CCDS	company core data sheet
CMO	contract manufacturing organisation
CONSORT	Consolidated Standards of Reporting Trials
CPM	clinical project manager
CRA	clinical research associate
CRO	contract research organisation
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
eC-SSRS	electronic self-rated version, Columbia-Suicide Severity Rating Scale
EDC	electronic data capture
ePRO	electronic patient reported outcome
FAS	full analysis set
FSFV	first subject first visit
GCP	good clinical practice
GPV	global pharmacovigilance
HIV	human immunodeficiency virus
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICI	international coordinating investigator
IEC	independent ethics committee
IL-17(RA)	interleukin 17 (receptor A)
IMP	investigational medicinal product
IWRS	interactive web response system

5 Schedule of procedures

Panel 2 Schedule of trial procedures

	Screening	**Treatment phase**												**Follow-up**
Visit	V1	V2[1)] Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 End of treatment	Unscheduled visit[2)] or early termination visit[3)]	V13[4)]
Visit Week/Day	Up to 28 days prior to V2	0/0	1/7	2/14	3/21	4/28	6/42	8/56	12/84	16/112	20/140	24/168		26/182 or 32/224[4)]
Visit window (days)[5)]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3
Trial population and eligibility (Sections 11.2.3 and 11.3)														
Informed consent[6]	x													
Eligibillity criteria	x	x[7]												
Medical history, incl. concurrent illness	x													
Previous anti-psoreatic theraphy	x													
Concomitant medication/procedures	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	x
Other investigator assessments only at screeing/baseline (Section 11.2)														
Demographics	x													
Height	x													
Investigational medicinal product and randomisation (Section 10)														
Randomisation		x												
IWRS	x	x						x	x	x	x		(x)	
Handing out IMP:														
Brodalumab		x						x	x	x	x		(x)	
Fumaric acid esters		x						x	x		x		(x)	
Treatment instruction	x[8]	x[9]	x[9]											
Drug accountability/ Treatment compliance			x	x	x	x	x	x	x	x	x	x	(x)*	
Blinded assessments of efficacy Section 11.4.1)														
PASI	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	
sPGA		x	x	x	x	x	x	x	x	x	x	x	(x)*	
BSA involvement	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	
NAPSI		x							x			x	(x)*	

	Screening	**Treatment phase**												**Follow-up**
Visit	V1	V2[1)] Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 End of treatment	Unscheduled visit[2)] or early termination visit[3)]	V13[4)]
Visit Week/Day	Up to 28 days prior to V2	0/0	1/7	2/14	3/21	4/28	6/42	8/56	12/84	16/112	20/140	24/168		26/182 or 32/224[4)]
Visit window (days)[5)]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3
e-PROs at clinic (Section 11.4.2):[10]														
DLQI	x	x				x			x	x	x	x	(x)*	
eC-SSRS	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	
PHQ-8	x	x		x		x	x	x	x	x	x	x	(x)*	
e-PRO at home (Section 11.4.2.4):														
PSI (24h recall)		Daily at home during entire treatment phase using a ePRO device												
Vital signs (Section 11.5.1):														
Blood pressure		x	x	x	x	x	x	x	x	x	x	x	(x)*	x
Heart rate		x	x	x	x	x	x	x	x	x	x	x	(x)*	x
Respiration rate		x							x			x	(x)*	
Temperature		x							x			x	(x)*	
Blood/urine sampling (Section 11.6.1):														
Serum pregnancy test[11]	x												(x)	
QuantiFERON-TB Gold	x												(x)	
Biochemistry[12]	x	x				x		x	x	x	x	x	(x)*	
Haematology[13]	x	x				x		x	x	x	x	x	(x)*	
Urine analysis[14]	x	x				x		x	x	x	x	x	(x)*	
Adverse events,physical examination and weight (Sections 12, 11.5.2, and 11.5.3):														
Adverse events[15]	x	x	x	x	x	x	x	x	x	x	x	x	(x)*	x
Physical examination	x	x							x			x	(x)*	
Weight	x	x							x			x	(x)*	
Subject returning investigational medicinal product (Section 10.9.3):														
Brodalumab								x	x	x	x	x	(x)*	
Fumaric acid esters			x	x	x	x	x	x	x	x	x	x	(x)*	
End of trial form												x	(x)*	
Reminders														
Handout ID card	x													
Handout and instruct in ePRO device use		x												

8 Trial design

8.1 Overall trial design

Overview
This is a randomised, open-label, active-controlled, parallel group, multi-centre trial with investigator-blinded efficacy assessments comparing the efficacy of subcutaneous injections of brodalumab to oral administration of fumaric acid esters in adults with moderate to severe plaque psoriasis. Eligible subjects will be randomised 1:1 to receive one of the following treatments, after stratification according to body weight (<100 kg or ≥100 kg):

- Brodalumab 210 mg, subcutaneous injections; or
- Fumaric acid esters, up to 240 mg dimethyl fumarate, oral administrations

The clinical trial consists of 3 phases:
The individual phases and visit structure are further described below and overviews of the trial design and scheduled procedures are displayed in Panel 1 and Panel 2.

Screening phase (Week -4 to Week 0)
A screening visit will take place up to a maximum of 28 days prior to the treatment phase.

Before any trial related procedure is started, the subjects will receive the necessary written and verbal information and instructions, including the informed consent form (written informed consent) and the written subject information sheet. Each subject will receive a unique subject number and eligibility will be determined by clinical examination and confirmation of subject selection criteria.

Treatment phase (Week 0 to Week 24)
The start of the treatment phase is defined as Week 0 (baseline). At this visit, eligibility will be confirmed by re-checking the eligibility criteria in subjects who were eligible based on previous examinations and the lab results received from central lab for the samples taken at the screening visit. The investigator must ensure that lab values which are used to assess eligibility have been received and reviewed. If still eligible, the subject will continue in the trial and receive a unique randomisation number that determines the application scheme of IMP for the individual subject (see Section 10.3).

Baseline, efficacy, and safety assessments during the trial are described in Section 11. Efficacy assessments are performed by an assessor blinded to treatment.

Follow-up phase (Week 24 to Week 26/32)
The follow-up visit is scheduled approximately 5 half-lifes after last administration of IMP.

