Cover Page

Study title: Efficacy and safety comparison of brodalumab versus guselkumab in adult subjects with moderate -to -severe plaque psoriasis and inadequate response to ustekinumab; COBRA
LEO Pharma number: LP0160-1510
NCT number: NCT04533737
Date: 10-Mar-2022

Clinical Trial Protocol

LP0160-1510

Efficacy and safety comparison of brodalumab versus guselkumab in adult subjects with moderate -to -severe plaque psoriasis and inadequate response to ustekinumab; COBRA

Phase 4 – efficacy trial

A randomised, blinded, parallel-group, multi-site, clinical trial

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:**	**LP0160-1510**
	Date:	**10-Mar-2022**
	EudraCT no:	**2019-004099-20**
	Version:	**5.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within LEO Pharma Clinical Vault are considered to be a legally binding equivalent of traditional handwritten signatures. The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD, MSc Eng, PhD
Biostatistics lead, Medical Sciences

PPD, MD
Vice president, Medical Sciences

PPD, PhD
Global Head Clinical Operations Project, Clinical Project Management

Approval statement signatory investigator

The signatory investigator approves the clinical trial protocol by manually signing the signatory investigator clinical trial protocol approval form, which is a separate document appended to this document.

The following person has approved this clinical trial protocol:

PPD, MD, PhD
Signatory investigator

Acknowledgement statement investigators

Each participating investigator must agree to the approved clinical trial protocol by signing a clinical trial protocol acknowledgement form or similar document.

Protocol amendment summary of changes table

Document history

Document	Date	Type of protocol amendment
Amendment 3 (substantial)	**10-Mar-2022**	**Global**
Amendment 2 (substantial)	22-Jan-2021	Global
Amendment 1 (substantial)	19-Aug-2020	Global
Original protocol	18-Jun-2020	Not applicable

Amendment 3 (10-Mar-2022)

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 or subsequent regulation.

Overall rationale for the amendment:

The main reason for this amendment is to reduce the sample size and amend the eligibility criteria to ease recruitment.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section no. and name	Description of change	Brief rationale
3 Schematic of trial design	Total number of subjects changed from 260 to 240 subjects and in each treatment group from 130 to 120 subjects.	Sample size reduced from 260 to 240 subjects.

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures	~~QuantiFERON® test~~ **Tuberculosis test**	To allow tuberculosis test to be performed at local laboratory.
4 Schedule of trial procedures, footnote 5	Footnote 5: ~~QuantiFERON® or purified protein derivative (PPD) test. The PPD test is only accepted if it is a requirement from local health authorities (see inclusion criterion 5).~~ **Tuberculosis test can be performed at the central laboratory. If a local laboratory test is performed to confirm this criterion, the local laboratory should be assessed before the local testing is performed.** Footnote 6: **PP-PASI and PP-IGA to be completed for all subjects at Visits 1 and 2. Subsequently,** only subjects with palmoplantar psoriasis at baseline **(Visit 2)** will be followed using the separate tools PP-PASI and PP-IGA. Footnote 8: The DLQI**,** SF-36v2, and **PHQ-8** questionnaires should be completed by the subject prior to the investigator, safety, and **C-SSRS** ~~other~~ assessments. For the sequence of assessments to be performed at each visit, please see Panel 8. Footnote 16:	To allow tuberculosis test to be performed at local laboratory. To clarify when PP-PASI and PP-IGA are to be performed. Order of assessments changed to ease the process at trial site. Correcting a clerical error

Section no. and name	Description of change	Brief rationale
	In case of abnormal dipstick results at ~~baseline~~ **screening**, a urine sample will be sent to the central laboratory for albumin-to-creatinine ratio.	
7.2 Number of subjects needed	This trial will be conducted at approximately 75 sites in Europe~~ and Australia~~. Assuming a screening failure of ~~15~~ **18**%, approximately ~~306~~ **293** subjects will be screened, and ~~260~~ **240** eligible subjects will be randomised in a 1:1 ratio to treatment with either brodalumab or guselkumab.	Removing Australia as a participating country and reducing the sample size to 240 subjects.
8.2 Inclusion criteria, inclusion criterion 4	Subject has inadequately controlled plaque psoriasis currently treated with ustekinumab, and fulfils ALL of the following criteria: • Ustekinumab administered at least 3 times at or higher than the approved dose or frequency **before randomisation** ~~for at least 24 weeks~~ (Stelara® SmPC) (17). • Investigator's Global Assessment (IGA) ≥2 at screening and baseline. • Absolute PASI >3 at screening and baseline. ~~• The last administration of ustekinumab was ≥12 weeks before randomisation.~~	To ease the identification of subjects who have not benefitted sufficiently from ustekinumab treatment.
8.2 Inclusion criteria, inclusion criterion 5	~~Subject has a negative test for tuberculosis at screening (negative QuantiFERON® test or purified protein derivative [PPD] test*).~~ ~~Subject without a history of Bacillus Calmette-Guérin (BCG) vaccination who has~~	To allow tuberculosis test to be performed at local laboratory.

Section no. and name	Description of change	Brief rationale
	~~a positive PPD test or a positive or indeterminate QuantiFERON® test is allowed if the subject has ALL of the following:~~ ~~• No symptoms or signs of tuberculosis as evaluated by the investigator.~~ ~~• Documented prophylactic treatment of latent tuberculosis according to local standard of care initiated at least 1 month prior to first administration of IMP.~~ ~~• No known exposure to a case of active tuberculosis after most recent prophylaxis.~~ ~~• No evidence of active tuberculosis based on documented assessment by a pulmonologist or a tuberculosis specialist (phthisiologist).~~ ~~*The PPD test is only accepted if it is a requirement from local health authorities.~~ **Subject has no evidence of active tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment. Subjects with adequately treated latent tuberculosis, according to local guidelines, are eligible.** **a. A tuberculosis test can be performed at the central laboratory.** **b. If a local laboratory test is performed to confirm this criterium, the local laboratory should be assessed before the local testing is performed.**	

Section no. and name	Description of change	Brief rationale
8.3 Exclusion criteria, exclusion criterion 20	~~Subject has previously received more than 1 TNFα inhibitor.~~ **NOTE: This exclusion criterion is not applicable in this version of the protocol. It is kept to avoid re-numbering of the exclusion criteria.**	To ease the recruitment of subjects.
8.4.2.2 Re-screening	All screening and laboratory assessments must be repeated except **tuberculosis test** ~~QuantiFERON® test or the PPD test~~, if negative at first screening.	To allow tuberculosis test to be performed at local laboratory.
9.3 Treatment assignment	Randomisation will be stratified by baseline **(Visit 2)** body weight (≤100 kg and >100 kg).	For clarification.
9.7 Prohibited medications and procedures, Panel 7	Ustekinumab: ~~12 weeks prior to~~ First administration of IMP	To align with the revised inclusion criterion 4.
9.10 Reporting product complaints	Fax number: +45 **6910 2468** ~~7226 3287~~	New fax number.
11.1 Overview, Panel 8	Order of assessments changed so PHQ-8 is performed together with DLQI and SF-36v2 before all other assessments.	To ease the assessment process at trial site.
11.4.4.1 Overview, Panel 15	**Tuberculosis test (if applicable)** ~~QuantiFERON® test (only at screening) PPD test (only at screening)~~ Definition of PPD deleted from table footnote.	To allow tuberculosis test to be performed at local laboratory.

