Cover Page

Official title: A Phase 4 Trial Comparing the Efficacy of Subcutaneous Injections of Brodalumab to Oral Administrations of Fumaric Acid Esters in Adults With Moderate to Severe Plaque Psoriasis
LEO Pharma number: LP0160-1327
NCT number: NCT03331835
Date: 17-Apr-2018

Clinical Trial Protocol LP0160-1327

A phase 4 trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of fumaric acid esters in adults with moderate to severe plaque psoriasis

Phase 4 trial

A 24-week, randomised, open-label, active-controlled, parallel group, multi-centre trial with investigator-blinded efficacy assessments

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH-GCP and the applicable regulatory requirement(s)

LEO Pharma A/S	**Trial ID:**	**LP0160-1327**
	Date:	**17-Apr-2018**
	EudraCT No:	**2016-003867-21**
	Version:	**4.0**

1 Clinical trial protocol statement

1.1 Approval statement LEO Pharma A/S

The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD , MSc Stat

Biostatistics Lead, Global Clinical Operations

PPD , MD

Global Medical Science Director, Medical Sciences and Safety

PPD , MSc Pharm

Clinical Operations Lead, Global Clinical Operations

1.2 Approval statement international coordinating investigator

The international coordinating investigator approves the clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by manually signing the International Coordinating Investigator Clinical Trial Protocol Approval Form, which is a separate document adjoined to this document.

The following person has approved this clinical trial protocol:

Ulrich Mrowietz, Prof. Dr. med.

International Coordinating Investigator

1.3 Acknowledgement statement investigator(s)

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by signing the clinical trial protocol acknowledgement form or a similar document.

Protocol amendments and summary of changes tables

Document history

Document	Date
Amendment 2 (substantial), eTMF version 4.0	17-Apr-2018
Amendment 1 (substantial), eTMF version 3.0	12-Oct-2017
Original protocol including e-signature, eTMF version 2.0	20-Jun-2017
Original protocol, eTMF version 1.0	20-Jun-2017

Amendment 2 (17-Apr-2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The reason for the amendment is to clarify that exclusion criteria related to the PROs eC-SSRS and PHQ-8 pertain to both the screening and the baseline visit. Also, the wording for the eC-SSRS criteria, and the described assessment hereof, has been updated to reflect the report from the eC-SSRS. The wording in eTMF version 3.0 of the protocol was based on the paper version of the C-SSRS.

Substantial changes to the original protocol are provided in the table below. When applicable, original text is cited in quotation marks (‘’) with deletions as ~~strike-through~~, additions in **bold**, and descriptive comments in *italics*. Minor editorial revisions have also been applied during this amendment without further indication.

Substantial changes in Amendment 2	Affected Section(s)	Rationale for change
The header versioning (and front page) has been aligned with the eTMF versioning (the electronic archiving system). Hence, with this amendment the header version has been updated from version 2.0 to 4.0.	All sections	To align header versioning with the eTMF versioning.
The “V11” column in the schedule of procedures is now marked “x” for the task “returning fumaric acid esters”.	Panel 2	This was missing by mistake.

Substantial changes in Amendment 2	**Affected Section(s)**	**Rationale for change**
12. **Any positive finding in history of suicidal behaviour (e.g., 'actual suicide attempts', 'interrupted attempts', 'aborted attempts', or 'preparatory actions') based on the eC-SSRS questionnaire at screening or baseline.** ~~Subjects with a history of suicidal behaviour.~~ 13. Any **positive finding in** suicidal ideation of **level** ~~severity~~ 4 or 5 **('some intent to act, no plan' or 'specific plan and intent')** based on the eC-SSRS questionnaire at screening **or baseline**. 14. A PHQ-8 score of ≥10 corresponding to moderate to severe depression at screening **or baseline**.	Sections 2, 6.6, 9.3, 11.4.2.2, 11.4.2.3, and Appendix 1	Clarification that exclusion criteria related to the PROs eC-SSRS and PHQ-8 pertain to both the screening and the baseline visit. Also, the wording for the eC-SSRS criteria has been updated to reflect the report of the electronic version of the C-SSRS.
The described eC-SSRS assessment has been updated to reflect the report of the eC-SSRS. Appendixes 5C and 5D, containing the paper version of the C-SSRS, have been deleted.	Section 11.4.2.3 and Appendix 5	Appendixes 5C and 5D in the previous version of the protocol were deleted since it was realized that they deviated slightly from the report of the electronic version of the C-SSRS (the eC-SSRS). Instead, further details from the eC-SSRS report format are included in the assessment description in Section 11.4.2.3.
Psoriasis is a **chronic** inflammatory ~~skin disease~~ **disorder associated with significant morbidity and mortality** that occurs in approximately 2% of the population worldwide (Augustin et al. 2010, **Gelfand et al. 2007**, Rachakonda et al. 2014).	Section 6.1	Clarification that psoriasis is chronic and associated with significant morbidity and mortality
Planned quarter of last subject last visit (LSLV): **Q1 2019** ~~Q4 2018~~	Section 8.1	Updated planned time schedule due to recruitment challenges.

Substantial changes in Amendment 2	**Affected Section(s)**	**Rationale for change**
~~No cases of overdose have been reported in clinical studies.~~ Doses up to 700 mg intravenously have been administered in clinical studies with no evidence of dose limiting toxicity. In the event of an overdose, the subject should be monitored and treated symptomatically, and supportive measures instituted at the discretion of the investigator.	Section 10.2.2	Deleted since overdose has now been reported with use of brodalumab. The overdose did not lead to any adverse event.
•Anaphylactic reaction or other severe systemic reaction to IMP ~~injection~~.	Section 10.8.1	"injection" is deleted since this criterion for discontinuing IMP qualifies for both brodalumab and fumaric acid esters.
Fumaric acid esters: The subject must bring used, partly used, and unused IMP including empty packaging material at every site visit for compliance check. At every dispensing visit and at the end of treatment (visit 12), the subject must return all used, partly used, and unused IMP including empty packaging material to the site. ~~Fumaric acid esters: The subject must bring used/partly used and unused including empty packaging material of fumaric acid esters at every site visit. From visit 3 until visit 11, the unused fumaric acid esters tablets must be taken back home by the subjects for further use. At the end of treatment (visit 12) the subject must return all used/partly used and unused IMP including empty packaging material of fumaric acid esters.~~	Section 10.9.3	The schedule for returning used, partially used, and unused fumaric acid esters has been updated to every dispensing visit. This change is implemented to minimise the risk of any accidental usage of expired IMP.
11.4.2 Patient reported outcomes – **Efficacy and safety**	Section 11.4.2	The header is updated to clarify that the PROs address both efficacy (DLQI and PSI) and safety (eC-SSRS and PHQ-8)
The differences in response rates between treatment groups will be analysed using the Cochran-Mantel-Haenszel test **with stratification by** ~~and~~ weight **group** (≥100 kg or <100 kg).	Section 13.3.5	Clarification of the primary analysis.
A sensitivity analysis will be made where ineligible subjects randomised in error into the trial are excluded from the analysis.	Section 13.3.5	This sensitivity analysis is included to assess/limit inference based on ineligible subjects randomised in error into the trial.

Amendment 1 (12-Oct-2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The reason for the amendment is to implement requirements from the health authorities in Germany.

Substantial changes to the original protocol are provided in the table below. When applicable, original text is cited in quotation marks (‘’) with deletions as ~~strike-through~~ and additions in **bold**.

Substantial changes in Amendment 1	**Affected Section(s)**	**Rationale for change**
Sample size and analysis of primary endpoint updated. Endpoint structure updated 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 • PASI improvement (%) from baseline at Week 24 • ~~Static Physician’s Global Assessment (sPGA) scale score of 0 or 1 at Week 24~~ • Change from baseline at Week 24 in affected body surface area (BSA)’	Protocol summary Section 7 (Panel 3) Section 13.1 13.3.5(sample size) Section 13.3.4 (endpoints) Section 13.3.5 (analysis of primary endpoint)	To align with the health authorities request.
Extra secondary endpoint introduced: **‘Burden of symptoms assessed as the normalised area under the curve (AUC) of PSI from baseline to the last available assessment’**	Section 7 (Panel 3) Section 13.3.4	To align with the health authorities request.
Inclusion criterion no. 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.)’**	Section 9.2 Appendix 1	To avoid efficacy loss of oral contraceptive pills in case of subjects who may suffer from gastro-intestinal side effects.
Exclusion criterion no. 2:		

Substantial changes in Amendment 1	**Affected Section(s)**	**Rationale for change**
Previous or current ~~phototherapy~~ **PUVA (psoralens and ultraviolet A)** ~~therapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, etc).~~ Exclusion criterion no. 3: **'Have received phototherapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, tanning beds, etc. within 4 weeks of baseline'**	Protocol summary Section 9.3 Appendix 1	To accommodate the change in the local health authorities' interpretation of guidelines regarding phototherapy.
Exclusion criterion no. 6: 'Clinically significant abnormal ~~laboratory~~ values at screening **within assessments of biochemistry, urine, and haematology (such as differential blood count and platelets)** at the discretion of the investigator.'	Section 9.3 Appendix 1	To align with the side effects of Fumaderm® according to SmPC.
Exclusion criterion no. 7: 'Subjects with **any of the following laboratory abnormalities at screening:** a) Leukocyte cell count below 3×10^9/L or lymphocyte count below 0.7×10^9/L. **b) Aspartate aminotransferase (AST) or alanine transferase (ALT) > 2× ULN (upper level of normal limit).** **c) Absolute neutrophil count < 2× 10^9/L.** d) **Serum creatinine > ULN.**'	Protocol summary, Section 9.3, and Appendix 1	To align with the side effects of Fumaderm® according to SmPC.
Exclusion criterion no. 12: 'Subjects with a history of suicidal behaviour ~~(suicide attempt)'~~	Protocol summary, Section 9.3, and Appendix 1	To clarify that all subjects who have previously shown suicidal behaviour must be excluded, regardless of the behaviour having resulted in a suicide attempt or not.
Updated criteria for previous anti-psoriatic therapy: '~~All~~ previous anti-psoriatic **topical** treatment used by the subjects to treat their psoriasis vulgaris over the past 2 years prior to screening ~~must be topical therapy~~ (OTC topicals, topical non-steroid, topical steroids, topical combination etc.) ~~and~~ **must be recorded**. **Any history of phototherapy must also be recorded.** ~~' and must be recorded as such'~~	Section 10.5	Clarification that previous anti-psoriatic topical treatment will be recorded 2 years back in time, whereas any history of phototherapy must be recorded.
'**Subjects should be discontinued from treatment with fumaric acid esters if any of the following applies:** - **Blood creatinine levels > ULN.**	Section 10.8.2	To align with the side effects and discontinuation criteria according to the Fumaderm® SmPC.