- If treated with brodalumab, the follow-up visit is scheduled at Week 32 (8 weeks after the end of treatment visit at Week 24).
- If treated with fumaric acid esters, the follow-up visit is scheduled at Week 26 (2 weeks after the end of treatment visit at Week 24).

Trial schedule
The duration of the trial is planned as follows:

- Planned quarter of first subject first visit (FSFV): Q4 2017
- Planned quarter of last subject first visit (LSFV): Q2 2018
- Planned quarter of last subject last visit (LSLV): Q1 2019

8.2 Number of subjects needed

Assuming a screening failure rate of 15%, approximately 240 subjects will be screened to obtain 204 randomised subjects.

The statistical power considerations for this sample size (n=204) are described in Section 13.1.

The trial will be conducted at approximately 30 sites in Germany.

8.3 Scientific rationale for trial design

Randomised treatment allocation is applied as a methodology to reduce confounding by equalising factors (independent variables) not accounted for in the experimental design.

Open-label treatment with blinded efficacy assessment is applied since the route of administration differs, and since the complexity of applying double dummy blinding is considered inappropriate due to the individual dose adjustment scheme of fumaric acid esters. A blinded assessor will perform all efficacy assessment not knowing the assigned treatment, while the investigator will be unblinded. The investigator is unblinded since dose adjustment may be necessary for subjects randomised to fumaric acid esters.

A parallel design is applied to ensure correct temporal evaluation and to avoid any carry over effect from one treatment period to another, acknowledging the fact that, especially for biologic treatments, the effect may continue for weeks to months after treatment cessation.

8.4 End of trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial, including the follow-up visit scheduled at Week 32 for brodalumab and at Week 26 for fumaric acid esters. The End of Trial Form must be completed for all randomised subjects. The filled form includes date of last dose, last attended scheduled visit number, and primary reason for withdrawal, if applicable.

The end of the trial is defined as the date of the last visit of the last subject in the trial.

9 Trial population and withdrawal

9.1 Subject eligibility

The (sub)investigator must only randomise subjects who meet all eligibility criteria, who are not put at undue risk by participating in the trial, and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be checked according to the inclusion and exclusion criteria at the screening visit and the baseline visit.

Any implementation of national requirements/law for the subject's participation in the clinical trial must be ensured and described in the documentation submitted to authorities/ethics committees, as applicable.

9.2 Inclusion criteria

1. Signed and dated informed consent has been obtained
2. Men or women ≥18 years of age at the time of screening
3. Subjects with chronic plaque type psoriasis diagnosed at least 6 months before randomisation
4. Subjects with moderate to severe plaque psoriasis in whom topical therapy only is not adequate and who are candidates for systemic therapy, defined at randomisation by PASI >10, affected BSA >10%, and DLQI >10
5. Subject has no known history of active tuberculosis
6. Subject has a negative test for tuberculosis taken at screening (negative QuantiFERON test)

assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, then the subject will be considered to have withdrawn from the trial with 'lost to follow-up' as the primary reason.

11.2.3 Medical history

Relevant past and concurrent medical illness must be recorded based on subject interview. The duration of psoriasis will be recorded (to the nearest whole year).

11.3 Concomitant medication and procedures

Use of concomitant medication must be recorded in the subject's medical record and the eCRF (e.g. treatment/drug name, route of administration, total daily dose, indication and dates of start and stop).

For details about previous anti-psoriatic therapy see Section 10.5.

11.4 Efficacy assessments

11.4.1 Blinded assessments

The blinded assessor must make the following assessments at visits specified in the schedule of trial procedures: PASI, sPGA, BSA and NAPSI (see Panel 2). The assessments will be captured in the eCRF.

The blinded assessor who performs the assessments must be a medically qualified physician trained in the assessments and must remain blinded towards treatment of the subject through the course of the trial. If possible, each subject should have their assessments done by the same assessor throughout the trial. Extra care should be taken to ensure that the same assessor performs the baseline and end of treatment assessments (Week 24), where the co-primary endpoints data is collected. If necessary, trial visits may be rescheduled within the specified window to accommodate when the specific assessor will be available.

The trial site will maintain a written plan detailing which staff members are blinded/unblinded and the process of IMP administration used to maintain the blind.

11.4.1.1 Psoriasis Area and Severity Index (PASI)

The blinded assessor will assess the extent of psoriasis and the severity of the clinical signs (redness, thickness and scaliness) by body region (head and neck, upper extremities, trunk, and lower extremities).

The **extent** of psoriatic involvement will be recorded for each of the four regions (head and neck, upper extremities, trunk, and lower extremities) using the following scale:

Panel 7 Psoriasis area and severity index – Extent

Score	Extent of psoriatic involvement
0	No involvement
1	<10%
2	10 - 29%
3	30 - 49%
4	50 - 69%
5	70 - 89%
6	90 - 100%

This assessment of extent is the percentage of that *body region* that is affected and **not** the percentage BSA affected. For example, if one arm was totally affected, and the other arm was totally unaffected, the extent assessment for the arms would be 50% (half of the arms affected).

Note:

'head and neck' includes head and neck

'upper extremities' includes arms and hands

'trunk' includes the axilla and groin

'lower extremities' includes legs including the buttocks and feet

The **severity** of the psoriasis in each of the four regions (head and neck, upper extremities, trunk, and lower extremities) will be recorded for each of the signs of redness, thickness and scaliness. For each clinical sign, a single score reflecting the average severity of all psoriatic lesions on the given body region will be determined according to the scale below:

The PHQ-8 takes approximately 3 minutes to complete.

PHQ-8 scores ≥10 must be reported as an AE and the subject referred to a mental health professional (score ≥10 is cut-point for defining current depression; Kroenke et al. 2009). Subjects scoring ≥15, corresponding to moderately severe to severe depression, must in addition be withdrawn from the trial, see Section 10.8.1.

11.4.2.3 Electronic self-rated version, Columbia-Suicide Severity Rating Scale (eC-SSRS)

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of SIB (Mundt et al. 2010, Posner et al. 2011).