Section no. and name	Description of change	Brief rationale
12.1 Scientific rationale for trial design	Inadequate response to ustekinumab is defined as IGA ≥2 after at least 3 doses **at or higher than the approved dose or frequency** ~~and 24 weeks of treatment~~, and this correlates well with the currently acceptable treatment goals. ~~Evaluation of the eligible psoriatic subjects who have had at least 24 weeks of ustekinumab exposure will ensure the feasibility of the trial and the homogenous disease population.~~	To align with the revised inclusion criterion 4.
13.4.1 Investigator reporting responsibilities	Fax number: +45 **6910 2468** ~~7226 3287~~	New fax number.
14.1 Sample size	Updated with description of new sample size calculation.	To provide a rationale for the new sample size of 240 subjects.
14.3.6 Estimand strategy	Procedures for multiple imputation in 'hypothetical' strategies for addressing intercurrent events and in handling of missing data updated. Main analyses of primary estimands for binary and continuous endpoints clarified with regards to the combination of results from multiply imputed datasets. Prior TNF-α inhibitor use at baseline (≤1, >1) included as a factor in all analysis models. Scope of Sensitivity analysis 2 of the primary estimand for binary endpoints expanded to also assess robustness with respect to the assumption that the effect of treatment does not depend on prior TNF-α inhibitor use at baseline (≤1, >1).	To align with other LP0160 protocols. To handle the change of eligibility criteria in the analysis.

Section no. and name	Description of change	Brief rationale
14.3.7 Analysis of efficacy endpoints	For each binary endpoint it has been specified whether the underlying assessment will be considered on a continuous or ordinal scale.	To aid in the specification of procedures for multiple imputation.
Appendix 3C Subject and data confidentiality	Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial**, as well as reporting obligations in the event of any data breach**.	For clarification.
Appendix 3G Financial disclosure	Investigators are responsible for providing information on financial interests **and update this information, should any relevant change occur,** during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.	For clarification.
Appendix 4 Short version of eligibility criteria	Aligned with revisions of inclusion criteria 5 and exclusion criterion 20. PPD definition deleted from table footnotes.	Alignment.
Appendix 6 COVID-19 pandemic contingency plan	Assessments will be performed via the use of a trial-specific mobile application on the subject's own smartphone **or via the use of other video software used by the trial site in their normal clinical practice and in agreement with the sponsor and following notification of the relevant ethics committee** and by completing the PHQ-8 questionnaire	To allow the use of already available software that the trial staff is familiar with.

Section no. and name	Description of change	Brief rationale
	via a webpage (hereafter termed 'video visits').	
Appendix 6 COVID-19 pandemic contingency plan	**Delivery of IMP to a subject may also be performed by the subject's spouse or other relative or delegated person of trust who can pick up the IMP at the trial site and deliver to the subject.**	To make it easier to deliver IMP to the subject.
Appendix 6 COVID-19 pandemic contingency plan	Delivery of IMP to subjects and self-injection: 2. Prepare and ship/**hand out to subject's relative or delegated person of trust** (refer to trial product handling manual for instructions): o IMPs allocated via the IRT including instruction for use and other supplies. o Urine pregnancy test kits, if applicable. Care should be taken to keep blinded site staff from becoming unblinded while preparing the shipment/**package for hand out to subject's relative or delegated person of trust**. 3. Site staff are responsible for establishing contact with the subject as soon as he/she receives the IMP ~~shipment~~.	To make it easier to deliver IMP to the subject.
Appendix 6 COVID-19 pandemic contingency plan	Delivery of IMP to subjects and self-injection: 4. At the date of self-injection, the unblinded site staff contacts the subject via the video function in the trial-specific mobile application **or other**	To allow the use of already available software that the trial staff is familiar with.

Section no. and name	Description of change	Brief rationale
	software used by the trial site in their normal clinical practice and completes the following:	
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Table of contents

List of panels

List of abbreviations

ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
APP	Application
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BSA	body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMO	contract manufacturing organisation
COVID-19	Coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
eDiary	electronic diary
ePRO	electronic patient-reported outcome
FAS	full analysis set
FWER	familywise error rate
GCP	Good Clinical Practice
HCP	healthcare professional
HIV	human immunodeficiency virus
IB	investigator’s brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number

IE	intercurrent event
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IL	Interleukin
IL-17RA	interleukin-17 receptor subunit A
IL-23p19	interleukin-23 subunit p19
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intention-to-treat
LS	least square
MACE	major adverse cardiovascular events
MAR	missing at random
MSM	multi-state model
MedDRA	Medical Dictionary for Regulatory Activities
NRI	non-responder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI 75/90/100	75%/90%/100% improvement from baseline in PASI score
PHQ-8	Patient Health Questionnaire-8
PP-PASI	palmoplantar PASI
PP-IGA	palmoplantar IGA
PRO	patient-reported outcome
Q2W	every 2 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SD	standard deviation
SF-36v2	36-Item Short Form Health Survey version 2, acute recall
SIB	suicidal ideation and behaviour
SmPC	summary of product characteristics
SOC	system organ class
sPGA	static Physician's Global Assessment
sPGA-G	sPGA of genitalia
Th	T-helper

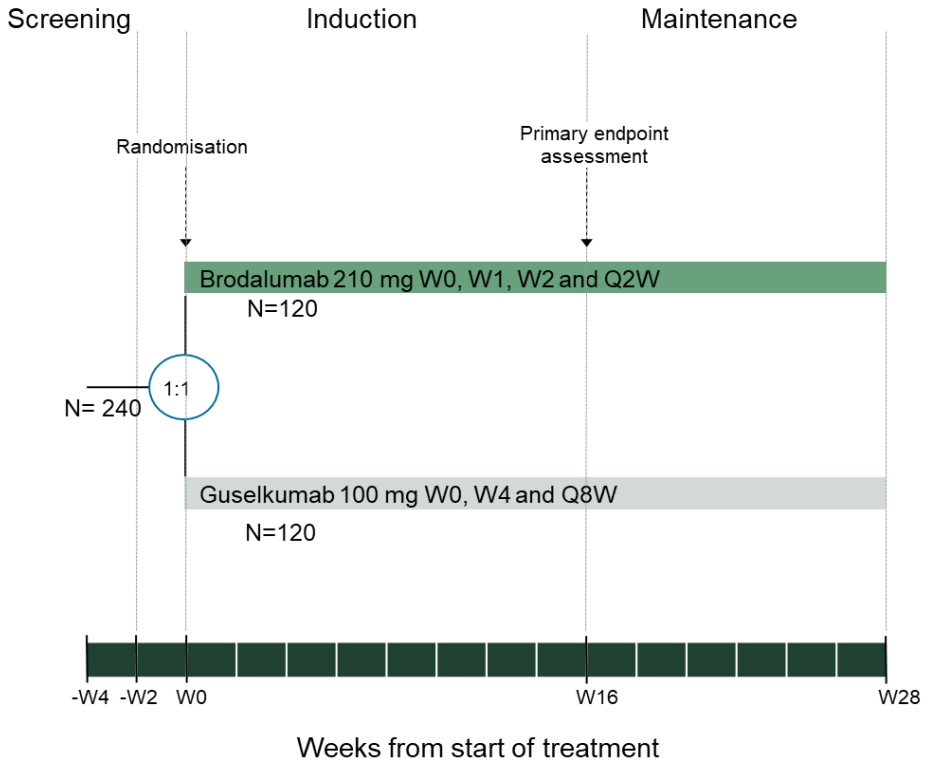
TNF-α	tumour necrosis factor-α
TTE	Time-to-event
ULN	upper limit of normal

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td colspan="2">LP0160-1510
2019-004099-20</td></tr>
<tr><td>Title of trial</td><td colspan="2">Efficacy and safety comparison of brodalumab versus guselkumab in adult subjects with moderate-to-severe plaque psoriasis and inadequate response to ustekinumab.</td></tr>
<tr><td>Short title of trial</td><td colspan="2">Efficacy and safety of brodalumab compared with guselkumab in the treatment of plaque psoriasis after inadequate response to ustekinumab; COBRA.</td></tr>
<tr><td>Main objectives and endpoints</td><td colspan="2"><table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td></td></tr>
<tr><td>To compare the efficacy of brodalumab with guselkumab in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.</td><td>Primary endpoint
• Having PASI[1] 100 response at Week 16.</td></tr>
<tr><td>Secondary objectives</td><td></td></tr>
<tr><td>To evaluate the efficacy of brodalumab compared with guselkumab while on treatment for up to 28 weeks in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.</td><td>Key secondary endpoint
• Time to PASI 100 response.