Substantial changes in Amendment 1	**Affected Section(s)**	**Rationale for change**
- **Clinically significant changes in haematology values or confirmed proteinuria or haematuria not related to an ongoing urinary tract infection or renal calculus/nephrolith (at the discretion of the investigator).'**		
Clarification of the handling of fumaric acid esters. For fumaric acid esters, original kit cartons should be reused instead of new blank white kit cartons.	Section 10.9.1	The original kit cartons are not tamper sealed.
Clarification on drug accountability for IMP '~~Only used and empty packaging material of brodalumab must be returned by the subject. At end of treatment visit (visit 12) the subject should return all used/partly used and unused including empty packaging material of brodalumab.~~' **'The subject must bring only unused and empty packaging material of brodalumab at every dispensing visit (visit 2, 8, 9, 10, and 11). Used syringes should be discarded in disposal containers. At end of treatment (visit 12) the subject must return all unused IMP, empty packaging material and disposal containers containing used IMP.'**	Section 10.9.3	To emphasise that the subjects need to bring unused and empty packaging material of brodalumab at every dispensing visit.
Re-wording section regarding reporting of product complaints	Section 10.11	Clarification that product complaints related to the IMP itself and any device deficiency must be reported as product complaints. Clarification that critical complaints are subject to expedited reporting and that adverse events in connection with product complaints are to be reported as adverse events or serious adverse events as appropriate.
Updated guidance text regarding calculation of body surface area (BSA) to state that the blinded assessor will use the surface area of the subject's hand (palm and fingers) as a reference measurement to calculate the percentage of each body region that is affected by psoriasis. New BSA percentages introduced for head and neck (10%), upper extremities (20%), the trunk including the axillae and groin (30%), and lower extremities, including the buttocks (40%).	Section 11.4.1.3	To align with the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) standard and to make the psoriatic assessment more feasible.
Correction of blood volume drawn at each visit as well as the total volume of blood drawn during the trial	Section 11.6.1.2	Correction

Substantial changes in Amendment 1	**Affected Section(s)**	**Rationale for change**
Added paragraph to statistical analysis of patient reported outcomes on how to calculate the AUC for PSI total scores: '**The AUC for the PSI total score will be calculated for each subject**...'	Section 13.3.7	To accommodate the inclusion of the extra secondary endpoint related to PSI (see Panel 3).
Added information about patient insurance and coverage: 'LEO has **obtained** ~~taken out relevant~~ **a patient** insurance~~s~~ **as well as a travel accident insurance** covering the subjects in the present clinical trial in accordance with **national** ~~applicable~~ law~~s~~ and regulations. **A copy of the conditions of the patient insurance as well as of the accident insurance will be handed out to the subject with the informed consent'**	Appendix 4F	Clarification of insurance coverage and note to investigator/ trial staff about copy of insurance conditions is to follow the inform consent form.
Addition of DLQI instruction page, including information on scoring and how to interpret the results	Appendix 5B	Clarification regarding DLQI scoring and results interpretation.
Minor editorial and document formatting revisions	Throughout this document	Minor, have therefore not been summarised.

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List of abbreviations and definitions

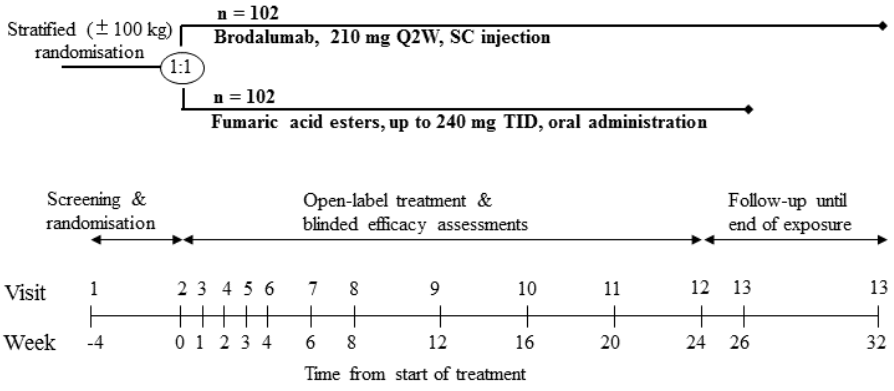
AESI	adverse events of special interest
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen

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

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

SmPC	summary of product characteristics
SOC	system organ class
sPGA	static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TID	three times a day
ULN	upper limit of normal
UV A/B	ultraviolet A/B
WBC	white blood cell count
WMA	World Medical Association

2 Protocol summary

Trial ID	LEO ID: LP0160-1327; EudraCT: 2016-003867-21
Title of trial	A phase 4 trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of fumaric acid esters in adults with moderate to severe plaque psoriasis
Trial rationale	The rationale is to demonstrate added benefit of brodalumab versus a selected systemic comparator in treatment of moderate to severe plaque psoriasis in Germany in subjects who have not previously received systemic treatment for psoriasis. Fumaric acid esters have been selected as the comparator because it is an established systemic treatment of psoriasis in Germany.
Primary objective	To compare the efficacy of subcutaneous injections of brodalumab to oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis who are naive to systemic treatment
Endpoints for the primary objective	*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 • PASI improvement (%) from baseline at Week 24 • Change from baseline at Week 24 in affected body surface area (BSA)
Trial design	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):  •

Main criteria for inclusion	• Men or women ≥18 years of age at the time of screening • Subjects with chronic plaque type psoriasis diagnosed for at least 6 months before randomisation • 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 • Subject has no known history of active tuberculosis • Subject has a negative test for tuberculosis taken at screening (negative QuantiFERON test) • Subject and/or subject's designee is/are capable of administering subcutaneous injections
Main criteria for exclusion	• Previous or current systemic treatment of plaque psoriasis or known contraindication for systemic therapy. • Previous or current PUVA (psoralens and ultraviolet A) therapy. • Washouts and non-permitted drugs: a) Have received phototherapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, tanning beds etc. within 4 weeks of baseline. b) Have had topical psoriasis treatment within 2 weeks of baseline (exceptions: bland emollients without urea or beta or alpha hydroxy acids). c) Have received any biologic immune modulating treatment used for indication other than psoriasis within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer. d) Have received any other systemic immune modulating treatment (including but not limited to oral retinoids, methotrexate, calcineurin inhibitors, oral or parenteral corticosteroids etc. used for indication other than psoriasis) within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer. • Subjects with any of the following laboratory abnormalities at screening: a) Leukocyte cell count below 3×10^9/L or lymphocyte count below 0.7×10^9/L. b) Aspartate aminotransferase (AST) or alanine transferase (ALT) > 2× ULN (upper level of normal limit). c) Absolute neutrophil count < 2×10^9/L. d) Serum creatinine > ULN. • History of depressive disorder within the last 2 years including current anti-depressive treatment. • Any positive finding in history of suicidal behaviour (e.g., 'actual suicide attempts', 'interrupted attempts', 'aborted attempts', or 'preparatory actions') based on the eC-SSRS questionnaire at screening or baseline. • Any positive finding in suicidal ideation of level 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the eC-SSRS questionnaire at screening or baseline. • A PHQ-8 score of ≥10 corresponding to moderate to severe depression at screening or baseline.
Investigational medicinal product(s)	Brodalumab: 210 mg brodalumab in 1.5 mL solution for subcutaneous injection (140 mg/mL). Each kit contains 2 syringes. Fumaric acid esters: 30 or 120 mg Fumaric acid tablets for oral administrations. Fumaderm® Initial package contains 40 tablets of 30 mg and Fumaderm® package contains 70 tablets of 120 mg.

Duration of treatment	Screening period up to 28 days, treatment period of 24 weeks, and follow-up period is 8 weeks for brodalumab and 2 weeks for fumaric acid esters (approximately 5 half-lifes for each).
Number of subjects	A maximum of 204 subjects will be randomly assigned to study treatment such that more than approximately 102 evaluable subjects complete the trial.
Number of trial sites	Approximately 30 clinical sites in Germany
Statistical methods	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 and weight (≥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. 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 analyzed using the Cochran-Mantel-Haenszel test. The trial is considered a success if superiority is confirmed for both primary endpoints.
Coordinating investigator	Ulrich Mrowietz, Prof. Dr. med.
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

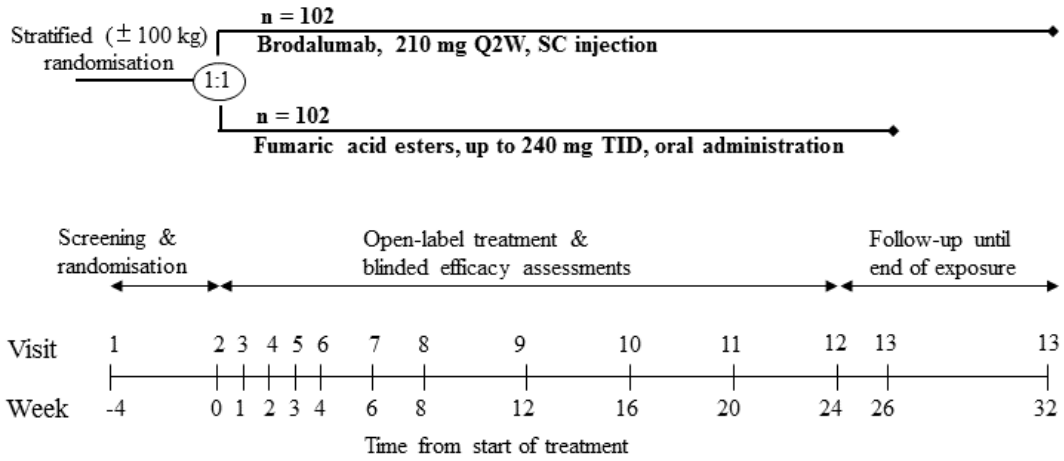
For submission to IECs and/or regulatory authorities, attach schedule of trial procedures (Panel 2)

3 Trial identification

EudraCT number: 2016-003867-21

4 Schematic of trial design

Panel 1 Trial design



n: number of subjects randomised to each arm; SC: subcutaneous; TID: three times a day; Q2W: every two weeks (in accordance with the label, the brodalumab regimen includes an additional loading dose one week after the first administration)

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												

	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.