The eC-SSRS divides SIB into suicidal ideation (level 1-5), suicidal behaviour, and non-suicidal self-injurious behaviour:

Suicidal ideation

- Level 1: Wish to be dead or not to wake up
- Level 2: Non-specific thoughts
- Level 3: Specific thoughts of method
- Level 4: Some intent to act, no plan
- Level 5: Specific plan and intent

Suicidal behaviour

- Actual suicide attempts
- Interrupted attempts
- Aborted attempts
- Preparatory actions

Non-suicidal self-injurious behaviour

- Non-suicidal self-injurious behaviours

The eC-SSRS takes approximately 3 to 10 minutes to complete.

At all visits with scheduled assessment of SIB, using the eC-SSRS, the questionnaire must be filled by the subject after all other visit activities have been completed.

e) Blood pressure (BP), systolic and diastolic (mmHg)
f) Heart rate (beats per minute)
g) Temperature (Celsius with one decimal)
h) Respiration rate (beats per minute)

The vital signs must be assessed after approximately 5 minutes in a resting position.

Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF (see Appendix 4D). If an abnormal vital sign at any other visit than the screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with the principles for data entry in Section 12.2.

11.5.2 Physical examination

An abbreviated physical examination will be performed by the investigator and must include:

i) General appearance
j) Lymph nodes
k) Dermatologic examination of the skin

Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF (see Appendix 4D). If an abnormal finding at any other visit than the screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with the principles for data entry in Section 12.2.

11.5.3 Weight

The subjects must be wearing indoor clothing without shoes when weight is determined (kilograms, one decimal).

11.5.4 Pregnancy test

Female subjects of childbearing potential must have a serum beta hCG performed at the trial site at the screening visit (visit 1). An urine pregnancy test must be performed at visits described in the schedule of trial procedures (see Panel 2). In case of a positive urine test, a serum beta hCG must be performed for the purpose of confirmation.

11.5.5 Adverse events

AEs must be assessed and recorded as specified in Section 12.

11.6 Other safety assessments

11.6.1 Laboratory testing

11.6.1.1 Safety laboratory blood analysis

Blood samples will be drawn for analysis of laboratory parameters according to the schedule of trial procedures (Panel 2).

The following blood sample tests will be analysed at central laboratory: serum chemistry, haematology, serum pregnancy, urinalysis (incl. urine pregnancy tests).

The central laboratory will provide a trial specific laboratory manual that outlines handling, labelling, and shipping procedures for all samples. All blood samples will be obtained by venepuncture before IMP administration. The date and time of sample collection will be recorded in the source documents at the site.

The serum chemistry, haematology and other tests are listed below:

Panel 10 Analysts

Chemistry	Haematology and differential	Other
Sodium Potassium Magnesium Bicarbonate Albumin BUN Creatinine Uric acid Total bilirubin Direct bilirubin Alk phosphatase AST ALT CRP	RBC Haemoglobin Haematocrit Platelets WBC Differential (absolute count and %): - Neutrophils - Lymphocytes - Monocytes - Eosinophils - Basophils	Serum beta hCG QuantiFERON-TB Gold

The investigator must evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date. The signed and dated version of the lab results will be filed with the investigator’s trial documentation. If a laboratory result is abnormal and of clinical significance, it will be up to the investigator’s discretion to decide if the subject should be enrolled into the trial.

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF (see Appendix 4D). If an abnormal laboratory results are found at any other visit than the screening visit is considered by the investigator to be clinically

significant, it will be reported as an AE in accordance with the principles for data entry in Section 12.2.

The laboratory provides results to the trial sites in SI units.

Handling, storage, destruction and shipment instructions are provided in a separate laboratory manual.

11.6.1.2 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry and other tests. The blood volume at each visit depends on the visit and will vary from 6.0 mL to 12.0 mL. The total volume of blood drawn over the entire trial duration will be approximately 60 mL, which is less than the volume of blood drawn during a single blood donation (approximately 500 mL).

11.6.1.3 Safety urinalysis

Urine samples will be taken for analysis of the parameters listed below, at the visits specified in the schedule of trial procedures (Panel 2).

Panel 11 Urine analysis

Urine:
-Specific gravity
-pH
-Occult blood
-Protein
-Glucose
-Leucocyte esterase
-Ketones
-Urine pregnancy tests

12 Adverse events

- AEs and serious adverse events (SAEs) are defined in Appendix 2: Definitions of adverse events and serious adverse events.
- Classification of AEs in terms of severity, causality and outcome are defined in Appendix 3: Classification of adverse events.

12.1 Collection of adverse events

AEs must be collected from time of first trial related activity after the subject has signed the informed consent form until completion of the clinical trial. Hence, until the follow-up visit

scheduled at Week 32 for subjects allocated to brodalumab and at Week 26 for subjects allocated to fumaric acid esters.

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the (sub)investigator about AEs, for example: “How have you felt since I saw you last?” No specific symptoms should be asked for.

12.2 Reporting of adverse events

AEs reported by the subject or observed by the (sub)investigator must be recorded on the AE form of the eCRF and should be described in the following manner:

The *AE term* will be in precise English medical terminology (i.e. not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (for example allergic contact dermatitis).

The *duration* of the AE must be reported by the start date and stop date of the event. In addition, it must be recorded whether the AE started prior to start of IMP.

AEs must be classified in terms of severity, causality and outcome according to the definitions in Appendix 3: Classification of adverse events.

12.2.1 Actions taken as a consequence of an AE

Action taken with trial treatment: Any action taken with IMP as a consequence of the AE must be recorded (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, not applicable or unknown).

Other action taken: any other action taken as a result of the AE must be recorded (none, concomitant medication, concomitant procedure).

Withdrawn due to AE: it must be recorded whether the AE leads to withdrawal from the trial.

12.2.2 Reporting of serious adverse events

The criteria that define an AE as serious (i.e. an SAE) are defined in Appendix 2: Definitions of Adverse Events and Serious Adverse Events

12.2.2.1 Investigator reporting responsibilities

Any SAE must be reported to LEO on the (paper) 'SAE Form – Clinical Trials' within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP, comparator or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

The completed SAE form must be faxed or scanned and e-mailed to Global Pharmacovigilance LEO, using the following fax number or e-mail address:

- E-mail address: drug.safety@leo-pharma.com
- Fax number: +45 7226 3287

It may be relevant for the (sub)investigator to enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Pharmacovigilance LEO may request further information in order to fully assess the SAE. The (sub)investigator must forward such information to Global Pharmacovigilance, LEO upon request by fax or e-mail (see contact details above).