Secondary endpoint
• Time to PASI 90 response.</td></tr>
<tr><td>To evaluate the efficacy of brodalumab compared with guselkumab through Week 28 in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.</td><td>Secondary endpoints
• Having PASI 100 response, assessed separately at Weeks 4, 8, and 28.
• Having PASI 90 response, assessed separately at Weeks 4, 8, 16, and 28.
• Having IGA[2] of 0, assessed separately at Week 16 and Week 28.
• Having IGA of 0 or 1, assessed separately at Week 16 and Week 28.
• Having DLQI[3] total score of 0 or 1, assessed separately at Weeks 4, 8, 12, 16, 20, 24, and 28.
• Change in SF-36v2[4] score from baseline, assessed separately at Weeks 4, 8, 16, and 28.</td></tr>
</table></td></tr>
</table>

	To evaluate the safety of brodalumab compared with guselkumab throughout the trial (28 weeks) in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Secondary endpoints* • Occurrence of treatment-emergent AEs from baseline to Week 28.
	Abbreviations: AE = adverse event; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in PASI score; PASI 90 = 90% improvement from baseline in PASI score; SF-36v2 = 36-Item Short Form Health Survey version 2. 1) The PASI is the most widely used tool in clinical trials to assess the severity and extent of psoriasis. It is a composite index with scores ranging from 0 to 72, with higher values indicating a more severe or more extensive condition. 2) The IGA is an instrument used in clinical trials to rate the severity of psoriasis and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). 3) The DLQI is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items and 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. 4) The SF-36v2 is a 36-item general health status assessment. Subjects will answer each question by selecting 1 of 3 to 6 categorical response options. The SF-36v2 yields scores for 8 health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and 2 psychometrically derived summary scores (a physical component summary and a mental component summary).	
Final collection of data for the primary endpoint	Week 16	
Trial design	This is a phase 4, randomised, blinded (subject- and assessor-blinded, by dummy injections), parallel-group, multi-site, clinical trial consisting of a 2- to 4-week screening period and a 28-week treatment period (comprised of a 16-week induction period and a 12-week maintenance period).	

	 **Abbreviations:** Q2W = every 2 weeks; Q8W = every 8 weeks; W = week.
Main assessments	The key efficacy assessments are Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment (IGA). The patient-reported outcomes for efficacy include Dermatology Life Quality Index (DLQI) and 36-Item Short Form Health Survey version 2 (SF-36v2). The safety assessments include treatment-emergent adverse events (AE) reporting.

Main criteria for inclusion	• Subject is ≥18 years of age at the time of screening.
	• Subject has a diagnosis of plaque psoriasis for at least 6 months before the first administration of investigational medicinal product (IMP) as determined by the investigator.
	• Subject has inadequately controlled plaque psoriasis currently treated with ustekinumab, and fulfil ALL of the following criteria:
	  ○ Ustekinumab administered at least 3 times at or higher than the approved dose or frequency before randomisation.
	  ○ IGA ≥2 at screening and baseline.
	  ○ Absolute PASI >3 at screening and baseline.
	• Subject has no evidence of active tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment. Subjects with adequately treated latent tuberculosis, according to local guidelines, are eligible.

Main criteria for exclusion	• Subject was diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of IMP on plaque psoriasis. • Subject has clinically important active infections or infestations, chronic, recurrent, or latent infections or infestations, or is immunocompromised (e.g. human immunodeficiency virus). • Subject has any systemic disease (e.g. renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled. • Subject has a known history of Crohn's disease. • Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma. • Subject has a history of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma. • Subject has a known history of active tuberculosis. • Subject has a history of suicidal behaviour (i.e. 'actual suicide attempt', 'interrupted attempt', 'aborted attempt', or 'preparatory acts or behaviour') based on the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire at screening or baseline. • Subject has any suicidal ideation of severity 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the C-SSRS questionnaire at screening or baseline. • Subject has a Patient Health Questionnaire-8 (PHQ-8) score of ≥10, corresponding to moderate-to-severe depression at screening or baseline. • Subject has previously been treated with any anti-interleukin (IL)-17A, anti-IL-17 receptor subunit A, or anti-IL-23 besides ustekinumab. • Subject has known or suspected hypersensitivity to any component(s) of the IMPs.
Investigational medicinal products	• Kyntheum® (210 mg brodalumab in 1.5 mL solution, 140 mg/mL) for subcutaneous injection. • Tremfya® (100 mg guselkumab in 1.0 mL solution, 100 mg/mL) for subcutaneous injection. • Placebo 1.0 mL (dummy 1 to mimic guselkumab: brodalumab solution without active ingredient) in 1.0 mL solution for subcutaneous injection. • Placebo 1.5 mL (dummy 2 to mimic brodalumab: brodalumab solution without active ingredient) in 1.5 mL solution for subcutaneous injection.
Duration of trial participation	A 2- to 4-week screening period and a 28-week treatment period.
Number of subjects	A total of 240 eligible subjects will be randomised in a 1:1 ratio to treatment with either brodalumab or guselkumab.

Number and distribution of trial sites	Approximately 75 sites in Europe.
Statistical methods	*Primary and key secondary endpoints* The difference in response rates at Week 16 between the brodalumab and guselkumab arms will be analysed based on logistic regression, adjusted for baseline body weight (≤100 kg, >100 kg), prior TNF-α inhibitor use at baseline (≤1, >1) and baseline PASI score. Missing data will be assumed to be missing at random. In order to quantify the difference in the response rates, the odds ratio and risk difference, along with the associated 95% confidence intervals, will also be reported. The time to PASI 100 will be analysed according to Gray's test, stratified by baseline body weight (≤100 kg, >100 kg). Gray's test accounts for the occurrence of the competing risk, permanent discontinuation of IMP. Inference will be based on the estimated cumulative incidence of achieving a PASI 100 response derived from the Aalen-Johansen estimator. The estimated cumulative incidence functions will be presented by treatment arm and baseline body weight (≤100 kg, >100 kg) along with 95% confidence bands. In addition, the estimated sub-distributional hazard ratio from a Fine and Gray model, stratified by baseline body weight (≤100 kg, >100 kg) and adjusted for prior TNF-α inhibitor use at baseline (≤1, >1) and baseline PASI score, will be presented along with the corresponding 95% CI. To control the familywise error rate, a hierarchical testing procedure, indicating the order in which the primary and key secondary endpoints are to be tested, has been pre-specified.
Signatory investigator	PPD, MD, PhD PPD Germany
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