3) Subjects, who are withdrawn from the trial or discontinues trial treatment for any reason, should attend an early termination visit as soon as possible after last dose to have all early termination assessments performed. All mandatory assessments applicable for an early termination visit are marked with an asterix (*). If a subject discontinues trial treatment or withdraws at a visit, then all mandatory assessments for an early termination visit must be performed at this particular visit.

4) Follow-up visit should be conducted no sooner than approximately 5 half-lifes after the last administration of investigational medicinal product. Hence,
- at 8 weeks (±3 days) after Week 24 or early termination visit for subjects allocated to brodalumab; and
- at 2 weeks (±3 days) after Week 24 or early termination visit for subjects allocated to fumaric acid esters.
Additional follow-up visit(s) should be performed only in case an AE is ongoing at the initial follow-up visit and is either a non-serious AE classified as possibly or probably related to investigational medicinal product or an SAE. No data will be collected at the additional follow-up visit(s). Where the (sub)investigator considers it appropriate, any additional follow-up visit(s) may be performed as a telephone contact.

5) All visit-dates should be scheduled relative to the baseline visit, except for the follow-up visit which should be scheduled relative to the date of end of treatment visit (captured at Week 24 or at an early treatment withdrawal visit) and the investigational medicinal product (see note 4).

6) Informed consent must be signed both by subject and (sub)investigator (medically qualified) before any trial related procedures are carried out.

7) Re-evaluation of in-/exclusion criteria, including review of results from the central laboratory of screening samples.

8) At screening, all subjects will receive information that if they are randomised to brodalumab they will have to self-administer the subcutaneous injections. The subjects must confirm that he/she or the subject's designated person will be able to administer the subcutaneous injections that randomisation to brodalumab would entail.

9) The 2 first administered brodalumab doses, at baseline and Week 1, 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, IMP should be administered at home by subject or the subject's designated person (subcutaneous injection if randomised to brodalumab and oral administration if randomised to fumaric acid esters).

10) The DLQI should be completed by the subject prior to all other trial procedures and the electronic self-rated version, columbia-suicide severity rating scale (eC-SSRS) and the patient health questionnaire-8 (PHQ-8) should be completed after all other assessments have been performed.

11) Serum beta hCG test must be done in female subjects of childbearing potential (must also be done at visits after screening if a urine test is positive for pregnancy).

12) Sodium, potassium, magnesium, bicarbonate, albumin, blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin, direct bilirubin, Alk phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP).

13) RBC (red blood cell count), haemoglobin, haematocrit, platelets, white blood cell count (WBC), and differential (absolute count and %): neutrophils, lymphocytes, monocytes, eosinophils and basophils.

14) Specific gravity, pH, occult blood, protein, glucose, leucocyte esterase, ketones, and urine pregnancy test.

15) AEs will be collected from time of first trial related activity after the subject has signed the informed consent form. Pre-existing conditions identified as a result of the screening procedures should be reported as medical history.

6 Introduction and rationale

6.1 Psoriasis vulgaris

Psoriasis is a chronic inflammatory disorder associated with significant morbidity and mortality that occurs in approximately 2% of the population worldwide (Augustin et al. 2010, Gelfand et al. 2007, Rachakonda et al. 2014). It is a chronic polygenic inherited disease of uncontrolled cutaneous inflammation that manifests, in the majority of subjects, as plaque type psoriasis, clinically seen as sharply demarcated, elevated, scaling, erythematous plaques located predominantly on the scalp, extensor sides of elbows and knees, and the sacral region (Griffiths and Barker 2007, Langley et al. 2005, Griffiths et al. 2007). These skin lesions can be painful, pruritic, and may cause significant emotional and physical discomfort (Dubertret et al. 2006). In addition to skin manifestations, psoriasis is associated with multiple comorbidities, for instance arthritis, cardiovascular disease, and psychiatric conditions such as depression and anxiety (Griffiths and Barker 2007, Gisondi et al. 2007).

The majority of subjects with psoriasis has mild to moderate disease and can be treated with topical therapies (Menter et al. 2009). In subjects with moderate to severe psoriasis, phototherapy or systemic treatment, including biologic agents, are recommended (possibly adjunct to topical treatment) (Menter et al. 2009, Nast et al. 2012).

6.2 Experience with investigational medicinal product

6.2.1 Brodalumab

Brodalumab is a recombinant fully human monoclonal immunoglobulin IgG2-antibody that binds with high affinity to human interleukin 17 receptor A (IL-17RA). Brodalumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy in EU, Japan, and USA.

Blocking IL-17RA inhibits IL-17 cytokine-induced responses and results in reduced or normalised inflammation of the skin in subjects with psoriasis. Ixekizumab and secukinumab share the same treatment target, by inhibiting the biological activity of IL-17A. But by blocking IL-17RA (the receptor), brodalumab also inhibits the biological activity on this receptor by other interleukins in the IL-17 family (namely, IL-17F, IL-17A/F heterodimer, and IL-17E also known as IL-25) (Gooderham et al. 2015).

The dose regimen for brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients is 210 mg by subcutaneous injection at Weeks 0, 1, and 2, and then 210 mg every 2 weeks (Q2W).

Brodalumab efficacy:

The efficacy of brodalumab for the treatment of psoriasis has been confirmed in 3 pivotal phase 3 placebo-controlled clinical trials, in which 2 of the trials also included an ustekinumab comparator arm. The pivotal trials enrolled subjects of 18 to 75 years of age with stable moderate to severe plaque psoriasis diagnosed at least 6 months before the first dose of investigational medicinal product (IMP). At baseline, the enrolled subjects had plaque type psoriasis with Psoriasis Area and Severity Index (PASI) score of at least 12, static Physician's Global Assessment (sPGA) score of at least 3, and at least 10% body surface area (BSA) involvement. In all 3 trials, brodalumab was superior to placebo ($p<0.001$) for the co-primary endpoints (PASI 75 and sPGA of 0 or 1) as well as the secondary endpoints at Week 12 (PASI 100, sPGA of 0, and PSI).

At Week 12, brodalumab 210 mg treated patients achieved response rates of 86% for PASI 75, 80% for sPGA0/1, and 44% for PASI 100 (AMAGINE-2 trial, EU summary of product characteristics (SmPC)).

Brodalumab safety:

During the brodalumab development programme, the most commonly reported adverse reactions in brodalumab-treated subjects included arthralgia, headache, fatigue, diarrhoea, and oropharyngeal pain (see reference safety information in Appendix 6). There were no very common adverse reactions.

During the brodalumab development programme, important identified and important potential risks have been identified to be further investigated after launch. These include serious infections, major adverse cardiovascular events (MACE), and malignancies. These important identified and important potential risks originate from the product's immunomodulatory activity and are shared by biologics in general. Furthermore, suicidal ideation and behaviour (SIB) have been identified as an important potential risks based on rare events occurring during the brodalumab development programme. A causal relationship between brodalumab treatment and SIB has not been established, and there is no known mechanism of action by which brodalumab would be associated with triggers of self-injurious or suicidal behaviour, such as depression, mood disorders, and affective disorders or behaviours (Chiricozzi et al. 2016).

During the 12-week placebo-controlled trial period in plaque psoriasis, infections were reported in 25.4% of patients treated with brodalumab compared with 23.4% of patients treated with placebo. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, and influenza, which did not necessitate treatment discontinuation. Serious infections occurred in 0.5% of

patients treated with brodalumab and in 0.2% of patients treated with placebo. Higher rates of fungal infections, primarily non-serious skin and mucosal candida infections were observed in brodalumab patients compared to placebo patients, 1.8% versus 0.9%, respectively.

Antibodies to brodalumab developed in 2.7% (122/4461) of patients treated with brodalumab for up to 52 weeks in psoriasis clinical trials (0.3% of these patients had anti-brodalumab antibodies at baseline). Of these patients, none had neutralising antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with anti-brodalumab antibody development.

For further details, please see the EU SmPC for Kyntheum®.

6.2.2 Fumaric acid esters

Fumaric acid esters have been used to treat psoriasis since 1959. An oral preparation containing dimethyl fumarate and monoethyl fumarate salts, Fumaderm®, is licensed in Germany for treating adults with moderate to severe plaque psoriasis in whom topical therapy is not effective. It is available in two strengths, Fumaderm® Initial containing 30 mg dimethyl fumarate per tablet and Fumaderm® containing 120 mg dimethyl fumarate per tablet.

Systemic therapy with fumaric acid esters is based on an established dosing scheme with a gradual increase to improve tolerability, especially with regards to gastrointestinal side effects. The dose is adjusted on an individual basis according to the response to therapy and the occurrence of side effects.

Fumaric acid esters efficacy:
The response rate for fumaric acid esters is expected to be lower than for brodalumab. In a systemic review, the rate is reported to be on par with methotrexate (Smith 2017). Methotrexate (MTX) for 24 weeks is reported to achieve at least PASI 75 in 51% of patients (Mrowietz and Warren et al. 2017).