The investigator must notify the local independent ethics committee(s) (IEC(s)) of SAEs as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial (i.e. after the safety follow-up visit defined in Section 11.1) should not be routinely sought or collected. However, such events must be reported, without undue delay, to Global Pharmacovigilance LEO (see contact details above) if the investigator becomes aware of them.

12.2.2.2 LEO reporting responsibilities

Global Pharmacovigilance, LEO is responsible for assessing whether or not an SAE is expected. The relevant reference documents for this clinical trial are:

- For brodalumab, the latest version of the company core safety information
- For fumaric acid esters, the latest version of the SmPC for Fumaderm®

The reference safety information for brodalumab (Appendix 6) is based on the company core data sheet (CCDS). The CCDS is chosen to ensure consistency in case evaluation and assessment of listedness/expectedness for different trials and spontaneous reporting. Further, changes to the safety profile are implemented in the CCDS immediately.

Panel 12 Adverse events of special interest

Adverse event of special interest	Additional information to be provided
SIB	This AESI may be serious or non-serious. A specific adverse event form will need to be filled out whenever a SIB event is reported. This form will also include specific event related questions.
Serious infections	No additional information except for the described procedure for serious adverse event.
MACE	No additional information except for the described procedure for serious adverse event.
Malignancy diagnosed after randomisation (except basal cell carcinoma, squamous cell carcinoma, and cervical carcinoma in situ)	Procedure as described for serious adverse event including: Histology report Oncology assessment Treatment (surgery, radiation, chemotherapy, other)

12.4 Reporting of other events

12.4.1 Overdose

An overdose is defined as a subject receiving a dose of IMP in excess of that specified in this protocol.

The term overdose must be documented on the AE form of the eCRF. In addition, AEs originating from overdose must be documented on a separate line. If the AE originating from overdose is serious expedited reporting is required (see Section 11.2.2.1).

In the event of an overdose, the patient should be monitored and treated symptomatically, and supportive measures instituted to the discretion of the investigator

12.4.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of a medicinal product while in the control of the (sub)investigator or subject. Broadly, medication errors fall into four categories: wrong medication, wrong dose (including strength, form, concentration, and amount), wrong route of administration, or wrong subject.

The medication error specifying the category of error (see definitions above) must be documented on the AE form of the eCRF. In addition, AEs originating from a medication error must be documented on a separate line. If the AE originating from medication error is serious expedited reporting is required (see Section 12.2.2.1).

12.4.3 Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

The term misuse must be documented on the AE form of the eCRF. In addition, AEs originating from misuse must be documented on a separate line. If the AE originating from misuse is serious expedited reporting is required (see Section 12.2.2.1).

12.4.4 Abuse

Abuse relates to the sporadic or persistent, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects.

The term abuse must be documented on the AE form of the eCRF. In addition, AEs originating from abuse must be documented on a separate line. If the AE originating from abuse is serious expedited reporting is required (see Section 12.2.2.1).

12.4.5 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to baseline, must be reported as an AE. If the AE originating from aggravation of condition is serious expedited reporting is required (see Section 12.2.2.1).

12.4.6 Lack of efficacy

Not applicable.

12.5 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possible/probable related to the investigational product for 8 weeks after last treatment for brodalumab or for 2 weeks after last treatment for fumaric acid esters, or until the final outcome is determined, whichever comes first. SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and cannot be expected to recover during trial or safety follow-up periods, for example chronic illnesses, the final outcome should be considered recovered and a statement that the SAE has stabilised should be added to the narrative in the SAE form. Please note that the event should not be reported as 'recovered' in the eCRF and on the SAE form.

12.6 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined within the EU Directive 2001/20/EC as *"…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (EU 2001/20/EC, article 10).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO, regulatory authority(ies), or IEC(s).

The investigator must immediately inform LEO - by contacting the clinical project manager or medical expert - of this change in the clinical trial procedure or of the temporary halt providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO must act immediately upon receipt of the urgent safety measure notification in accordance with the internal procedures, which are based on the EU guideline.

13 Statistical methods

13.1 Sample size

The effect on psoriasis symptoms of subcutaneous injections of brodalumab will be compared to oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis who are naïve to systemic treatment.

Formally, this will be formulated by testing the null hypotheses of equality of proportion of PASI 75 response and sPGA (0 or 1) success to treatment with brodalumab compared with treatment with fumaric acid esters; against the alternative hypothesis that the two proportions differ.

The sample size is determined using Fisher's exact test for the two independent proportions under the assumption of a two-sided test of size 5%. Based on experience from previous trials with brodalumab and fumaric acid esters in subjects with moderate to severe psoriasis, conservative estimates for the proportion of PASI 75 responders of 80% for brodalumab and between 50% and 70% for fumaric acid esters (Nast et al. 2012) are used in the sample size calculation (using Proc Power in SAS version 9.4). Assuming a dropout rate of 50% for

fumaric acid esters, a PASI 75 response rate combined with NRI will correspond to a total rate of responders of 25%. A dropout rate of less than 40% with brodalumab, a PASI 75 response rate will correspond to a total rate of responders of 48%.

For sPGA, the expected rate of sPGA success is 37.4% with fumaric acid esters (Mrowietz and Szepietowski et al. 2017), while varying rates above 60% has been seen in the previous brodalumab trials.

An overview of the estimated power within the given spread of response rates, is presented in Panel 13.

Panel 13 Estimated power by sample size and response rate (number of subjects per group)

	PASI 75 Fumaric acid esters response rate = 50% (total response rate = 25%)	**PASI 75 Fumaric acid esters response rate = 60% (total response rate = 30%)**	**PASI 75 Fumaric acid esters response rate = 70% (total response rate = 35%)**	**sPGA success Fumaric acid esters response rate = 37.4%**
N = 91	0.873	0.652	0.372	0.833
N = 102	0.910	0.708	0.416	0.876
N = 118	0.947	0.776	0.476	0.921
N = 144	0.978	0.858	0.566	0.963

Assuming independence between PASI 75 and sPGA the power to show superiority of brodalumab compared to fumaric acid esters will be 0.91*0.876 = 80% with 102 subjects in each treatment arm.