2 Trial identification

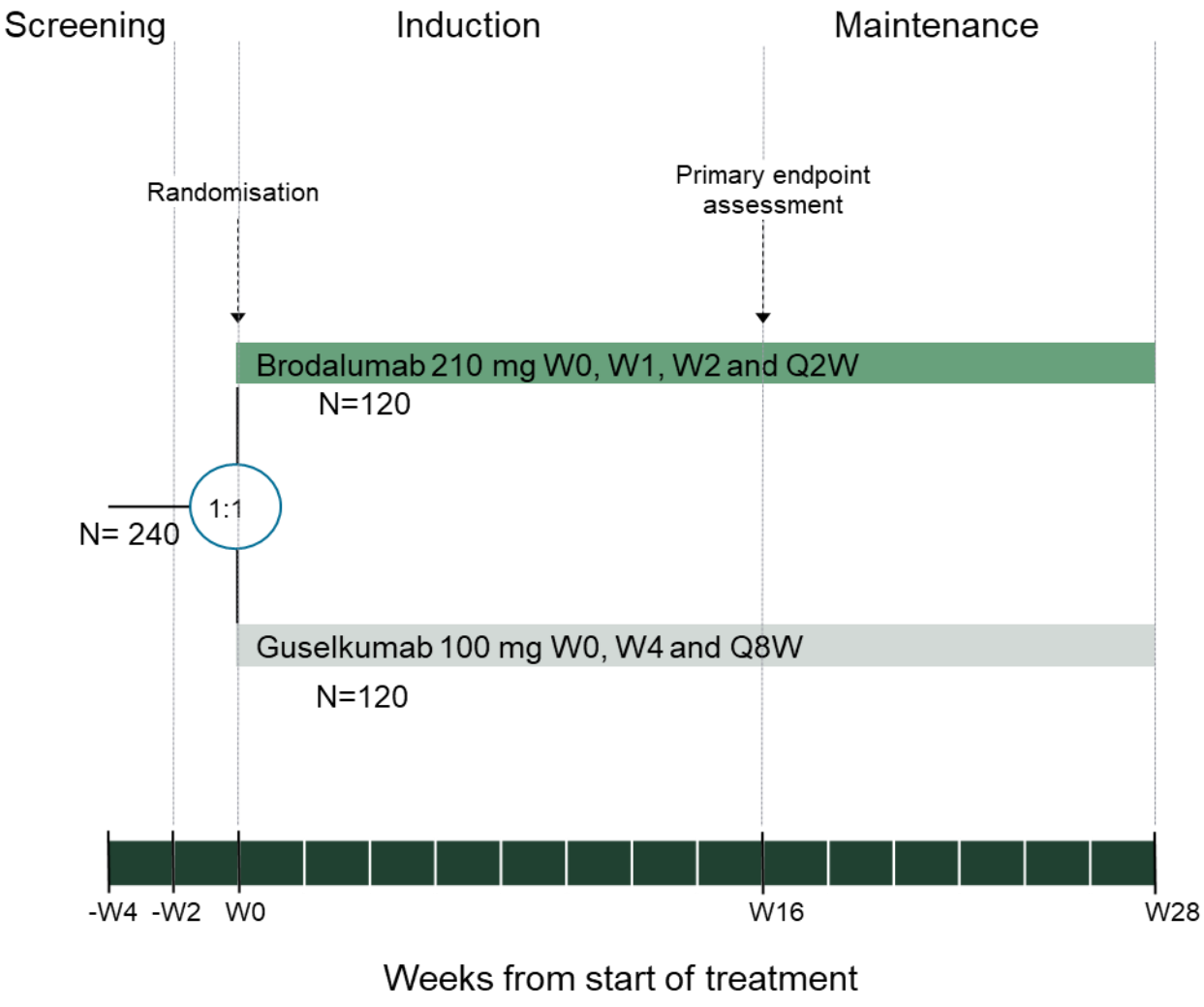
EudraCT number: 2019-004099-20.

ClinicalTrials.gov number: NCT04533737.

The clinical trial protocol will be registered in local registries if required by local legislation.

3 Schematic of trial design

Panel 1: Trial design



Abbreviations: Q2W = every 2 weeks; Q8W = every 8 weeks; W = week.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures – screening to Visit 11 (Week 16)

		Screening	Treatment (induction) period										Early termination visit[2] As soon as possible within 2 weeks after last IMP	Unscheduled visit, if applicable[3]	References (protocol section)
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (primary endpoint visit)**			
Week		**-4/-2 to 0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**			
Visit window (days)[1]		**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Total population and eligibility															
Informed consent[4]		X													Appendix 3B
Subject eligibility		X	X												8.2 and 8.3
Investigator assessments at screening/baseline only															
Demographics		X													11.2.1
Trial disease(s)		X													11.2.2
Trial disease treatment history		X													11.2.3
Medical history		X													11.2.4
Substance use: tobacco, alcohol		X													11.2.5
HIV, HBV, HCV tests		X												(X)	11.4.4
Tuberculosis test[5]		X												(X)	11.4.4
Treatments and randomisation															
Randomisation			X												9.3
Arm 1	Administration of brodalumab		X	X	X	X	X	X	X	X	X	X		(X)	9.2

		Screening	Treatment (induction) period										Early termination visit[2] As soon as possible within 2 weeks after last IMP	Unscheduled visit, if applicable[3]	References (protocol section)
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (primary endpoint visit)**			
Week		**-4/-2 to 0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**			
Visit window (days)[1]		**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
	Administration of dummy 1		X			X				X				(X)	9.2
Arm 2	Administration of guselkumab		X			X				X				(X)	9.2
	Administration of dummy 2		X	X	X	X	X	X	X	X	X	X		(X)	9.2
Concomitant medication/procedures		X	X	X	X	X	X	X	X	X	X	X	X	(X)	9.6
Treatment compliance			X	X	X	X	X	X	X	X	X	X		(X)	9.8.4
Investigator assessments of efficacy															
PASI		X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.3.1.1
IGA		X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.3.2.1
PP-PASI[6]		X	X			X		X				X	X	(X)	11.3.1.2
PP-IGA[6]		X	X			X		X				X	X	(X)	11.3.2.2
sPGA-G[7]		X	X			X		X				X	X	(X)	11.3.3
Subject assessments of efficacy and health-related quality of life															
DLQI[8]		X	X			X		X		X		X	X	(X)	11.3.4.1
SF-36v2[8]		X	X			X		X				X	X	(X)	11.3.4.2
eDiary device hand-out and training		X													11.3.4
Pruritus NRS[9]		<=Daily at home during entire treatment period using an eDiary device =>											X[10]		11.3.4.3
Pain NRS[9]		<=Daily at home during entire treatment period using an eDiary device =>											X[10]		11.3.4.4

	Screening	Treatment (induction) period										Early termination visit[2] As soon as possible within 2 weeks after last IMP	Unscheduled visit, if applicable[3]	References (protocol section)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 (primary endpoint visit)**			
Week	**-4/-2 to 0**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**			
Visit window (days)[1]	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
eDiary device return												(X)[11]		11.3.4
Investigator assessments of safety														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.4.1
Physical examination	X	X									X	X	(X)	11.4.2
Body measurements[12]	X	X									X	X	(X)	11.4.3
Biochemistry[13], haematology[14], urinalysis (urine dipstick)[15]	X	X									X	X	(X)	11.4.4
Albumin-to-creatinine ratio (urinalysis)[16]	(X)												(X)	11.4.4
Urine pregnancy test[17]		X			X		X		X		X	X	(X)	11.4.4
Serum pregnancy test[17]	X	(X)			(X)		(X)		(X)		(X)	(X)	(X)	11.4.4
AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	(X)	13
Patient-reported outcomes of safety														
C-SSRS[18]	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.5.2
PHQ-8[8]	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.5.3
Concluding forms in the eCRF														
End-of-treatment form[19]												X		11.6.1
End-of-trial form[20]												(X)[20]		11.6.2

Footnotes to this panel are found below Panel 3.

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; eDiary = electronic diary; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PHQ-8 = Patient Health Questionnaire-8; PP-IGA = palmoplantar IGA; PP-PASI = palmoplantar PASI; SF-36v2 = 36-Item Short Form Health Survey version 2; SAE = serious adverse event; sPGA-G = static Physician's Global Assessment of genitalia.