In the European Consensus, fumaric acid esters and MTX are considered slow-acting drugs and the endpoint should therefore be measured between Week 16 and Week 24 (Mrowietz and Szepietowski et al. 2017). In most reports on fumaric acid esters, clinical effects are from open studies and only few studies have been performed using evidence based criteria (Nast et al. 2012). For fumaric acid esters, the S3 guideline estimates a PASI 75 in 50 to 70% of patients at Week 16 (Nast et al. 2012). However, in a trial comparing fumarates versus MTX, only 39% of evaluable patients in the fumarates group had a ≥75% reduction in PASI at Week 20 (the rate was 32% in the MTX group) (Fallah Arani et al. 2011).

In an observational study, mean PASI scores were reduced from 19.84 to 7.35 after 12 months (63% improvement) (Walker et al. 2014), and it was noted that several multi-centre trials had demonstrated the efficacy of fumaric acid esters in psoriasis with a PASI 75 in about 50% of patients.

Fumaric acid esters safety:
Very common adverse reactions include flushing, diarrhoea, and mild forms of lymphocytopenia and leukocytopenia.

Common adverse reactions include gastrointestinal disorders (bloating, cramps, and flatulence), severe forms of lymphocytopenia, and transient eosinophilia.

Trial treatment discontinuation criteria specific to subjects in the fumaric acid esters group, are provided in Section 10.8.2.

For further details, see the SmPC for Fumaderm®.

6.3 Trial rationale

The rationale is to demonstrate added benefit of brodalumab versus a selected systemic comparator in treatment of moderate to severe plaque psoriasis in Germany in subjects who have not previously received systemic treatment for psoriasis.

Fumaric acid esters have been selected as the comparator because it is an established systemic treatment of psoriasis in Germany.

6.4 Justification for dose

6.4.1 Brodalumab

210 mg 2QW brodalumab by subcutaneous injections is the recommended dose in the approved label. In the clinical development programme, this dose regimen demonstrated improved skin clearance across the key efficacy endpoints of PASI 75 response, PASI 100 response, and sPGA success (0 or 1), relative to the comparator ustekinumab.

The 210 mg brodalumab dose has been established as a well-tolerated dose with few and manageable AEs.

6.4.2 Fumaric acid esters

Systemic therapy with fumaric acid esters is based on an established dosing scheme with a gradual increase in dosage to improve tolerability, especially with regards to gastrointestinal

side effects. The dose is adjusted on an individual basis according to the response to therapy and the occurrence of side effects, as described in the label.

6.5 Benefit-risk assessment

A positive benefit-risk assessment of brodalumab and fumaric acid esters has been granted by relevant regulatory authorities via the market authorisation for each IMP in Germany.

Further details on benefits and risks with each IMP are described in Section 6.2.

6.6 Ethical considerations

The IMPs will be used according to the label in the indicated population, and therefore no ethical concern has been identified for this trial. The subjects will be followed using all relevant safety assessments for the duration of the trial.

SIB, including completed suicide, has been reported in patients treated with brodalumab. The majority of patients with SIB had a history of depression and/or suicidal behaviour. A causal association between treatment with brodalumab and an increased risk of SIB events has not been established, and there is no known mechanism of action by which brodalumab would be associated with triggers of self-injurious or suicidal behaviour, such as depression, mood disorders, and affective disorders or behaviours (Chiricozzi et al. 2016).

Subjects are monitored for depression and SIB by the Patient Health Questionnaire-8 (PHQ-8) and the electronic self-rated version of the Columbia-Suicide Severity Rating Scale questionnaires (eC-SSRS). The investigator must discontinue subjects from trial treatment in case of any positive finding of suicidal ideation of level 4 or 5, any positive finding in history of suicidal behaviour, or a PHQ-8 score ≥15 corresponding to moderately severe to severe depression (see Sections 11.4.2.2 and 11.4.2.3 for description of the PHQ-8 and eC-SSRS assessments).

Subjects with a recent history of depression (within 2 years), any positive finding of suicidal ideation (eC-SSRS level 4 or 5), or any positive finding in history of suicidal behaviour (PHQ-8 score ≥10) are excluded from the trial.

7 Trial objectives and endpoints

Panel 3 Objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of subcutaneous injections of brodalumab to oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis who are naive to systemic treatment.	*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 • PASI improvement (%) from baseline at Week 24 • Change from baseline at Week 24 in affected body surface area (BSA)
Secondary objectives	
To compare the effect on patient reported outcomes of subcutaneous injections of brodalumab to oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis.	*Secondary endpoints:* • 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
To evaluate the safety and tolerability of subcutaneous injections of brodalumab versus oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis.	*Secondary point:* • Frequency of AEs and SAEs by preferred term
Exploratory objective	
To explore the effect of subcutaneous injections of brodalumab versus oral administration of fumaric acid esters on nail involvement in subjects with moderate to severe plaque psoriasis and a NAPSI score of at least 6 on target nail.	*Other endpoint:* • Change from baseline at Week 24 in Nail Psoriasis Severity Index (NAPSI) total score

Endpoints and analyses hereof are further described in Section 13.3

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)

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:

a. Have received phototherapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, tanning beds etc.) within 4 weeks of baseline.

b. Have had topical psoriasis treatment within 2 weeks of baseline (exceptions: bland emollients without urea or beta or alpha hydroxy acids).

c. Have received any biologic immune modulating treatment used for indication other than psoriasis within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer.

d. Have received any other systemic immune modulating treatment (including but not limited to oral retinoids, methotrexate, calcineurin inhibitors, oral or parenteral corticosteroids etc. used for indication other than psoriasis) within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer.

4. Clinically important active infections or infestations, chronic, recurrent or latent infections, infestations or immunocompromised (e.g. HIV).

5. Presence of significant uncontrolled cerebral, cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematologic, neurologic, or neuropsychiatric disorders.

6. 'Clinically significant abnormal values at screening within assessments of biochemistry, urine, and haematology (such as differential blood count and platelets) at the discretion of the investigator.'

7. Subjects with any of the following laboratory abnormalities at screening:

   a. Leukocyte cell count below 3×10^9/L or lymphocyte count below 0.7×10^9/L.

   b. Aspartate aminotransferase (AST) or alanine transferase (ALT) > 2× ULN (upper level of normal limit)

   c. Absolute neutrophil count < 2×10^9/L

   d. Serum creatinine > ULN

8. Subjects with severe gastrointestinal diseases including, but not limited to, ventricular and duodenal ulcers.

9. Subject with a known history of Crohn's disease or history of psoriatic arthritis with a need for treatment.

10. Planned surgery, which in the opinion of the investigator would influence the planned treatment of the IMP.

11. History of depressive disorder within the last 2 years including current anti-depressive treatment.

12. Any positive finding in history of suicidal behaviour (e.g., 'actual suicide attempts', 'interrupted attempts', 'aborted attempts', or 'preparatory actions') based on the eC-SSRS questionnaire at screening or baseline.

13. Any positive finding in suicidal ideation of level 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the eC-SSRS questionnaire at screening or baseline.

14. A PHQ-8 score of ≥10 corresponding to moderate to severe depression at screening or baseline.

15. History of cancer:

    a. Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.

    b. Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.

16. Known or suspected hypersensitivity to component(s) of the IMPs.

17. Current participation in any other interventional clinical trial, ending another interventional clinical trial less than 4 weeks prior to screening visit, or receiving other investigational agents (based on interview of the subject).

18. Subjects who have received treatment with any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration) within the last 4 weeks prior to screening visit.

19. Previously enrolled in this clinical trial.

20. In the opinion of the (sub)investigator, the subject is unlikely to comply with the clinical trial protocol (e.g. due to alcoholism, drug addiction or psychotic state).

21. Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a CRO involved in the trial.

22. Subjects under guardianship, hospitalised in a public or private institution, for a reason other than the research, or subject deprived of freedom.

23. Female subjects who are pregnant or breastfeeding.

24. Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this trial to be detrimental to the subject.

9.4 Subject enrolment

Trial participation begins once written informed consent is obtained (see Appendix 4B for details on the informed consent process). Once informed consent is obtained, a subject identification number (subject ID) will be assigned by a central interactive web response system (IWRS) and the screening evaluations to assess eligibility criteria may begin. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. A master log of all consented subjects will be maintained at the trial site.

Screening failures are defined as subjects who consent to participate in the trial but are not subsequently randomly assigned to trial treatment. A minimal set of screening failure information is required to ensure a transparent reporting that meets the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (Schulz et al. 2010) and to respond to queries from regulatory authorities. Minimal information includes demography, screening failure details, eligibility criteria, and any AEs and SAEs. Follow up of SAEs must be carried out according to Section 12.5.

Individuals who do not meet the criteria for participation in this trial (screening failures) may not be re-screened. However, if the reason for screening failure is administrative and not due to the subject failing to meet the eligibility criteria, re-screening may be permitted (this will require approval by the sponsor's medical expert after thorough review of all data from the original screening visit in the electronic case report form (eCRF). Individuals who are allowed rescreening will get a new subject ID (old subject ID must be provided in a comment in the eCRF).

The investigator will maintain a list of all randomised subjects at the trial site including each subject's identity, date of enrolment and corresponding subject ID so that any subject may be identified if required for any reason. The list must not be copied or retained by LEO.

9.5 Discontinuation

9.5.1 Discontinuation rules and replacement

A subject may withdraw from trial or from treatment at any time (prior to first dose or during treatment period) at his/her own request. A subject may be withdrawn at any time at the discretion of the investigator. Discontinued subjects will not be replaced.

Medical reasons for discontinuation of IMP are given in Section 10.8.1.

9.5.2 Early termination assessments

Subjects who are withdrawn or discontinues trial treatment for any reason, should attend an early termination visit as soon as possible after last dose, to have all early termination assessments performed. Early termination assessments are identical to the assessments scheduled for the end of treatment visit (Week 24).

If a subject discontinues IMP or withdraws from trial at a site visit, then this visit should be converted into an early termination visits and all applicable early termination assessments must be performed. The early termination is captured in the eCRF as an unscheduled visit by selecting the early termination option.

The subjects should attend a follow-up visit 8 weeks after the early termination visit for brodalumab or 2 weeks after the early termination visit for fumaric acid esters. The investigator will review and follow up any AEs according to Section 12.5.