13.2 Trial analysis sets

All subjects enrolled in the trial (i.e. subjects for whom informed consent has been obtained and who have been registered in the trial) will be accounted for in the clinical trial report.

All subjects randomised are included in the full analysis set (FAS) and will be used for efficacy analyses. Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1. If it is decided to exclude a randomised subject from the FAS, a justification addressing ICH E9 will be given. Subjects contribute to the evaluation ‘as randomised’.

A safety analysis (SAS) set will be defined as subjects receiving treatment with IMP. The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the statistical analysis plan update before breaking the

- PASI improvement (%) from baseline at Week 24
- Change from baseline at Week 24 in affected body surface area (BSA)
- Psoriasis Symptom Inventory (PSI) responder at Week 24 (total score ≤ 8, with no item scores > 1)
- PSI total score of 0 at Week 24
- Number of symptom-free days from randomisation to Week 24 (symptom-free day = daily total PSI of 0 on that day)
- Burden of symptoms assessed as the normalised area under the curve (AUC) of PSI from baseline to the last available assessment
- Change from baseline at Week 24 in Dermatology Life Quality Index (DLQI) total score
- DLQI total score of 0 or 1 at Week 24
- Frequency of AEs and SAEs by preferred term

Other endpoints:

- Change from baseline at Week 24 in Nail Psoriasis Severity Index (NAPSI) total score

13.3.5 Analysis of primary endpoint

The co-primary endpoints PASI 75 and sPGA (0 or 1) at Week 24 (end of treatment visit) will be evaluated on the FAS.

Estimates and 95% confidence intervals (CI) for the response rates and treatment differences will be presented. The differences in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test with stratification by weight group (≥100 kg or <100 kg). The null hypotheses of no difference in response rates between brodalumab and fumaric acid esters will be tested against the two-sided alternative that there is a difference on a 5% level. Subjects who drop-out of the trial before Week 24 (end of treatment visit) will be regarded as non-responders. A sensitivity analysis will be made where ineligible subjects randomised in error into the trial are excluded from the analysis.

As supportive analyses for the co-primary endpoints, a logistic regression model with baseline PASI or sPGA and weight group will be performed, and further, the mixed model for repeated measurements (MMRM) for PASI described below will be used to predict PASI 75 for subjects without assessments at Week 24 for an additional Cochran-Mantel-Haenszel analysis. Finally, subjects who drop-out of the trial before Week 24 will be LOCF imputed and analysed using the Cochran-Mantel-Haenszel test.

The trial is considered a success if superiority is confirmed for both primary endpoints.

13.3.6 Analysis of secondary efficacy endpoints

All binary endpoints will be analysed in a similar manner as the co-primary endpoints, by analysing the difference in response rates between treatment groups using the Cochran-Mantel-Haenszel test.

Continuous endpoints like absolute PASI score, % PASI improvement, and NAPSI improvement will be modelled by MMRM to compare treatments through Week 24. The mixed model will include treatment group, week, interaction between treatment and time, baseline PASI/NAPSI score, and baseline weight group as fixed factors. Within subject covariance will be estimated by an unstructured covariance matrix (if possible).

Number of symptom-free days will be summarised.

13.3.7 Analysis of patient reported outcomes

The PROs will be summarised by treatment and stratification group. Further DLQI, change from baseline will be compared between treatments by MMRM including treatment group, week, interaction between treatment and time, baseline DLQI score and baseline weight group as fixed factors. Within subject covariance will be estimated by an unstructured covariance matrix (if possible). DLQI total score of 0 or 1 will be analysed by a Cochran-Mantel-Haenszel model adjusting for baseline weight group.

The AUC for the PSI total score will be calculated for each subject using the standard trapezoidal rule. The AUC will be normalised by dividing with the time period from baseline to the last available assessment of the PSI total score. The normalisation converts the AUC to the original scale of the PSI total score. Missing assessments of the PSI total score in-between non-missing assessments will not be imputed, which corresponds to linear interpolation between the non-missing assessments of the PSI total score. The normalised AUCs will be analysed using an analysis of covariance (ANCOVA) with treatment group, baseline weight group and the baseline PSI total score as explanatory variables.

13.3.8 Analysis of safety

The analysis of safety will be based on the safety analysis set.

13.3.8.1 Adverse events

AEs will be coded during the trial according to the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be presented by preferred terms (PT) and primary system organ class (SOC).

Treatment-emergent AEs (TEAEs) will be summarised, however, all AEs recorded during the course of the trial will be included in the subject data listings. An event will be considered treatment-emergent if started on or after the first day of IMP and no later than 5 half-lifes after the last day on randomised treatment, or if started before the first use of IMP and worsened in severity thereafter. The tabulations described in the following will only include the treatment-emergent events.

An overall summary of the number of subjects with any TEAEs, the percentage of subjects with at least one event, the number of events and the event rate per 100 years will be presented. These summaries are done by SAEs, discontinuations from the trial due to AEs, treatment-related AEs, severe AEs, relation to device, outcome and AESIs.

Where there are several recordings of a specific AE within a subject, severity will be taken as the most severe recording for that specific AE. If a subject experience more than one AE of the same type, all severity evaluations should be recorded.

Where there are several recordings of causal relationship to a specific AE within a subject, causal relationship will be taken as the most-related recording from the last report of that AE.

Related AEs are defined as AEs for which the (sub)investigator has not described the causal relationship to IMP as ‘not related’.

Summary tables based on SOC and PT are made for all TEAEs, serious TEAEs, related AEs, severe TEAEs, TEAEs reported as AESIs, AEs leading to withdrawal, and TEAEs with preferred term that are experienced by at least 5% of the subjects in any treatment arm or by at least 5% of all subjects.

Finally, relevant AE listings will be created.

13.3.8.2 Other specific safety assessments

Adverse events reported as injection site reactions will be summarised separately based on SOC and PT. Furthermore, a corresponding list will be created.

13.3.8.3 Vital signs and physical examinations

The change in vital signs (BP, heart rate, body temperature and respiration rate) from baseline to Week 24 will be summarised as mean, standard deviation (SD), median, minimum and maximum values for each treatment group.

Furthermore, a shift table for vital signs showing the change from baseline to Week 24 in clinical assessments (normal; abnormal, not clinical significant; abnormal, clinical significant) will be performed.