Panel 3: Schedule of trial procedures – Visit 11 (Week 16) to Visit 17 (Week 28)

		Treatment (maintenance) period						Early termination visit[2] As soon as possible within 2 weeks after last IMP	Unscheduled visit, if applicable[3]	References (protocol section)
Visit		**12**	**13**	**14**	**15**	**16**	**17**			
Week		**18**	**20**	**22**	**24**	**26**	**28**			
Visit window (days)[1]		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatments										
Arm 1	Administration of brodalumab	X	X	X	X	X			(X)	9.2
	Administration of dummy 1		X						(X)	9.2
Arm 2	Administration of guselkumab		X						(X)	9.2
	Administration of dummy 2	X	X	X	X	X			(X)	9.2
Concomitant medication/procedures		X	X	X	X	X	X	X	(X)	9.6
Treatment compliance		X	X	X	X	X			(X)	9.8.4
Investigator assessments of efficacy										
PASI		X	X	X	X	X	X	X	(X)	11.3.1.1
IGA		X	X	X	X	X	X	X	(X)	11.3.2.1
PP-PASI[6]							X	X	(X)	11.3.1.2
PP-IGA[6]							X	X	(X)	11.3.2.2
sPGA-G[7]							X	X	(X)	11.3.3
Subject assessments of efficacy and health-related quality of life										
DLQI[8]			X		X		X	X	(X)	11.3.4.1
SF-36v2[8]							X	X	(X)	11.3.4.2

	Treatment (maintenance) period						Early termination visit[2]	Unscheduled visit, if applicable[3]	References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**As soon as possible within 2 weeks after last IMP**		
Week	**18**	**20**	**22**	**24**	**26**	**28**			
Visit window (days)[1]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Pruritus NRS[9]	<= Daily at home during entire treatment period using an eDiary device =>						X[10]	(X)	11.3.4.3
Pain NRS[9]	<= Daily at home during entire treatment period using an eDiary device =>						X[10]	(X)	11.3.4.4
eDiary device return						X	(X)[11]		11.3.4
Investigator assessments of safety									
Vital signs	X	X	X	X	X	X	X	(X)	11.4.1
Physical examination						X	X	(X)	11.4.2
Body measurements[12]						X	X	(X)	11.4.3
Biochemistry[13], haematology[14], urinalysis (urine dipstick)[15]						X	X	(X)	11.4.4
Albumin-to-creatinine ratio (urinalysis)[16]								(X)	11.4.4
Urine pregnancy test[17]		X		X		X	X	(X)	11.4.4
Serum pregnancy test[17]		(X)		(X)		(X)	(X)	(X)	11.4.4
AEs and SAEs	X	X	X	X	X	X	X	(X)	13
Patient-reported outcomes of safety									
C-SSRS[18]	X	X	X	X	X	X	X	(X)	11.5.2
PHQ-8[8]	X	X	X	X	X	X	X	(X)	11.5.3
Concluding forms in the eCRF									
End-of-treatment form[19]						X	X		11.6.1

	Treatment (maintenance) period						Early termination visit[2]	Unscheduled visit, if applicable[3]	References (protocol section)
Visit	**12**	**13**	**14**	**15**	**16**	**17**	**As soon as possible within 2 weeks after last IMP**		
Week	**18**	**20**	**22**	**24**	**26**	**28**			
Visit window (days)[1]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
End-of-trial form[20]						X	(X)[20]		11.6.2

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; eCRF = electronic case report form; ePRO = electronic patient-reported outcome; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PHQ-8 = Patient Health Questionnaire-8; PP-IGA = palmoplantar IGA; PP-PASI = palmoplantar PASI; SF-36v2 = 36-Item Short Form Health Survey version 2; SAE = serious adverse event; sPGA-G = static Physician's Global Assessment of genitalia.

Notes for Panel 2 and Panel 3

1) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to Visit 2 (Week 0, baseline). Visits outside of the allowed visit window still need to be performed, taking into consideration that an interval of minimum 7 days to the subsequent, respective IMP administration must be maintained (visits 3 and 4 are exempt from the 7-day gap requirement). If the trial visit cannot be rescheduled to maintain a minimum of 7 days to the subsequent scheduled dose, the sponsor's medical expert should be contacted.
2) Subjects who discontinue IMP for any reason should attend an early termination visit as soon as possible and within 2 weeks after the last IMP. If a subject discontinues IMP or withdraws from the trial at a scheduled visit, then all assessments for an early termination visit must be performed at this particular visit (see Sections 10.3 and 11.6 for further instructions). The subjects who discontinue IMP prior to Week 16 will be asked to attend at least the primary endpoint visit at Week 16.
3) An unscheduled visit can be performed by subject's needs or at the discretion of the investigator for the following purposes: AE follow-up (and related concomitant medication/procedures, if applicable), administration of IMP after temporary discontinuation, re-collection of blood and/or urine samples due to sampling or testing errors or need for follow-up on specific laboratory abnormalities, or suspected pregnancy. Procedures are marked in brackets '(X)' since they are optional depending on the reason for the unscheduled visit.
4) The informed consent form (ICF) must be signed prior to performing any protocol-related procedures, including, but not limited to, screening evaluations and wash-out of disallowed medications. Screening evaluations may start at a later date than the ICF was signed.
5) Tuberculosis test can be performed at the central laboratory. If a local laboratory test is performed to confirm this criterion, the local laboratory should be assessed before the local testing is performed.

6) PP-PASI and PP-IGA to be completed for all subjects at Visits 1 and 2. Subsequently, only subjects with palmoplantar psoriasis at baseline (Visit 2) will be followed using the separate tools PP-PASI and PP-IGA.
7) Only subjects with genital psoriasis at baseline will be followed using the separate tool sPGA-G.
8) The DLQI, SF-36v2, and PHQ-8 questionnaires should be completed by the subject prior to the investigator, safety, and C-SSRS assessments. For the sequence of assessments to be performed at each visit, please see Panel 8.
9) To be completed daily by the subject from screening onwards. The subject must bring the device at Visit 2 (Week 0, baseline) for site to collect it from subjects who do not meet randomisation criteria (screening failures). The eDiary must be returned to the site at the last visit (e.g. final visit at Week 28 or early termination visit).
10) Must be completed at the early termination visit, if not already done at home before the visit.
11) The eDiary device return is marked '(X)' since this is optional depending on the subject's willingness to continue with all the remaining visits and assessments.
12) Height and weight. Height is only measured at screening.
13) Sodium, potassium, calcium, bicarbonate, albumin, blood urea nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, and glucose. At Visit 1 (screening), the biochemistry assessments must also include estimated glomerular filtration rate (eGFR).
14) Red blood cell count, haemoglobin, haematocrit, platelets, white blood cell count, and differential (absolute count and %): neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
15) Specific gravity, pH, occult blood, protein, glucose, leucocyte esterase, and ketones. In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts).
16) In case of abnormal dipstick results at screening, a urine sample will be sent to the central laboratory for albumin-to-creatinine ratio.
17) Only women of childbearing potential. At screening, a serum pregnancy test is always performed. For other visits, if a urine pregnancy test is positive, a serum pregnancy test must be done to confirm the result.
18) The C-SSRS must be completed after all other assessments, but before administration of IMP. The 'baseline' paper version of the C-SRSS is used at screening and the 'since last visit' paper version is used at all subsequent visits.
19) An end-of-treatment form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP.
20) An end-of-trial-form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP or withdraw from the trial, at their last trial visit.

5 Introduction and trial rationale

5.1 Plaque psoriasis

Psoriasis is a chronic immune-mediated inflammatory disease characterised by patches of red, dry, itchy, and scaly skin, occurring in approximately 2% of the population worldwide. Plaque psoriasis is the most common type of psoriasis, corresponding to approximately 90% of all types (1).

Current data revealed that the main pathophysiological driver is the interleukin-23 (IL-23)/T-helper (Th) 17-cell axis. Th17 cells are activated by IL-23, thereby producing vast amounts of proinflammatory cytokines (e.g. IL-17A, tumour necrosis factor-α [TNF-α], IL-22, and IL-17F). IL-17A and IL-17F bind to the IL-17 receptor subunit A (IL-17RA), which generates the inflammatory response that causes keratinocytes to proliferate, leading to the formation of psoriatic plaques (2).