If a subject withdraws from the trial, he/she may request destruction of any samples taken that are not tested, and the investigator must document this in the site's trial records.

Reason(s) for discontinuation must be recorded in the medical records and the eCRF (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, other).

9.5.3 Lost to follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled/unscheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fail to return to the trial site for a required visit:

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the

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.

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 4 Identification of investigational medicinal products

Finished product brand name	Dosage form	Concentration and formulation	Manufacturer
Kyntheum®	Each pre-filled syringe contains 210 mg of brodalumab in 1.5 mL solution for subcutaneous injection (140 mg/mL)	Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: - Proline - Glutamate - Polysorbate 20 - Water for injections	Amgen Inc.
Fumaderm® Initial	Tablets for oral use	Each tablet contains the following fumaric acid esters: - 30 mg dimethyl fumarate, - 67 mg ethyl hydrogen fumarate calcium salt, - 5 mg ethyl hydrogen fumarate magnesium salt, - 3 mg ethyl hydrogen fumarate zinc salt. Formulated as white gastro-resistant tablets with following excipients: Croscarmellose sodium, talc, magnesium stearate, titanium dioxide (E171), methacrylic acid - methyl methacrylate copolymer (1:1), methacrylic acid - ethyl acrylate copolymer (1:1), macrogol 6000, simethicone, povidone, triethyl citrate, microcrystalline cellulose, and highly dispersed silicon dioxide.	Biogen GmbH
Fumaderm®	Tablets for oral use	Each tablet contains the following fumaric acid esters: - 120 mg dimethyl fumarate, - 87 mg ethyl hydrogen fumarate calcium salt, - 5 mg ethyl hydrogen fumarate magnesium salt, - 3 mg ethyl hydrogen fumarate zinc salt. Formulated as blue gastro-resistant tablets with the following excipients: Croscarmellose sodium, talc, magnesium stearate, titanium dioxide (E171), indigo carmine (E132), methacrylic acid - methyl methacrylate copolymer (1:1), methacrylic acid - ethyl acrylate copolymer (1:1), macrogol 6000, simethicone, povidone, triethyl citrate, microcrystalline cellulose, and highly dispersed silicon dioxide.	Biogen GmbH

Panel 5 Brodalumab dose scheme

Route of administration	Subcutaneous injections
Dosing range	210 mg
Dosing frequency	Weekly for the initial 3 doses and hereafter Q2W up to Week 24:

Visit	V2	V3	V4	V5	V6	V7	V8	-	V9	-	V10	-	V11	-	V12
Week	0	1	2	3	4	6	8	10	12	14	16	18	20	22	24
Day	0	7	14	21	28	42	56	70	84	98	112	126	140	154	168
Dosing	**x**	**x**	**x**	**-**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**-**

Daily maximum	210 mg (1 dose) at scheduled treatment days
Time of day for dosing	Not defined

Fumaric acid esters

Fumaric acid esters tablets will be administered orally at home following the dose scheme in Panel 6. The first dose should be taken in the evening at day of the baseline visit (Day 0, visit 2).

NOTE: The last tablet of fumaric acid esters initial (30 mg dimethyl fumarate tablets) should be taken in the evening of Day 19. Hereafter, the regimen must be shifted to fumaric acid esters, 120 mg dimethyl fumarate tablets, starting with 1 tablet once daily in the evening from Day 20 to Day 27 (Week 3 regimen, see Panel 6).

Each subject will only receive one package of Fumaderm® Initial and this package will be used to up-titrate the subject to tolerate Fumaderm®, for which individual dosing can be performed. Experience has shown that the initial therapeutic effects with fumaric acid esters can be expected from Week 4 to Week 6 (see SmPC for Fumaderm®).

The maximum daily dosage of 3×2 tablets must not be exceeded, and in many cases, administration of the maximum daily dose is not required as maintenance dose.

The fumaric acid esters are gastro-resistant tablets and must be swallowed whole with plenty of liquid, during or immediately after meals. Generally, it is important to ensure that enough liquid is drunk over the course of the day (1½ to 2 litres).

Panel 6 Fumaric acid esters dose scheme

Route of administration		Oral administration	
Dosing range		From 30 to 240 mg dimethyl fumarate per oral administration	
Dosing frequency		1 to 3 times daily during titration with 30 and 120 mg dimethyl fumarate tablets (see scheme). After 9 weeks, the dose can be up to 2×120 mg 3 times a day:	
		30 mg dimethyl fumarate (No. of tablets per day)	120 mg dimethyl fumarate (No. of tablets per day)
	Week 0	0-0-1	-
	Week 1	1-0-1	-
	Week 2	1-1-1	-
	Week 3	-	0-0-1
	Week 4	-	1-0-1
	Week 5	-	1-1-1
	Week 6	-	1-1-2
	Week 7	-	2-1-2
	Week 8	-	2-2-2
Daily maximum		720 mg (3 times 2 tablets)	
Time of day for dosing		Morning, noon and evening	

10.2.2 Precautions/overdose

Brodalumab: Doses up to 700 mg intravenously have been administered in clinical studies with no evidence of dose limiting toxicity. In the event of an overdose, the subject should be monitored and treated symptomatically, and supportive measures instituted at the discretion of the investigator.

Fumaric acid esters: For special warnings and precautions for use, please refer to the SmPC for Fumaderm® Initial/Fumaderm®. There are no known therapeutic interventions to enhance elimination of fumaric acid esters nor is there a known antidote. In the event of overdose, the subject should be monitored and treated symptomatically, and supportive measures instituted at the discretion of the investigator.

10.3 Treatment assignment

10.3.1 Randomisation

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised to receive treatment with either brodalumab or

fumaric acid esters. Treatment assignment will be pre-planned according to a computer generated randomisation schedule in a 1:1 ratio.

Randomisation will be with stratification by body weight (<100 kg or ≥100 kg) using an IWRS system.

Each investigator site will be supplied with sufficient IMPs for the trial on an ongoing basis controlled by the IWRS.

10.3.2 Blinding

This is an open-label trial. Due to potential dose adjustments needed for subjects randomised to fumaric acid esters, the investigator and subject will need to know the treatment allocated. Furthermore, applying double dummy blinding is considered too demanding from a subject perspective, since home treatment would then involve both subcutaneous injections and oral administrations at varying time points.

Blinded assessments of PASI, sPGA, BSA, and NAPSI will be performed. Blinded assessors who perform the assessment must be medically qualified physicians trained in the assessments. During the assessments, the subjects will be instructed not to reveal the treatment allocation and the blinded assessor must avoid asking questions that could reveal treatment allocation. All involved personnel will be instructed to desist from any discussions regarding safety, efficacy, treatment allocation of the study and subjects in the presence of the blinded assessor. In case a blinded assessor becomes unblinded, a new assessor should be appointed to perform the assessments of the subject going forward.

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 blinded assessor performs the baseline and end of treatment visit (Week 24) assessments, where the co-primary endpoints are assessed. If necessary, trial visits may be rescheduled within the specified window to accommodate when the specific assessor will be available.

10.3.3 Emergency unblinding of individual subject treatment

Not applicable. This is an open-label trial.

10.4 Concomitant medication and procedures

Concomitant medication is defined as any medication used by a subject during the clinical trial apart from the IMP.

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

10.5 Previous anti-psoriatic therapy

Previous anti-psoriatic topical treatment used by the subjects to treat their psoriasis vulgaris over the past 2 years prior to screening (OTC topicals, topical non-steroid, topical steroids, topical combination, etc.) must be recorded. Any history of phototherapy must also be recorded.

10.6 Prohibited medication and procedures

The use of medications or procedures as defined in the exclusion criteria, is not permitted during the trial.

Subjects who require use of a prohibited medication should be discontinued from IMP. The following concomitant therapies or treatments are prohibited throughout trial participation:

1. Any phototherapy: ultraviolet A light therapy with or without psoralen, ultraviolet B light therapy, excimer laser etc.
2. Any biologic immune modulator, including but not limited to etanercept, anakinra, adalimumab, infliximab, ustekinumab, and IL-17 inhibitors
3. Any systemic therapy for psoriasis and other indications, including but not limited to oral retinoids, methotrexate, systemically administered calcineurin inhibitors (e.g. ciclosporin), or oral or parenteral corticosteroids
4. Any topical therapy for psoriasis:
    a. Topical steroids of any strength
    b. Other topical therapies for psoriasis (e.g., calcineurin inhibitors and vitamin D analogues), with the exception that bland emollients without urea or beta or alpha hydroxy acids are allowed
    c. Shampoos with steroids

10.7 Rescue treatment

No rescue medication is allowed. It will be at the discretion of the investigator to ensure treatment of subjects who discontinue the trial/IMP or ensuring that the subjects are referred to other physician(s) according to standard practice.

10.8 Dose modification and investigational medicinal product discontinuation rules

Please refer to Section 9.5 for general procedures related to IMP discontinuation. Medical reasons for IMP discontinuation are described below.

10.8.1 Reason for discontinuation of investigational medicinal product

Subjects must be **discontinued** from IMP in the event of:

- Anaphylactic reaction or other severe systemic reaction to IMP.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Diagnosis of a malignancy during the trial, excluding carcinoma in situ of the cervix, or localised squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immuno-compromised status.
- Severe laboratory abnormalities:
  a) ALT and/or AST values >3× ULN with total bilirubin >2× ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
  b) Confirmed AST and/or ALT >5× ULN (for more than 2 weeks).
- If a subject is found to have any suicidal behaviour (actual suicide attempts, interrupted attempts, aborted attempts, or preparatory actions) or any suicidal ideation of level 4 (active suicidal ideation with some intent to act, without specific plan) or level 5 (active suicidal ideation with specific plan and intent) on any eC-SSRS assessment, the subject must be discontinued and referred to a mental health professional.
- If a subject is found to have a PHQ-8 score of ≥15, corresponding to moderately severe to severe depression, the subject must be withdrawn and referred to a mental health professional.