Finally, a shift table for physical examinations (general appearance, lymph nodes and dermatologic examination) showing the change from baseline to Week 24 in clinical assessments (normal; abnormal, not clinical significant; abnormal, clinical significant) will be performed.

13.3.8.4 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to Week 24 will be summarised as mean, SD, median, minimum and maximum values for each treatment group.

Laboratory parameters will be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value is below, within or above the reference range, respectively. A shift table will be produced showing the categories at baseline against those at Week 24. Subjects with laboratory parameters outside the reference range will be listed.

13.3.9 Interim analysis

No interim analyses are planned.

13.3.10 General principles

All statistical analyses of efficacy endpoints will be based on the FAS and safety endpoints on the safety analysis set (SAS). All significance tests will be two-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence. No corrections for multiplicity will be performed.

If not mentioned otherwise, endpoints will be summarised descriptively at each visit by treatment and in total.

An observed-cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit). For categorical endpoints number of subjects not attending each specific visit will also be added.

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, median, SD, minimum, and maximum values.

In general, for endpoints evaluated as change from baseline and/or where a baseline adjustment is applied, baseline is defined as information collected at the randomisation visit (Visit 2), if not otherwise stated. If the assessment is not available at the randomisation visit but at the screening visit (Visit 1) then this will be used instead.

All the analyses specified in the protocol will be reviewed in relation to the blinded data obtained and the statistical analysis plan update will be finalised before breaking the randomisation code.

Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in the statistical analysis plan update (SAPU) and/or in the clinical trial report dependent on the type of deviation.

For endpoints evaluated over time, plots will be made to explore the trajectory with time.

13.3.11 Handling of missing values

Missing data for categorical endpoints will be imputed with non-responder imputation. Missing data for continuous endpoints will be dealt with by a mixed model for repeated measurements.

14 References

Augustin M, Reich K, Glaeske G, Schaefer I, Radtke M. Co-morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. Acta Derm Venereol. 2010;90(2):147-51.

Bushnell DM, Martin ML, McCarrier K, Gordon K, Huang X et al Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatolog Treat. 2013;24(5):356-60.

Chiricozzi A, Romanelli M, Saraceno R, Torres T. No meaningful association between suicidal behavior and the use of IL-17A-neutralizing or IL-17RA-blocking agents. Expert Opin Drug Safety. 2016;15(12):1653-1659.

Dubertret L, Mrowietz U, Ranki A, van de Kerkhof PC, Chimenti S, et al. EUROPSO Patient Survey Group. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. Br J Dermatol. 2006;155(4):729-36.

- is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic broncospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

Outcome

The *outcome* of the event should be classified and handled as follows:

Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
Recovered/resolved with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded. In case of a SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to (sub)investigator, e.g. subject lost to follow-up.

Appendix 5B: Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix 6 Reference safety information

This reference safety information document is based on the current version of the company core safety document that is version 1.0 of the CCDS.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients:

- Proline
- Glutamate
- Polysorbate 20
- Water for injections

Active Crohn's disease.

Clinically important active infections (e.g. active tuberculosis; see Section below).

SPECIAL WARNING AND SPECIAL PRECAUTIONS FOR USE

Crohn's Disease

There is limited data in patients with a history of Crohn's disease. Exercise caution when prescribing Kyntheum® to patients with a history of Crohn's disease. Patients with a history of Crohn's disease should be followed for signs and symptoms of active Crohn's disease. If patients develop active Crohn's disease, treatment should be discontinued permanently.

Suicidal ideation and behaviour

Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum®. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum® and increased risk of suicidal ideation and behaviour has not been established.

Carefully weigh the risk and benefit of treatment with Kyntheum® for patients with a history of depression and/or suicidal ideation or behaviour, or patients who develop such symptoms. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur.

Infections

Kyntheum® may increase the risk of infections.

LSFV	last subject first visit
LSLV	last subject last visit
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MTX	methotrexate
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PASI 75	responder cut-point defining responders as subjects with at least 75% improvement from baseline in PASI
PASI 90	responder cut-point defining responders as subjects with at least 90% improvement from baseline in PASI
PASI 100	responder cut-point defining responders as subjects with 100% improvement from baseline in PASI
PHQ-8	Patient Health Questionnaire-8
PML	progressive multifocal leukoencephalopathy
PSI	Psoriasis Symptom Inventory
PUVA	psoralens and ultraviolet A
Q2W	every two weeks (in this trial, this regimen includes an additional loading dose one week after initiation of brodalumab)
RBC	red blood cell count
SAE	serious adverse event
SAPU	statistical analysis plan update
SAS	safety analysis
SC	subcutaneous
SIB	suicidal ideation and behaviour

	Screening	**Treatment phase**											**Follow-up**
Visit	V1	V2[1)] Baseline	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 End of treatment	Unscheduled visit[2)] or early termination visit[3)]	V13[4)]
Visit Week/Day	Up to 28 days prior to V2	0/0	1/7	2/14	3/21	4/28	6/42	8/56	12/84	16/112	20/140	24/168		26/182 or 32/224[4)]
Visit window (days)[5)]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3
Reminders – Continued														
Dispense disposal containers for brodalumab syringes		x												
Handout cooler bag for transport of brodalumab		x												
Subject information folder		x												
Subject to bring ePRO device with them to site visit			x	x	x	x	x	x	x	x	x	x	(x)*	
Review ePRO device answers			x	x	x	x	x	x	x	x	x	x	(x)*	
Subject to return ePRO, disposal containers, and cooler bag to site												x	(x)*	

1) Subjects must be randomised within 28 days after screening or as soon as all inclusion and exclusion criteria are confirmed. Allow time for results from screening samples to be available from central lab.

2) An unscheduled visit can be performed before the follow-up visit for the following purposes: By individual need at the discretion of the investigator, AE follow-up (and related concomitant medication/procedures, if applicable), re-instructing the subject in procedures for home treatment with the investigational medicinal product, re-collection of blood and/or urine samples in case of medical need of following up on specific test abnormalities, suspection of pregnancy, or in case of sampling or testing errors necessitating the colletion of new samples. Procedures are marked in brackets “(x)” since they are optional depending on the reason for the unscheduled visit.