Within the last decades, biologic therapies targeting different steps of the pathway have been introduced. This led to a revolution in the treatment paradigm of moderate-to-severe plaque psoriasis and made complete clearance of the skin a realistic treatment goal (3).

Despite the improved treatment options, it is well recognised that patients may have an inadequate response to biologics due to a variety of reasons, including initial lack of efficacy (primary failures), loss of efficacy over time (secondary failures), and the advent of adverse events (AEs) or contraindications to the therapy. Hence, comparisons between therapies after a biologic failure could provide more data which can facilitate the physicians' decisions.

5.2 Experience with investigational medicinal products

Brodalumab

Brodalumab is a recombinant fully human monoclonal immunoglobulin G2 antibody that binds with high affinity to human IL-17RA, thereby blocking multiple cytokines from the IL-17 family. Blocking IL-17RA inhibits multiple IL-17 cytokine-induced inflammatory responses and results in reduced or normalised inflammation of the skin in patients with psoriasis. Brodalumab is approved in EU, Canada, Japan, Taiwan, Thailand, and the USA for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy.

The approved dosage regimen of 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 followed by 210 mg every 2 weeks (Q2W).

Brodalumab efficacy:
The efficacy of brodalumab for the treatment of psoriasis has been confirmed in 3 placebo-controlled phase 3 trials, in which 2 of the trials also included an ustekinumab comparator arm.

The overall benefit-risk profile of brodalumab was shown to be positive in treatment of subjects with moderate-to-severe plaque psoriasis regardless of baseline demographics and subpopulations studied.

Brodalumab safety:
The most commonly reported adverse reactions in brodalumab-treated subjects include arthralgia, headache, fatigue, diarrhoea, and oropharyngeal pain. There are no very common adverse reactions (see investigator's brochure [IB]).

During the 12-week placebo-controlled trial period in plaque psoriasis, infections were reported in 28.2% of subjects treated with Kyntheum® compared with 23.4% of subjects treated with placebo. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, influenza, and sinusitis, which did not necessitate treatment discontinuation. Serious infections occurred in 0.5% of subjects treated with Kyntheum® and in 0.1% of subjects treated with placebo. Higher rates of fungal infections, primarily non-serious skin and mucosal candida infections, were observed in Kyntheum® subjects (2.5%) compared with placebo subjects (1.0%; see the IB).

Anti-drug antibodies (ADA) to brodalumab developed in 2.2% (88/3935) of subjects treated with Kyntheum® for up to 52 weeks in psoriasis clinical trials (0.3% of the subjects had ADA at baseline). Of these subjects, none had neutralising antibodies, and there was no evidence of any association between ADA development and altered pharmacokinetic profile, clinical response, or safety profile. For further details, please see the IB.

Guselkumab

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody to the p19 subunit of IL-23 (IL-23p19). It is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. The NAVIGATE trial

demonstrated that approximately 12% of subjects, who were randomised to guselkumab after inadequate response to ustekinumab, achieved complete clearance (100% improvement in Psoriasis Area and Severity Index score; PASI 100) after 12 weeks, 18% after 16 weeks, 22% after 28 weeks, and 20% after 36 weeks (4).

The most common adverse reactions of guselkumab include upper respiratory tract infections, headache, injection site reactions, arthralgia, diarrhoea, gastroenteritis, fungal skin infections, and herpes simplex infections.

For further details on guselkumab efficacy and safety, please see EU summary of product characteristics (SmPC) for Tremfya® (5).

5.3 Trial rationale

With increasing availability of novel biologics with new targets, the complexity of choosing the appropriate biologic treatment is ever more challenging for physicians. This applies not only to choosing the most efficacious treatment for the patient, but also to deciding on subsequent treatment options if the patient has inadequate response to a biologic treatment.

Ustekinumab modulates proinflammatory signalling through the inhibition of IL-12 and IL-23. Several trials evaluating efficacy of more modern biologic treatments have demonstrated superiority of the newer agents (targeting IL-17A, IL-23p19, or IL-17RA) over ustekinumab (6-11).

The efficacy of brodalumab for the treatment of psoriasis has been confirmed in 3 placebo-controlled phase 3 trials, 2 of which included an ustekinumab comparator arm (AMAGINE-2 and -3). A subanalysis of these trials showed that rescue treatment with brodalumab improved skin outcomes among subjects with inadequate response to ustekinumab (9, 10, 12).

The head-to-head trial of guselkumab versus ustekinumab in subjects inadequately treated with ustekinumab (NAVIGATE trial) has demonstrated increased psoriasis improvement in subjects randomised to guselkumab compared with those randomised to continue on ustekinumab (4).

By comparing data from the AMAGINE and the NAVIGATE trials, it was concluded that brodalumab treatment would lead to significantly higher PASI 100 rates than guselkumab treatment after 16 weeks of treatment (34.7% vs. approximately 18%, respectively) (4, 12). No trials have, however, directly compared IL-17RA antagonism with IL-23p19 inhibition.

Therefore, the primary objective of this trial is to compare the efficacy of brodalumab versus guselkumab in adult subjects with moderate-to-severe plaque psoriasis and inadequate response to ustekinumab, thereby providing results that could support decision-making in the clinical setting.

The primary endpoint is PASI 100 at Week 16. PASI 100 is chosen due to substantial evidence highlighting the importance of complete clearance from the patient's perspective, improving quality of life and decreasing the disease burden (13). Moreover, PASI 100 allows better and most accurate differentiation between highly efficacious treatments available for the treatment of psoriasis today.

5.4 Ethical considerations

This trial will be conducted in accordance with the ethical principles that have their origins in International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines in compliance with the approved protocol and applicable regulatory requirements.

In accordance with the current version of ICH GCP guidelines, qualified medical personnel employed by LEO Pharma will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial.

In this trial, all subjects will be treated with biologic medications approved in EU for the treatment of moderate-to-severe plaque psoriasis. Since the trial has no placebo arm, any ethical considerations regarding withholdment of treatment do not apply.

No children or other vulnerable subjects incapable of giving informed consent will be included in this clinical trial. Pregnant or breastfeeding women and women trying to conceive will not be included in the trial. Women of childbearing potential must agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until 12 weeks after discontinuation of treatment with investigational medicinal product (IMP). In addition, all women of childbearing potential will have a pregnancy test performed before, during, and after trial procedures to minimise the risk of foetuses being exposed to the IMPs.

Suicidal ideation and behaviour (SIB), including completed suicide, have been reported in patients treated with brodalumab. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with brodalumab and increased risk of SIB has not been established (14).

Since a history of prior depression and/or SIB are known risk factors for new SIB events (15), subjects with a recent history of depression (within 2 years), Patient Health Questionnaire-8

(PHQ-8) score ≥10, Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation level 4 or 5, or any suicidal behaviour are excluded from participation in the trial. In addition, subjects will be continuously monitored for depression and SIB by the PHQ-8 and the C-SSRS. The investigator must discontinue subjects from IMP in case of C-SSRS suicidal ideation level 4 or 5, any suicidal behaviour, or a PHQ-8 score ≥15 corresponding to moderately severe-to-severe depression (16).

The trial design chosen for this efficacy and safety trial is regarded as ethically justified and adherent with ethical requirements.

5.5 Benefit/risk assessment

Brodalumab and guselkumab are approved treatments for adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.

Data from this trial will provide more information on the efficacy and safety of the treatments to support the choice of treatment after inadequate response to ustekinumab.

The risk to subjects in this trial will be minimised by fulfilment of all eligibility criteria and by close clinical monitoring. To ensure the safety and well-being of subjects participating in this trial, there will be ongoing monitoring of the subjects, reporting of any AEs, and well-defined IMP discontinuation criteria (Section 10).