10.8.2 Specific to subjects allocated to fumaric acid esters

Progressive multifocal leukoencephalopathy (PML) cases have occurred with fumaric acid esters and other products containing fumarates in the setting of moderate to severe prolonged

lymphopenia. PML is an opportunistic infection caused by John-Cunningham virus, which may be fatal or result in severe disability. Hence:

- If the lymphocyte count drops below 0.7×10^9/L, the dose should be halved. If during a follow-up check **after 4 weeks** the lymphocyte count remains below this value, then treatment with fumaric acid esters must be discontinued.
- If the lymphocyte count drops below 0.5×10^9/L, treatment with fumaric acid esters must be discontinued.
- If the leukocyte cell count drops below 3×10^9/L, treatment with fumaric acid esters must be discontinued immediately.
- Subjects should be discontinued from treatment with fumaric acid esters if any of the following applies:
  a) Blood creatinine levels > ULN.
  b) Clinically significant changes in haematology values or confirmed proteinuria or haematuria not related to an ongoing urinary tract infection or renal calculus/nephrolith (at the discretion of the investigator).

10.9 Treatment logistics and accountability

10.9.1 Labelling and packaging of investigational medicinal product

The labelling of IMPs will be in accordance with Annex 13, local regulations and trial requirements. Details are provided below:

Brodalumab
Brodalumab will be packaged in individually numbered kits. The brodalumab pack size includes 2 pre-filled syringes packed in blank white cartons.

Each syringe will be labelled with a single panel label that allows the level of fluid in the syringe to be visible.

Each kit carton will be labelled with one single panel label and tamper sealed.

Fumaric acid esters
Fumaric acid esters will be packaged in individually numbered kits. The Fumaric acid esters pack sizes include either 40 tablets per pack (Fumaderm® Initial; 4 blister packs each containing 10 tablets) or 70 tablets per pack (Fumaderm®; 7 blister packs each containing 10 tablets) and both types are packed in original commercial cartons.

Each blister will be labelled with a single panel label.

Each carton will be labelled with a single panel label and tamper sealed.

10.9.2 Storage of investigational medicinal products

At clinical trial site
All LEO supplied IMPs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

Brodalumab must be stored at 2-8°C (protected from light) and fumaric acid esters at ≤25°C at the site. The temperature during storage must be monitored by a calibrated, stationary and continuously recording system. Minimum requirement is a calibrated min/max thermometer.

A temperature log must be kept to document the storage within the right temperature interval. Temperature should be checked at least every working day.

Transport from site to subject's home
The subjects' randomised to brodalumab treatment will receive a cooler bag for transportation of brodalumab from site home of the subject.

10.9.3 Drug accountability

The investigator is fully responsible for the accountability of IMPs at the trial site by continuously documenting all transactions using IWRS.

Dispensing of IMPs may be delegated, e.g. to a hospital pharmacy, as locally applicable.

Fumaric acid esters: The subject must bring used, partly used, and unused IMP including empty packaging material at every site visit for compliance check. At every dispensing visit and at the end of treatment (visit 12), the subject must return all used, partly used, and unused IMP including empty packaging material to the site.

Brodalumab: The subject must bring only unused and empty packaging material of brodalumab at every dispensing visit (visit 2, 8, 9, 10, and 11). Used syringes should be discarded in disposal containers. At end of treatment (visit 12), the subject must return all unused IMP, empty packaging material, and disposal containers containing used IMP.

Returned IMP (used/partly used or unused IMP including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated IMP. At end of treatment (visit 12), disposal containers and cooler bags must be returned by the subject.

All IMPs supplied by the contract manufacturing organisation (CMO) on behalf of LEO must be returned to the CMO. Prior to their return, they must be fully accounted for by the monitor with the help of the person responsible for dispensing the IMPs. Accountability must be documented by using drug accountability forms. The CRA will only do drug accountability by verifying the drug accountability performed by the investigator or designated site staff.

IMPs may be returned from the trial site either to the CMO directly or via the LEO Pharma A/S affiliate or CRO responsible for running the clinical trial.

10.9.4 Investigational medicinal product destruction

Used and unused IMP(s) will be destroyed by the CMO according to approved procedures.

10.9.5 Treatment compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject treatment compliance.

Treatment compliance will be assessed by monitoring of drug accountability, see Section 10.9.3, and from interviewing the subjects.

If a subject is found to be non-compliant, the (sub)investigator should remind the subject of the importance of following the instructions given, including taking the IMPs as prescribed. Compliance/non-compliance and the reason for it must be recorded in the eCRF.

The date of first dose of IMP (baseline visit/Day 0) must be recorded in the eCRF.

For subsequent visits in the treatment phase, the investigator must record the latest date of IMP administration and total daily dose relative to the specific visit in the eCRF.

For subjects randomised to brodalumab: The investigator must ask the subject about each dose and whether the full dose was injected. This should be recorded in the eCRF as either full dose, partial dose, or no dose injected. If either partial or no dose was injected, a reason for not injecting the full dose must be provided.

For subject randomised to fumaric acid esters: During the treatment phase (from baseline to Week 24), the investigator must record the prescribed total daily dose of fumaric acid esters in the eCRF. Based upon the effect and adverse events reported by the subject, the investigator should make individual dose adjustment. The investigator must also record whether or not the subject follows the prescribed dosing instruction. Reason for deviation from prescribed dose instructed to the subject must be recorded in the eCRF (AE, optimal

effect, or other). If the reason for deviation is an AE, this AE should be reported according to Section 12.2.

10.10 Provision for subject care following trial completion

To ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

10.11 Reporting product complaints

Any defects or issues with the IMP as well as any device deficiency (including malfunctions, use errors, and inadequate labelling) must be reported to Global Pharmacovigilance, LEO on the trial-specific (paper) Complaint Form within 3 days of first knowledge.

Critical complaints (defined as any issue, defect, or device deficiency that has or potentially could have a serious impact for the subject [e.g., SAE or large particles in the syringe]) must be reported to Global Pharmacovigilance, LEO within 24 hours.

Complaint forms should contain a detailed description of the defect, issue, or device deficiency, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the IMP or due to a device deficiency will be reported by the investigator as described in Section 12.2.

Refer to the pharmacy manual for information on how to update the kit status in the IWRS.

During the investigation of the product complaint, the device must be stored at labelled conditions unless otherwise instructed; the trial site will be notified whether the device needs to be returned for further investigation or may be destroyed.

Global Pharmacovigilance, LEO contact information for reporting product complaints:

Fax number: +45 7226 3287

E-mail address: drug.safety@leo-pharma.com

11 Trial schedule and assessments

11.1 Overview

Overview of the assessments and procedures applicable to each visit is outlined in Panel 2. Specific details for each assessment and procedure are described in the following sections.

During the course of the trial from screening to the follow-up visit (Week 26/32), unscheduled visits may be needed. It is at the discretion of the investigator to decide which assessments should be performed at an unscheduled visit.

Assessments/procedures at any trial visit must be performed in the following order:

- ePRO: DLQI must be completed by the subject prior to all other trial procedures
- Investigator-blinded assessments (performed only by adequately trained investigators; the same investigator should perform all the evaluations for a given subject throughout the entire trial period)
- Safety and laboratory assessments
- Other assessments and procedures
- ePRO: eC-SSRS and PHQ-8 should be completed by the subject after AE reporting has been completed. Investigator must review the questionnaires and take action, if required, before subject is sent home (see Section 11.4.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

At screening (visit 1) the following demographic details will be recorded:

- Month and year of birth
- Sex
- Race: American Indian or Alaska Native; Asian, Black or African American; Native Hawaiian or Other Pacific Islander; White; Other
- Ethnicity: Hispanic or Latino; Not Hispanic or Latino

11.2.2 Height

The subject's height must be measured in cm (without shoes). The height must be measured using a calibrated meter.

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:

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.

Panel 9 Static physician's global assessment of disease severity scale

Score	Short descriptor	Detailed descriptor
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild chickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable erythema; moderate (mild to coarse) scaling
4	Severe	Severe (marked) thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all lesions
5	Very severe	Very severe thickening with hard edges; deep dark red coloration; very severe/very coarse scaling covering all lesions

11.4.1.3 Assessment of the body surface area involvement (BSA)

The investigator must first evaluate eligibility of the inclusion criterion for the BSA before evaluating the total psoriatic involvement on the head and neck, upper extremities, trunk, and lower extremities.

The blinded assessor will use the surface area of the subject's hand (palm and fingers) as a reference measurement to calculate the percentage of each body region that is affected by psoriasis. One hand is approximately equal to 1% total BSA.

Furthermore, the complete body surface area (BSA=100%) can be divided into regions that approximates percentages of BSA as follows: head and neck (10%), upper extremities (20%), the trunk including the axillae and groin (30%), and finally the lower extremities, including the buttocks (40%).

11.4.1.4 Nail Psoriasis Severity Index (NAPSI)

The NAPSI scale is an objective, numeric, and reproducible grading system for nail psoriasis that incorporates the many different features of nail psoriasis. For assessments in this trial (including selection of target nail), a nail is graded using the NAPSI scale by first dividing the nail area with imaginary horizontal and vertical lines into 4 quarters. The following 8 clinical features of nail psoriasis are then scored based on the number of quarters in which the feature is present (0 to 4) to arrive at a NAPSI score of 0 to 32 for each nail:

- pitting
- leukonychia
- red spots in lunula

- nail plate crumbling
- oil drop (salmon patch) discoloration
- onycholysis
- nail bed hyperkeratosis
- splinter haemorrhages

In randomised subjects with nails involved with psoriasis, each nail will be scored at baseline to determine the worst nail (i.e., the nail with the highest NAPSI score). Those subjects whose nail with the highest NAPSI score is 6 or above at baseline visit will have this nail (the target nail) followed for the remainder of the trial. If multiple nails have the same highest score, only 1 target nail will be followed. Subjects whose nail with the highest NAPSI score is 5 or less will not have a designated target nail.

11.4.2 Patient reported outcomes – Efficacy and safety

The subject must make self-assessments at visits specified in the schedule of trial procedures (Panel 2).

The following assessments will be done by the subject and must be completed prior to any other procedure at the applicable visit. An ePRO tablet will be provided to the sites for the subject to use when answering the PROs at site.