7. A female subject of childbearing potential* is eligible to participate if she is not pregnant. This must be confirmed by a negative serum beta hCG pregnancy test at screening

   **Female subjects are considered of childbearing potential unless they have undergone hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or have been post-menopausal for at least one year prior to first visit.*

8. Female subjects of childbearing potential must be willing to use highly effective contraception* at trial entry and until 15 weeks after end of treatment. For subjects randomised to fumaric acid esters: oral contraceptive pills must be used with an additional contraceptive method (e.g. condom by partner, diaphragm, contraceptive gel, vaginal ring, etc.)

   **Highly effective contraception is defined as follows:*
   - *Sexual abstinence (when this is in line with the preferred and usual life style of the subject)*
   - *Vasectomised partner (given that the subject is monogamous)*
   - *Bilateral tubal occlusion*
   - *An intrauterine device (IUD)*
   - *Intrauterine hormone-releasing system (IUS)*
   - *Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*
   - *Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*

9. Male subject with a female partner of childbearing potential who is willing to use adequate contraceptive methods*. Male subjects should not donate sperm in this period

   **Adequate contraceptive methods as required by local regulation or practice for at least 15 weeks following last dose of investigational product.*

10. Subject and/or subject's designee is/are capable of administering subcutaneous injections

9.3 Exclusion criteria

1. Previous or current systemic treatment of plaque psoriasis or known contraindication for systemic therapy.
2. Previous or current PUVA (psoralens and ultraviolet A) therapy.
3. Washouts and non-permitted drugs:

10 Treatments

10.1 Investigational medicinal products description

Brodalumab and fumaric acid esters will be packaged in individually numbered kits. The brodalumab pack size includes 2 pre-filled syringes, while the fumaric acid esters pack sizes include 40 tablets per pack (fumaric acid esters initial; 4 blister packs each containing 10 tablets) or 70 tablets per pack (fumaric acid esters; 7 blister packs each containing 10 tablets). Refer to Panel 4 for further details.

10.2 Administration of investigational medicinal products

The IWRS system will assign the required kits numbers for each subject at each dispensing visit.

The first day of dosing is defined as Day 0 (baseline visit).

10.2.1 Dosing scheme

Brodalumab

Each brodalumab 210 mg dose will be given as 1 subcutaneous injection of a single-use pre-filled syringe of 210 mg (1.5 mL) according to the dose scheme in Panel 5.

Brodalumab must be injected in the upper legs (thighs) or stomach area (abdomen) by the subject or subject's designee. The subject's designee may also give injection(s) in the upper, outer arm.

At baseline and Week 1, subjects randomised to brodalumab and/or their designated person must receive training on self administration of brodalumab. At these two visits, brodalumab should be administered by the subject or designated person at the clinical trial site under supervision of the investigator or delegated person. After Week 1, brodalumab should be administered at home by subjects or their designated person. However, assisted administration at trial site may be allowed at the discretion of the investigator if wished for by the subject.

Panel 8 Psoriasis area and severity index – Severity

Score	**Redness**
0	None (no erythema)
1	Mild (faint erythema, pink to very light red)
2	Moderate (definite light red erythema)
3	Severe (dark red erythema)
4	Very severe (very dark red erythema)
Score	**Thickness**
0	None (no plaque elevation)
1	Mild (slight, barely perceptible elevation)
2	Moderate (definite elevation but not thick)
3	Severe (definite elevation, thick plaque with sharp edge)
4	Very severe (very thick plaque with sharp edge)
Score	**Scaliness**
0	None (no scaling)
1	Mild (sparse, fine scale, lesions only partially covered)
2	Moderate (coarser scales, most of lesions covered)
3	Severe (entire lesion covered with coarse scales)
4	Very severe (very thick coarse scales, possibly fissured)]

Based upon the PASI score at randomisation the investigator must evaluate eligibility, see inclusion criterion 4.

11.4.1.2 Static Physician's Global Assessment of disease severity (sPGA)

The blinded assessor will make a global assessment of the disease severity of psoriasis using the 6-point scale below. This assessment will represent the average lesion severity on the trunk and limbs. The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

Any positive finding in suicidal ideation of level 4 or 5 or any positive finding in history of suicidal behaviour must be reported as an AE and the subject referred to a mental health professional and withdrawn from the trial, see Section 10.8.1.

Documentation of the training and certification must be archived in the investigator trial file. This documentation must be in place before any eC-SSRS results are evaluated by the investigator.

11.4.2.4 Psoriasis symptom inventory (PSI)

Subjects will use an ePRO device to record their daily psoriasis symptoms using the PSI, a psoriasis specific patient reported outcome measure that has been developed on the basis of a literature review, in-depth physician interviews, psoriasis patient focus groups, and cognitive interviews (Bushnell et al. 2013; **Appendix 5A**).

The PSI consists of eight psoriasis-specific questions. Subjects will be requested to rate the severity of their symptoms in the last 24 hours from 'not at all' to 'very severe,' ranging from 0 to 4. Total scores range from 0 to 32 with higher scores indicating worse symptoms.

The PSI takes about 3 minutes to complete.

Site staff will train the subject on the proper use of the ePRO device at the baseline visit. Subjects should be instructed to complete the PSI once per day. The ePRO must be completed in the evening within a specified time window (for the early termination visit only, the PSI may be completed earlier in the day).

The investigator should not question the subject's answers. The investigator must review the data for timeliness and completeness.

Symptoms reported on the PSI will not be captured as AEs, unless they are specifically mentioned as an AE by the subject when they are asked the non-leading question: "How have you felt since I saw you last?" All data collected as part of the PSI will be reported in the trial report.

11.5 Safety assessments

11.5.1 Vital signs

Following vital signs must be measured:

Global Pharmacovigilance, LEO will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation in Germany.

The IEC(s) will be notified of SAEs according to the current applicable legislation in Germany.

All SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO, as described in the ICH E2A guideline, and which are unexpected (suspected, unexpected serious adverse reactions (SUSARs)), are subject to expedited reporting to regulatory authorities, and IEC(s) according to the current applicable legislation in Germany. Investigators will be notified of these on an ongoing basis.