The subjects in this trial will be blinded by additional (dummy) injections due to differences in the volume and administration frequency between brodalumab and guselkumab. Additional (dummy) injections are not expected to increase the low risk normally associated with injections. Similarly, the blood sampling procedure poses the same low risk as normally associated with this procedure.

Altogether, the risks associated with participating in this trial are considered low and are expected to be outweighed by the benefit of providing additional information for psoriasis patients and clinicians.

6 Trial objectives, endpoints, and estimands

Panel 4: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of brodalumab with guselkumab in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Primary endpoint* • Having PASI 100 response at Week 16.
Secondary objectives	
To evaluate the efficacy of brodalumab compared with guselkumab while on treatment for up to 28 weeks in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Key secondary endpoint* • Time to PASI 100 response. *Secondary endpoint* • Time to PASI 90 response.
To evaluate the efficacy of brodalumab compared with guselkumab through Week 28 in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Secondary endpoints* • Having PASI 100 response, assessed separately at Weeks 4, 8, and 28. • Having PASI 90 response, assessed separately at Weeks 4, 8, 16, and 28. • Having IGA of 0, assessed separately at Week 16 and Week 28. • Having IGA of 0 or 1, assessed separately at Week 16 and Week 28. • Having DLQI total score of 0 or 1, assessed separately at Weeks 4, 8, 12, 16, 20, 24, and 28. • Change in SF-36v2 from baseline, assessed separately at Weeks 4, 8, 16, and 28. *Exploratory endpoints* • Having IGA of 0 or 1 and at least a 2-grade improvement from baseline, assessed separately at Week 16 and Week 28. • Change from baseline in pruritus NRS 11 points (weekly average), assessed separately at Weeks 4, 8, 16, and 28. • Improvement of at least 4 units in pruritus NRS 11 points (weekly average), assessed separately at Weeks 4, 8, 16, and 28. • Change from baseline in pain NRS 11 points (weekly average), separately assessed at Weeks 4, 8, 16, and 28.

Objectives	Endpoints
	• Having absolute PASI ≤1, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≤2, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≥3, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≥5, assessed separately at Weeks 4, 8, 16, and 28. • Absolute PASI at Weeks 4, 8, 16, and 28. • Having PP-PASI 100 response, assessed separately at Weeks 4, 8, 16, and 28. • Having PP-IGA 0/1 response, assessed separately at Weeks 4, 8, 16, and 28. • Having sPGA-G 0/1 response, assessed separately at Weeks 4, 8, 16, and 28.
To evaluate the safety of brodalumab compared with guselkumab throughout the trial (28 weeks) in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Secondary endpoints* • Occurrence of treatment-emergent AEs from baseline to Week 28.

Abbreviations: AE = adverse event; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in PASI score; PASI 90 = 90% improvement from baseline in PASI score; PP-PASI = palmoplantar PASI; PP-IGA = palmoplantar IGA; SF-36v2 = 36-Item Short Form Health Survey version 2; sPGA-G = static Physician's Global Assessment of genitalia.

Panel 5: Estimands

Endpoint type	Primary/ Supplementary[1]	Estimand definition				
		Population	Treatment condition	Variable	Intercurrent events strategy[2]	Population level summary[3]
Binary based on investigator assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Having a response without prior permanent discontinuation of IMP independent of pandemic restrictions	'Composite', 'Hypothetical', 'Treatment-policy'	Odds ratio and LS-mean risk difference estimated by logistic regression
Binary based on subject assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Having a response without prior permanent discontinuation of IMP independent of pandemic restrictions	'Composite', 'Hypothetical', 'Hypothetical'	Odds ratio and LS-mean risk difference estimated by logistic regression

Endpoint type	Primary/ Supplementary[1]	Estimand definition				
		Population	Treatment condition	Variable	Intercurrent events strategy[2]	Population level summary[3]
Binary based on investigator assessments	First supplementary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Having a response	'Treatment-policy', 'Hypothetical', 'Treatment-policy'	Odds ratio and LS-mean risk difference estimated by logistic regression
Binary based on investigator assessments	Second supplementary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Having a response without prior permanent discontinuation of IMP independent of pandemic restrictions	'Composite', 'Hypothetical', 'Hypothetical'	Odds ratio and LS-mean risk difference estimated by logistic regression
Time-to-event	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Time to response prior to permanent discontinuation of IMP independent of pandemic restrictions	'While on treatment', 'Hypothetical', 'Treatment-policy'	Aalen-Johansen estimate of the cumulative incidence function
Continuous based on investigator assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Endpoint	'Treatment-policy', 'Hypothetical', 'Treatment-policy'	Difference in LS-means estimated by ANCOVA

Endpoint type	Primary/ Supplementary[1]	Estimand definition				
		Population	Treatment condition	Variable	Intercurrent events strategy[2]	Population level summary[3]
Continuous based on subject assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Endpoint	'Treatment-policy', 'Hypothetical', 'Hypothetical'	Difference in LS-means estimated by ANCOVA

Abbreviations: ANCOVA = analysis of covariance; IMP = investigational medicinal product; LS = least square.

1) For primary and key secondary endpoints, the main analysis associated with the primary estimand is used to assess significance based on the proposed multiplicity control procedure (see Section 14.3.8).
2) Refers to the strategies for handling occurrences of the intercurrent events permanent discontinuation of IMP independent of pandemic restrictions, permanent discontinuation of IMP due to pandemic restrictions, and unblinding of subjects, respectively, in the analysis.
3) Refers to the population level summary, which forms the basis for making treatment comparisons.
4) As defined in Sections 8.2 and 8.3.

7 Trial design

7.1 Overall trial design

This trial is a phase 4, randomised, blinded (subject and assessor), parallel-group, multi-site, clinical trial. The trial is designed to evaluate the efficacy and safety of standard administration of brodalumab compared with standard administration of guselkumab for the treatment of moderate-to-severe plaque psoriasis in adult subjects with inadequate response to ustekinumab.

A schematic of the trial design is provided in Section 3. The total duration of the trial will be approximately 32 weeks and includes 3 periods:

- Screening: Week -4/-2 to Week 0.
- Induction: Week 0 to Week 16.
- Maintenance: Week 16 to Week 28.

Screening period (Week -4/-2 to Week 0)
A screening visit will take place a maximum of 4 weeks and minimum of 2 weeks prior to the treatment period. The objective of the screening period is to enrol eligible and informed subjects. This entails wash-out of specified prohibited medication (Panel 7) and specified laboratory testing (Panel 15).

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

Induction period (Week 0 to Week 16)
The start of the treatment period is defined as Week 0 (baseline; Day 1). At this visit, eligibility will be confirmed by re-checking the eligibility criteria in subjects who were eligible based on previous examinations, review of sufficient wash-out of prohibited medication, and review of central laboratory results from the screening visit. If still eligible, the subject will continue in the trial and be randomised to either brodalumab or guselkumab treatment regimen as described below.

Arm 1 (brodalumab + dummy 1):

- Brodalumab 210 mg (1.5 ml) subcutaneously at Weeks 0, 1, 2, and then Q2W until the end of trial (last administration of brodalumab at Week 26).
- Dummy 1 (placebo 1.0 ml) subcutaneously at Weeks 0, 4, and then every 8 weeks (Q8W) until the end of trial (last administration of dummy 1 at Week 20).

Arm 2 (guselkumab + dummy 2):

- Guselkumab 100 mg (1.0 ml) subcutaneously at Weeks 0, 4, and then Q8W until the end of trial (last administration of guselkumab at Week 20).
- Dummy 2 (placebo 1.5 ml) subcutaneously at Weeks 0, 1, 2, and then Q2W until the end of trial (last administration of dummy 2 at Week 26).