11.4.2.1 Dermatology Life Quality Index (DLQI)

The DLQI is a validated questionnaire with content specific to subjects with dermatology conditions (Finlay and Khan, 1994; **Appendix 5B**). It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item is scored on a 4 point Likert scale (0 = not at all/not relevant; 1 = a little; 2 = a lot; 3 = very much). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life. The DLQI takes about 2 minutes to complete.

The investigator must evaluate eligibility of the inclusion criterion for the DLQI.

11.4.2.2 Patient Health Questionnaire-8 (PHQ-8)

The PHQ-8 is a validated and widely used 8 item version of the Patient Health Questionnaire depression scale designed to clinically assess patients for symptoms and signs of depression (Kroenke et al. 2009; **Appendix 5C**).

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.

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:

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.

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)

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

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

- 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.

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Appendix 1 Abbreviated eligibility criteria in accordance with CDISC requirements

Inclusion criteria in accordance with CDISC requirements (see Section 9.2 and 9.3 for full eligibility criteria)		
#	**Short definition**	**Detailed description**
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	Chronic plaque type psoriasis means diagnosed for 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 at randomisation	Defined at randomisation by: - PASI >10 and - 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).	
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 measures 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.	

Exclusion criteria in accordance with CDISC requirements (see Section 9.2 and 9.3 for full eligibility criteria)		
#	**Short Definition**	**Detailed description**
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:	a) Have received phototherapy (UVA light therapy without psoralens, UVB light therapy, excimer laser, tanning beds etc.) within 4 weeks of baseline. b) Have had topical psoriasis treatment within 2 weeks of baseline (exceptions: bland emollients without urea or beta or alpha hydroxy acids). c) Have received any biologic immune modulating treatment used for indication other than psoriasis within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer. d) Have received any other systemic immune modulating treatment (including but not limited to oral retinoids, methotrexate, calcineurin inhibitors, oral or parenteral corticosteroids etc. used for indication other than psoriasis) within 4 weeks of baseline or within a period of 5 half-lifes of the received treatment, whichever is longer.
4	Clinically important active infections or infestations, chronic, recurrent or latent infections, infestations or immunocompromised (e.g. HIV).	
5	Presence of significant uncontrolled cerebral, cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematologic, neurologic, or neuropsychiatric disorders.	
6	Clinically significant abnormal values at screening within assessments of biochemistry, urine, and haematology (such as differential blood count and platelets) at the discretion of the investigator.	

Exclusion criteria in accordance with CDISC requirements (see Section 9.2 and 9.3 for full eligibility criteria)		
#	**Short Definition**	**Detailed description**
7	Subjects with any of the following laboratory abnormalities at screening: a) Leukocyte cell count below 3×10^9/L or lymphocyte count below 0.7×10^9/L. b) Aspartate aminotransferase (AST) or alanine transferase (ALT) > 2× ULN (upper level of normal limit). c) Absolute neutrophil count < 2× 10^9/L. d) Serum creatinine > ULN.	
8	Subjects with severe gastrointestinal diseases including, but not limited to, ventricular and duodenal ulcers.	
9	Subject with a known history of Crohn's disease or history of psoriatic arthritis with a need for treatment.	
10	Planned surgery, which in the opinion of the investigator would influence the planned treatment of the IMP.	
11	History of depressive disorder within the last 2 years including current anti-depressive treatment.	
12	Any positive finding in history of suicidal behaviour based on the C-SSRS questionnaire at screening or baseline.	
13	Any positive finding in suicidal ideation of level 4 or 5 based on the C-SSRS questionnaire at screening or baseline.	
14	A PHQ-8 score of ≥10 corresponding to moderate to severe depression at screening or baseline.	
15	History of cancer.	a. Subjects who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained. b. Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.
16	Known or suspected hypersensitivity to component(s) of the IMPs.	

Exclusion criteria in accordance with CDISC requirements (see Section 9.2 and 9.3 for full eligibility criteria)		
#	**Short Definition**	**Detailed description**
17	Current or recent involvement in other interventional clinical trial.	Current participation in any other interventional clinical trial, ending another interventional clinical trial less than 4 weeks prior to screening visit, or receiving other investigational agents (based on interview of the subject).
18	Current or recent treatment with any non-marketed drug substance.	Subjects who have received treatment with any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration) within the last 4 weeks prior to screening visit
19	Previously enrolled in this clinical trial.	
20	In the opinion of the (sub)investigator, the subject is unlikely to comply with the clinical trial protocol (e.g. due to alcoholism, drug addiction or psychotic state).	
21	Subjects being the member of or being in close affiliation with trial personnel, sponsor or CRO.	Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a CRO involved in the trial.
22	Subjects under guardianship, hospitalised in a public or private institution, for a reason other than the research, or subject deprived of freedom.	
23	Female subjects who are pregnant or breastfeeding.	
24	Subject has any concurrent medical condition that, in the opinion of the investigator, could cause this trial to be detrimental to the subject	

Appendix 2: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

This definition includes:

- accidental injuries, events related to trial procedures, reasons for any unfavourable and unplanned change in medication (drug and/or dose), clinically significant worsening of pre-existing conditions, or reasons for admission to hospital or surgical procedures unless these were planned before enrolment. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP. In addition, any laboratory abnormality assessed as clinically significant by the (sub)investigator must be recorded as an AE.

Serious adverse event definition

An SAE is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE but should be documented in the subject's medical record
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- 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.

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.

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 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.

The subject's signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH-GCP (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subject card

At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address(es) and telephone number(s) of relevant trial site staff.

Appendix 4C: Subject and data confidentiality

This clinical trial protocol as well as all other information, data and results relating to this clinical trial and/or to the IMP is confidential information of LEO and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO may use any and all information, data and results from this clinical trial in connection with the development of the IMPs and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

Subjects will be assigned a unique identifier (subject ID) by LEO. Any subject's records or datasets that are transferred to LEO will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Subjects must be informed that their personal trial related data will be used by LEO in accordance with local data protection law.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by LEO, by appropriate IEC members, and by inspectors from regulatory authorities.

Processing of personal data

This protocol specifies the personal data on trial subjects (for example age, gender, health condition, height, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO and third parties acting on behalf of LEO.

Processing of personal data on behalf of LEO requires a written agreement between LEO and the relevant party which covers collection, processing and transfer of personal data in the clinical trial. In certain cases, an agreement on transfer of personal data may also be required.

Investigators and LEO must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy.

Subjects (or their legally acceptable representative) must be asked to consent to the collection, processing and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

LEO has obtained the necessary authorisations for the processing of personal data collected in the trial.

Appendix 4D: Record keeping, quality control, and data handling

Case report forms

Data will be collected by means of electronic data capture unless transmitted to LEO or designee electronically (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into eCRFs. Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

Principles for data entry

Clinically significant abnormal findings at the (first) screening visit will be documented as medical history in the eCRF.

If an abnormal finding (vital signs, physical examination, laboratory tests) at any other visit than the (first) screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with Section 12.2. Further, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom or illness observed after screening will be reported as an AE in accordance with Section 12.2.

Source data

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be one source defined at any time for any data elements.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified investigators.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met.
- Subject ID.
- The fact that the subject is participating in a clinical trial in psoriasis including treatment with brodalumab or fumaric acid esters for 24 weeks with a follow-up period of 2 or 8 weeks depending on treatment group.
- Other relevant medical information.

Trial monitoring

During the course of the trial the CRA(s) will visit the trial site. These visits have the following objectives: (i) to perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; (ii) to confirm that the safety and rights of subjects are being protected;

and (iii) to confirm that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH-GCP, and all applicable regulatory requirements.

The monitoring visit intervals will depend on the trial site's recruitment rate, the compliance of the trial site with the protocol and GCP.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO and included in the clinical trial report.

Sponsor audits, IEC review, and regulatory agency inspections
The clinical trial will be subject to audits conducted by LEO or inspections from domestic or foreign regulatory authorities or from IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO must be notified immediately.

Data handling
Subject data should be entered into the CRF as soon as possible after each visit in accordance with the requirements described in the Clinical Trial Agreement, if applicable. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

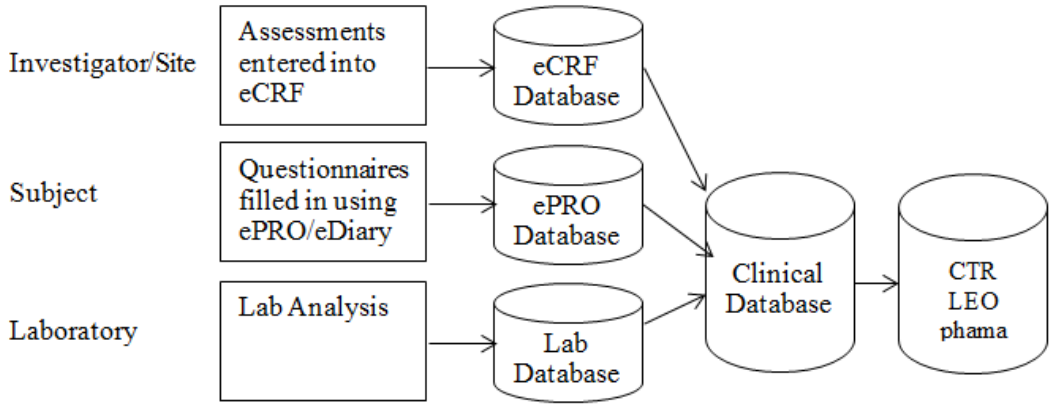
An electronic PRO (ePRO) solution will be used to capture patient reported data (data from questionnaires completed at the trial site and ePRO device data). By the use of an ePRO, data

will be available immediately after data entry and available for monitors and site personnel, including the investigator, with read access only. The ePRO system is a separate application from the eCRF and data captured from the eCRF and the ePRO will be stored on different servers during data capture. Data from both systems will be included in the final trial database.

External data transfers from vendors to LEO will be transmitted and handled via a secure file transfer protocol site.

Transmissions of electronic data from external data providers and of ePRO data to the clinical database are illustrated in Panel 14.

