vs. usual care. (AEoSI include, but are not limited to, infections, malignancies and joint complaints/new-onset psoriatic arthritis).
- Pharmacokinetics (PK) of each included drug in function of dose and anti-drug antibody formation per biologic
- (Changes in) health-status (SF-36), quality-adjusted life-years (EQ-5D-5L), volumes of care (iMTA Medical Consumption Questionnaire), loss of productivity and presenteeism (Productivity Cost Questionnaire) after 18 months in patients with dose tapering vs. usual care.[11-13]

Number of patients (planned and analysed): 244

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

- Plaque psoriasis (primarily)
- Treatment for 6 months at least with IL23 or IL17 inhibitor in a normal dose (dose advised by the label)
- PASI≤ 5 at inclusion and in previous 6 months (in previous 6 months, it should be clear from the patient record that psoriasis was clear/almost clear if no PASI scores are available).
- DLQI ≤ at inclusion

Test product product, dose and mode of administration, batch number:
Stepwise (67% and 50% or standard dose) dose reduction of the newer biologics, approved and reimbursed for the indication of moderate-to-severe psoriasis:

Biologic	Normal dose	First step DR	Second step DR
Secukinumab	300 mg/4 weeks	300 mg/6 weeks	300 mg/8 weeks
Ixekizumab	80 mg/4 weeks	80 mg/6 weeks	80 mg/8 weeks
Brodalumab	210 mg/2 weeks	210 mg/3 weeks	210 mg/4 weeks
Guselkumab	100 mg/8 weeks	100 mg/12 weeks	100 mg/16 weeks
Risankizumab	150 mg/12 weeks	150 mg/18 weeks	150 mg/24 weeks
Tildrakizumab	100 or 200 mg/12 weeks	100 or 200 mg/18 weeks	100 or 200 mg/24 weeks
Bimekizumab	320 mg/8 weeks	320 mg/12 weeks	320 mg/16 weeks

Abbreviations: DR dose reduction, mg milligram

Duration of treatment:
Treatment with IL23 or IL17 inhibitor started at least 6 months before inclusion.
During the study, daily practice was monitored in the group receiving the normal dose and the group randomized to the dose reduction group. This means that patients could also stop treatment with IL 23 or IL 17 inhibitors during the study

Reference therapy, dose and mode of administration, batch number
Standard-of care.

Name of Sponsor/Company: Radboudumc	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: NA	Volume:	
Name of Active Ingredient: NA	Page:	

Criteria for evaluation:

Efficacy NA

Safety NA

Statistical methods:
Data of the two per protocol analysis with last observation carried forward (PP1_LOCF and PP2_LOCF) and the intention-to-treat analysis with last observation carried forward (ITT_LOCF) was analyzed with IBM SPSS Statistics version 29. The analysis of the primary outcome in the intention-to-treat with multiple imputation (ITT_MI) was performed with R version 4.3.3.
Baseline characteristics, part of the primary outcome and most of the secondary outcomes were analyzed by descriptives. The confidence interval of the difference in proportion of persistent flares between DR and UC was calculated by a calculator based on the methods described by Newcombe.(12) Additional statistics used to analyze secondary outcomes were an unpaired t-test, analysis of covariance (ANCOVA) with baseline variables as covariates, and calculating a rate ratio (RR). Finally, for the cost-utility analysis, QALYs and total costs over a period of 18 months were analyzed on individual patient level and the data was bootstrapped with 1,000 replications resulting in a cost-utility plane and DCER.

Summary - Conclusions
This pragmatic, multicenter, randomized controlled trial showed that DR of IL-17 and IL-23 inhibitors by a two-step DR strategy of first 67% and second 50% of the standard dose, is non-inferior to UC. The difference in proportion of persistent flares between DR and UC did not exceed the non-inferiority margin of 15%. In addition, mean PASI and DLQI remained stable low in both DR and UC group over the period of 18 months and showed no statistically significant differences at 12 and 18 months. Finally, DR results in significant cost savings with a marginal decrease in QALY compared to UC indicating that DR of IL-17 and IL-23 inhibitors is also cost-effective.

Efficacy Results:

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PRIMARY OUTCOME:
Non-inferiority of DR was shown in all the analyses (PP1 LOCF, PP2 LOCF, ITT LOCF and ITT MI), thereby the primary outcome is reached.

SECONDARY OBJECTIVE 1: Successful dose reduction
After 12 months, 77% of patients had a successful DR in the PP1- and PP2_LOCF analysis, and 76% in the ITT_LOCF analysis. After 18 months, 75% of patients had a successful DR in the PP1_LOCF analysis, and 73% in the PP2- and ITT_LOCF analysis.

SECONDARY OBJECTIVE 2: Course of mean PASI and DLQI
All analyses showed low mean PASI and DLQI scores for both groups, ranging from 0 to a maximum of 1.3 over the course of 18 months.

SECONDARY OBJECTIVE 3: Incidence of short disease flares after 18 months
In the PP1_LOCF analysis, in the DR group, a total of 20 short disease flares occurred among 145 patients (14%) after 18 months. The incidence in the DR group of the PP1_LOCF analysis is comparable to the PP2_LOCF analysis (14%) and the ITT_LOCF analysis (16%). In the UC group, the incidence was 6%, 7%, and 6% for respectively the PP1-, PP2- and ITT_LOCF analysis.

SECONDARY OBJECTIVE 4: Difference in PASI score between DR and UC (every 3 months)
In PP1- and PP2_LOCF, at none of the time points there was a statistically significant difference in PASI score between DR and UC. In ITT_LOCF, there was only at month 9 a statistically significant difference in PASI score between DR and UC with a difference in mean PASI score of 0.38 (p=0.028).

SECONDARY OBJECTIVE 5: ANCOVA PASI and DLQI at 12 and 18 months
Both at 12 and 18 months, for both PASI and DLQI, there was no significant difference between DR and UC.

	DR mean (SEmean)	UC mean (SEmean)	p-value
PASI at month 12			
PP1_LOCF	0.98 (0.11)	0.77 (0.17)	0.300
PP2_LOCF	0.99 (0.11)	0.73 (0.16)	0.196
ITT_LOCF	1.11 (0.12)	0.71 (0.17)	0.051
PASI at month 18			
PP1_LOCF	0.85 (0.11)	0.71 (0.16)	0.460
PP2_LOCF	0.86 (0.11)	0.78 (0.16)	0.615
ITT_LOCF	0.97 (0.11)	0.74 (0.16)	0.189
DLQI at month 12			
PP1_LOCF	1.17 (0.19)	0.72 (0.27)	0.168
PP2_LOCF	1.20 (0.18)	0.72 (0.27)	0.143
ITT_LOCF	1.29 (0.18)	0.69 (0.25)	0.056
DLQI at month 18			
PP1_LOCF	0.94 (0.15)	0.63 (0.21)	0.234
PP2_LOCF	0.97 (0.15)	0.68 (0.21)	0.255
ITT_LOCF	1.12 (0.15)	0.63 (0.22)	0.070

SECONDARY OBJECTIVE 8: Cost-effectiveness of dose reduction vs. usual care
The cost-utility analysis showed that DR resulted in cost savings of approximately €8,000 euros compared to UC with a minimal decrease of –0.02 QALY. The DCER is high at €395,950/QALY, indicating that DR could result in significant cost savings while having a relatively modest impact on quality of life with a loss of –0.02 QALY.