12.3 Other events that require expedited reporting to LEO

12.3.1 Pregnancy

Any pregnancy occurring during the clinical trial must be reported to LEO within 24 hours of first knowledge using the (paper) Pregnancy Follow-up Form (Part I). All such pregnancies must be followed up until delivery or termination and final outcome must be reported on the (paper) Pregnancy Follow-up Form (Part II) within 24 hours of first knowledge.

The completed Pregnancy Follow-up Forms must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO (see Section 12.2.2.1 for contact details).

Pregnant subjects must discontinue IMP.

12.3.2 Adverse events of special interest

The following four adverse events of special interest (AESI) have been defined: SIB, serious infections, MACE defined as stroke, myocardial infarction, or cardiovascular death), and malignancy. These have been defined based on the known profile of brodalumab, emerging potential risks in the course of drug development, as well as other risks observed with other immune modulating biologics used for psoriasis.

The events might require that the investigator provides additional information to LEO (see Panel 12).

All AESI must be reported to LEO within 24 hours (see Section 12.2.2.1)

randomisation code/clinical trial report. Subjects in the safety analysis set contribute to the evaluation 'as treated'.

13.3 Statistical analysis

13.3.1 Disposition of subjects

A subject disposition will be made including information of number of subjects screened, randomised, exposed, completing and withdrawn (and reason for withdrawal), by treatment group and in total. This will also include number of subjects included in the FAS and safety analysis set, by treatment group and in total.

13.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects by treatment group. Presentations of age, sex, ethnicity, race, and baseline efficacy assessment by treatment will also be given by centre.

Demographics include age, sex, race, and ethnicity. Other baseline characteristics include vital signs (including height, weight, BMI), duration of psoriasis, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, and previous anti-psoriatic therapy.

13.3.3 Exposure and treatment compliance

Relevant exposure, compliance and drug accountability data will be tabulated.

13.3.4 Endpoints

In support of the objectives stated in Panel 3, the endpoints of the trial are prioritised as follows:

Co-primary endpoints:

- At least 75% improvement from baseline at Week 24 in Psoriasis Area and Severity Index (PASI)
- Static Physician's Global Assessment (sPGA) scale score of 0 or 1 at Week 24

Secondary endpoints:

- At least 90% improvement from baseline at Week 24 in PASI
- 100% improvement from baseline at Week 24 in PASI
- Change from baseline at Week 24 in PASI score

Fallah Arani S, Neumann H, Hop WCJ, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011;164(4):855–861.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.

Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospitalbased case-control study. Br J Dermatol. 2007;157(1):68-73.

Gooderham M, Posso-De Los Rios CJ, Rubio-Gomez GA, Papp K. Interleukin-17 (IL-17) inhibitors in the treatment of plaque psoriasis: a review. Skin Therapy Lett. 2015;20(1):1-5.

Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, et al. The Risk of Mortality in Patients With Psoriasis: Results From a Population-Based Study. Arch Dermatol. 2007; 143(12):1493-1499.

Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis.Lancet. 2007;370(9583):263-71.

Griffiths CE, Christophers E, Barker JN, Chalmers RJ, Chimenti S, et al. A classification of psoriasis vulgaris according to phenotype. Br J Dermatol. 2007;156(2):258-62.

Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, et al. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009;114(1–3):163–73.

Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64(Suppl 2):ii18-23;discussion II24-5.

Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, et al. American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60(4):643-59.

Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, Tebbs VM, Pau-Charles I. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm® - and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615-623.

Mrowietz U, Warren RB, von Kiedrowski R et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10068):528-537.

Appendix 3: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate or severe according to the (sub)investigator's clinical judgement:

Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

If the severity of an AE worsens, a new AE should be recorded. For the AE that worsens, a stop date should be entered in the eCRF and the outcome should be categorized as "not recovered / not resolved".

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probable, possible or not related according to the following:

Probably related	Follows a reasonable temporal sequence from administration of the IMP. Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the IMP. Disappears or decreases on cessation or reduction in dose of the IMP. Reappears or worsens upon re-challenge.
Possibly related	Follows a reasonable temporal sequence from the administration of the IMP. Could also be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the IMP.
Not related	Does not follow a reasonable temporal sequence from administration of the IMP. Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Does not reappear or worsen upon re-challenge. Does not follow a known pattern of response to the IMP.

Appendix 4: Trial governance considerations

Appendix 4A: Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Current version of applicable ICH-GCP guidelines.
- Applicable laws and regulations.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial as required.

The protocol, protocol amendments, subject information leaflet including the informed consent form (ICF), Investigator's Brochure, and other relevant documents (for example advertisements) must be submitted to an IEC by the investigator (in collaboration with LEO, if applicable) and reviewed and approved by the IEC prior to enrolment of subjects.

Any amendments to the protocol must be approved by/receive favourable opinion from relevant regulatory authorities and IECs as required prior to the implementation.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Notifying the local IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and adherence to applicable national and international legislation.

Appendix 4B: Informed consent process

Subjects shall receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

SCORING

The scoring of each question is as follows:

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

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life
2 – 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

During the 12-week placebo-controlled clinical trial period in patients with psoriasis, serious infections were observed in 0.5% of patients receiving Kyntheum® (see Section on undesirable effects).

Caution should be exercised when considering the use of Kyntheum® in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and Kyntheum® should not be administered until the infection resolves.

No cases of active tuberculosis were reported from clinical trials. However, Kyntheum® should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Kyntheum® in patients with latent tuberculosis.

Vaccinations

It is recommended that patients be brought up-to-date with all immunisations in accordance with local immunisation guidelines prior to initiation of treatment with Kyntheum®. Live vaccines should not be given concurrently with Kyntheum® (see Section below). No data are available on the response to live vaccines or the risk of infection, or transmission of infection after the administration of live vaccines in patients receiving Kyntheum®.

Vaccination of infants

Vaccination of infants with live vaccines following third trimester exposure to Kyntheum® should be discussed with a physician (see also Section on fertility, pregnancy and lactation).

Concomitant immunosuppressive therapy

The safety and efficacy of Kyntheum® in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Live vaccines should not be given concurrently with Kyntheum® (see Section on special warning and precautions for use).

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g. IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Although a role for interleukin (IL)-17A and IL-17RA in the regulation of CYP450 enzymes has not been reported, the effect of brodalumab on CYP3A4/3A5 activity was evaluated in a disease-drug-drug interaction study.