Panel 14 Transmission of electronic data



CTR: clinical trial report; ECG: electrocardiogram; eCRF: electronic case report form; ePRO: electronic patient reported outcome.

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents including the investigator trial file (ICH-GCP E6 guideline) until LEO informs the investigator that the documents are no longer to be retained or longer if required by local regulations.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (for example in case of an inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents even if the investigator leaves the trial site or retires before the end of the required storage period.

No records may be destroyed during the retention period without the written approval of LEO. No records may be transferred to another location or party without written acceptance from LEO.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

For archiving purposes, each investigator will be supplied with a copy of the eCRFs and ePRO data for all subjects enrolled at the trial site. This is done after completion of the trial and before access to the eCRF/ePRO is revoked. Audit trail information will be included. eCRFs and ePRO data must be available for inspection by authorised representatives from LEO, from regulatory authorities and/or IECs.

Appendix 4E: Registration, reporting and publication policy

Basic information of this clinical trial will be registered in the global data registry, www.clinicaltrials.gov before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this clinical trial will be posted on the corporate website of LEO in accordance with LEO's Position on Public Access to Clinical Trial Information, latest 12 months after trial completion. Results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

In the case of a multi-centre trial the first publication will be a joint multi-centre publication. Multi-centre publications will be prepared in collaboration between LEO and the members of a writing group, which shall be appointed by LEO.

Publication by an investigator of his/her trial results shall not be made public before the first multi-centre publication.

If no multi-centre publication has been submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer or other outside person, the investigator shall provide to LEO a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO, the

investigator shall remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO, delay the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, LEO and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the investigator after the first multi-centre publication has been published, the above-mentioned requirements must still be followed.

LEO complies with recommendations from the International Committee of Medical Journal Editors and with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA) and Pharmaceutical Research and Manufacturers of America (PhRMA) on disclosure of information about clinical trials, trial results and authorship.

Appendix 4F: Insurance

LEO has obtained a patient insurance as well as a travel accident assurance covering the subjects in the present clinical trial in accordance with the national law and regulations. A copy of the conditions of the patient insurance as well as of the accident insurance will be handed out to the subject with the informed consent.

Appendix 4G: Financial disclosure

Investigators will provide LEO with sufficient, accurate financial information as requested to allow LEO to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the clinical trial and for app. 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 4H: Trial and site closure

Premature termination of trial or trial site

LEO, the investigator, the IECs or competent authorities may decide to stop the clinical trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable

regulatory requirements, the investigator or LEO must promptly inform IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit:risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

Reasons for the early closure of a trial site by LEO or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, LEO's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further IMP development.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Trial enrolment will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Trial sites will be closed upon trial completion. LEO will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

When the randomisation code has been broken, the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites and will be asked to record this in the subject's medical record.

Appendix 4I: Responsibilities

The international coordinating investigator (ICI) is responsible for the approval of the clinical trial protocol, including any amendment(s) and the CTR on behalf of all clinical trial investigators and as agreed to in an International Coordinating Investigator Agreement.

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a Clinical Trial Agreement.

Appendix 5 Questionnaires

Appendix 5A: Psoriasis Symptom Inventory (PSI) – 24 hours recall

Psoriasis Symptom Inventory (PSI)

For each of the following questions, please mark (☑) the box of the one answer that best describes your experience.

In the questions below, the phrase "*skin lesions*" refers to the areas of your skin affected by your psoriasis.

For the following group of questions, the "**last 24 hours**" means from right now - back to yesterday at this same time.	**Not at all**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1) Overall, during the last 24 hours, how severe was the **itch** from your psoriasis?					
2) Overall, during the last 24 hours, how severe was the **redness** of your skin lesions?					
3) Overall, during the last 24 hours, how severe was the **scaling** of your skin lesions?					
4) Overall, during the last 24 hours, how severe was the **burning** of your skin lesions?					
5) Overall, during the last 24 hours, how severe was the **stinging** of your skin lesions?					
6) Overall, during the last 24 hours, how severe was the **cracking** of your skin lesions?					
7) Overall, during the last 24 hours, how severe was the **flaking** of your skin lesions?					
8) Overall, during the last 24 hours, how severe was the **pain** you felt from your skin lesions?					

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.

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

‘

Appendix 5C: Patient Health Questionnaire-8

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Troubleconcentratingonthings,suchas reading thenewspaperorwatchingtelevision.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

(For office coding: Total Score _____ = ___ + ___ + ___)

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MDPHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research in formation, contact Dr. Spitzera trls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc.

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.

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.

In patients with moderate to severe plaque psoriasis, a single subcutaneous dose of 210 mg brodalumab increased the exposure of midazolam, a CYP3A4/3A5 substrate by 24%. Based on the magnitude of change in exposure of midazolam, no dose adjustment of CYP3A4/3A5 substrates is necessary when administered concomitantly with Kyntheum®.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential
Women of childbearing potential should use an effective method of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy
There are no or limited amount of data from the use of brodalumab in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Human IgG2 is known to cross the placental barrier and brodalumab is a human IgG2, therefore, brodalumab has the potential to be transmitted from the mother to the developing foetus. As a precautionary measure, it is preferable to avoid the use of Kyntheum® in pregnancy.

As the metabolism of brodalumab is unknown in infants, benefit risk for exposure of the infant to live vaccines following third trimester exposure to Kyntheum® should be discussed with a physician.

Breast-feeding
It is unknown whether brodalumab is excreted in human milk. Brodalumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards.

A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Kyntheum® therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No data are available on the effect of brodalumab on human fertility. Animal studies did not show any effects on male and female reproductive organs and on sperm count, motility and morphology.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Kyntheum® has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The most commonly reported adverse reactions in all Kyntheum®-treated patients were arthralgia, headache, fatigue, diarrhoea and oropharyngeal pain.

Tabulated list of adverse reactions

Adverse reactions from clinical trials (Table1) are listed by MedDRA system organ class (SOC). Within each SOC, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

List of adverse reactions in clinical trials

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Influenza Tinea infections (including tinea pedis, tinea versicolor, tinea cruris)
	Uncommon	Candida infections (including oral, genital, and oesophageal infections)
Blood and lymphatic system disorders	Common	Neutropenia
Nervous system disorders	Common	Headache
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain
Gastrointestinal disorders	Common	Diarrhoea Nausea
Musculoskeletal and connective tissue disorders	Common	Arthralgia Myalgia
General disorders and administration site conditions	Common	Fatigue Injection site reactions (including injection site erythema, pain, pruritus, bruising, haemorrhage)

Description of selected adverse reactions

Infections
During the 12-week placebo-controlled trial period in plaque psoriasis, infections were reported in 25.4% of patients treated with Kyntheum® compared with 23.4% of patients treated with placebo. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, and influenza, which did not necessitate treatment discontinuation. Serious infections occurred in 0.5% of patients treated with Kyntheum® and in 0.2% of patients treated with placebo. Higher rates of fungal infections, primarily non-serious skin and mucosal candida infections, were observed

in Kyntheum® patients compared to placebo patients, 1.8% vs 0.9%, respectively. One serious case of cryptococcal meningitis and one serious case of coccidioidies infection were observed in clinical trials (see Section on special warning and precautions for use).

Through week 52, the exposure-adjusted event rates (per 100 patient-years) for infections were 114.6 for patients treated with Kyntheum® and 118.1 for patients treated with ustekinumab. The exposure-adjusted event rates (per 100 patient-years) for serious infections were 1.3 for patients treated with Kyntheum® and 1.0 for patients treated with ustekinumab.

Reduced absolute neutrophil count
During the 12-week placebo-controlled clinical trial period in patients with psoriasis, a decrease in absolute neutrophil count (ANC) was observed in 5.6% of patients receiving Kyntheum® , which was generally transient and reversible. Grade 3 and 4 have been observed occasionally. None of the Grade 3 or 4 ANC decreases in the psoriasis subset overall were associated with a serious infection.

Neutropenia
During the 12-week placebo-controlled period of clinical trials, neutropenia was reported in 0.8% of patients treated with Kyntheum® compared with 0.5% of patients treated with placebo. Most adverse reactions of Kyntheum®-associated neutropenia observed were mild, transient and reversible.

Neutropenia Grade 3 and 4 were reported in 0.4% of patients receiving Kyntheum compared to 0.2% of patients who received ustekinumab and none in patients receiving placebo. No serious infections were associated with neutropenia.

Immunogenicity
Antibodies to brodalumab developed in 2.7% (122/4461) of patients treated with Kyntheum®

for up to 52 weeks in psoriasis clinical trials (0.3% of these patients had anti-brodalumab antibodies at baseline). Of these patients, none had neutralising antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with anti-brodalumab antibody development.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

When reporting a suspected adverse reaction of a biological medicine, the name of the medicine and the batch number should be included.

OVERDOSE

Doses up to 700 mg intravenously have been administered in clinical trials with no evidence of dose limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Appendix 7 Contact list

Contact details for the clinical project manager, the appointed CRA, and the sponsor's medical expert are provided to the participating trial sites in a separate sponsor contact list.

Sponsor

LEO Pharma A/S (referred to as 'LEO' in this clinical trial protocol)
Industriparken 55
DK-Ballerup, DK

Protocol authors

International coordinating investigator (ICI)

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- Medical writer, PPD , LEO Pharma A/S, Denmark
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- Trial Statistician, PPD , LEO Pharma A/S, Denmark

Trial committees

Chair: Prof. Dr. med. PPD

Substitute: Prof. Dr. med. Dr. rer. nat. PPD

Office Address:

PPD

PPD PPD

PPD

PPD

CROs/vendors

Service	Name and address
CRO	PPD
	PPD , PPD
	PPD , PPD
Data management	PPD
	PPD
	PPD PPD , PPD
	Visiting addresses:
	PPD , PPD
	PPD , PPD PPD
ePRO	PPD
	PPD ,
	PPD
	PPD , PPD
Central Lab	CCI
	CCI
	CCI
	CCI , CCI
IWRS	PPD
	PPD
	PPD , PPD
CMO	CCI
	CCI
	CCI , CCI

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