The primary endpoint will be assessed at Week 16.

Maintenance period (Week 16 to Week 28)
The subjects will follow the treatment regimen described above. Last injections (brodalumab in Arm 1 and dummy 2 injection in Arm 2) will be given at Week 26. The subjects and assessors will be blinded throughout the trial.

Baseline, efficacy, and safety assessments during the trial are described in Section 11.

7.2 Number of subjects needed

This trial will be conducted at approximately 75 sites in Europe.

Assuming a screening failure of 18%, approximately 293 subjects will be screened, and 240 eligible subjects will be randomised in a 1:1 ratio to treatment with either brodalumab or guselkumab. Randomisation will be stratified by body weight (≤100 kg, >100 kg).

The statistical power considerations for this sample size are described in Section 14.1.

7.3 End-of-trial definition

A subject is considered to have completed the trial if having concluded all periods of the trial regardless of discontinuation of IMP.

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

Final collection of data for the primary endpoint occurs at Week 16 (Visit 11).

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, 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 verified according to the inclusion and exclusion criteria at visits specified in Section 4. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and independent ethics committees (IECs), as applicable.

8.2 Inclusion criteria

For inclusion into this trial, subjects must fulfil all of the following criteria:

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. Subject is ≥18 years of age at the time of screening.
3. Subject has a diagnosis of plaque psoriasis for at least 6 months before the first administration of IMP as determined by the investigator.
4. Subject has inadequately controlled plaque psoriasis currently treated with ustekinumab, and fulfils ALL of the following criteria:
   - Ustekinumab administered at least 3 times at or higher than the approved dose or frequency before randomisation (Stelara® SmPC) (17).
   - Investigator's Global Assessment (IGA) ≥2 at screening and baseline.
   - Absolute PASI >3 at screening and baseline.
5. Subject has no evidence of active tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment. Subjects with adequately treated latent tuberculosis, according to local guidelines, are eligible.
   a. A tuberculosis test can be performed at the central laboratory.

b. If a local laboratory test is performed to confirm this criterium, the local laboratory should be assessed before the local testing is performed.

6. Subject who is a woman of childbearing potential* must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline.

   * A woman is defined as being of childbearing potential if she is not postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening) and not surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

7. Subject who is a woman of childbearing potential* must use a highly effective** form of birth control throughout the trial and at least for 12 weeks after last administration of IMP.

   ** A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device, intrauterine hormone-releasing system, 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), sexual abstinence (when this is in line with the preferred and usual life style of the subject), or vasectomised partner (given that the subject is monogamous).

8.3 Exclusion criteria

Subjects must not enter the trial if they fulfil any of the following exclusion criteria:

Skin disease-related

1. Subject was diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of IMP on plaque psoriasis.

Other medical conditions

2. Subject has a planned surgery, which in the opinion of the investigator will interfere with the planned IMP treatment (any planned surgery that will be performed during the trial period must be recorded).
3. Subject has clinically important active infections or infestations, chronic, recurrent, or latent infections or infestations, or is immunocompromised (e.g. HIV).

4. Subject has a known history of hepatitis B, hepatitis C, or HIV. Positive hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis C virus antibody, or HIV antibody serology at screening. Subjects with positive anti-HBs are eligible provided that they have a negative HBsAg and negative HBc (blood pattern in vaccinated subjects).
5. Subject has any systemic disease (e.g. renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled.
6. Subject has a known history of Crohn's disease.
7. Subject had myocardial infarction, stroke, or unstable angina pectoris within the past 12 months prior to the first administration of IMP.
8. Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
9. Subject has a history of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
10. Subject has a known history of active tuberculosis.
11. Subject has a history of suicidal behaviour (i.e. 'actual suicide attempt', 'interrupted attempt', 'aborted attempt', or 'preparatory acts or behaviour') based on the C-SSRS questionnaire at screening or baseline.
12. Subject has any suicidal ideation of severity 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the C-SSRS questionnaire at screening or baseline.
13. Subject has a PHQ-8 score of ≥10, corresponding to moderate-to-severe depression at screening or baseline.
14. Subject has a history of depressive disorder with severe episode(s) within the last 2 years.
15. Subject has any concurrent medical condition that, in the opinion of the investigator, could cause the trial to be detrimental to the subject.

<u>Laboratory abnormalities</u>

16. Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results, including:
    - White blood cell (WBC) count $<3.00\times10^9$/L.
    - Absolute neutrophil count (ANC) $<2.00\times10^9$/L.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× the ULN (upper limit of normal).
- Serum direct bilirubin ≥1.5 mg/dL (≥25.7 μmol/L).

Wash-out and prohibited medications

17. Subject has used potent topical steroids, topical anthralin/dithranol, topical calcipotriol, or any formulation or potency of topical therapy, within 7 days prior to first administration of IMP (exceptions are specified*).

    * Upper mid-strength or lower potency topical steroids on the face, axillae, and groin; bland emollients (without urea or alpha or beta hydroxy acids); and shampoo without steroids are permitted.

18. Subject has used any of the following treatments* within 4 weeks prior to first administration of IMP.

    * Ultraviolet A light therapy (with or without psoralen); ultraviolet B light therapy; excimer laser; oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; fumarates; apremilast; oral or parenteral corticosteroids including intramuscular or intraarticular administration; or any other immunomodulating therapy for psoriasis or any other indication (otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses are permitted).

19. Subject has received any of the following biologic immunomodulating therapies prior to first administration of IMP:

    Approved agents:

    - Within 2 weeks for etanercept.
    - Within 4 weeks for adalimumab.
    - Within 10 weeks for certolizumab pegol.

    Other commercially available biologics:

    - Within 8 weeks for infliximab.

    Other experimental or commercially available biologic immunomodulators:

    - Within 4 weeks or 5 half-lives, whichever is longer.

20. ~~Subject has previously received more than 1 TNFα inhibitor.~~ **NOTE**: This exclusion criterion is not applicable in this version of the protocol. It is kept to avoid re-numbering of the exclusion criteria.

21. Subject has previously been treated with any anti-IL-17A, anti-IL-17RA, or anti-IL-23 besides ustekinumab.
22. Subject received live vaccine(s) within 4 weeks of the first administration of IMP.
23. Subject has received treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 4 weeks or 5 half-lives of the substance, whichever is longer, prior to screening.
24. Subject is currently enrolled in another investigational device or drug trial or ended participation in one within 4 weeks or 5 half-lives of the IMP, whichever is longer, prior to screening.

General

25. Subject has known or suspected hypersensitivity to any component(s) of the IMPs.
26. Subject is pregnant or lactating.
27. Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
28. Subject has previously been randomised in this clinical trial.
29. Subject has a language barrier, mental incapacity, unwillingness, or lack of ability to understand the trial-related procedures.
30. Subject is an employee of the trial site or any other individual directly involved with the planning or conduct of the trial, or immediate family member of such individual.
31. Subject is legally institutionalised.

8.4 Screening and screening failures

8.4.1 Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B 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 response technology (IRT) system and the screening evaluations to assess eligibility criteria may begin. The date of first screening activity could be on the same day or a later date than the informed consent form was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered ‘screened’ subjects.

The investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID. In addition, the investigator will maintain a log of all consented subjects at the trial site (subject identification list). This log will include each subject's identity, date of consent, and corresponding subject ID so that any subject may be identified if required for any reason. The log must not be copied or retained by LEO Pharma.

8.4.2 Screening failures

Screen failures are defined as subjects who consent to participate in the trial but are not subsequently randomised to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (18) and to respond to queries from regulatory authorities. As a minimum, the following data must be collected in the eCRF for screen failures:

- Date of informed consent(s).
- Demographics (date of birth, age, sex, ethnicity, race).
- Reason for screen failure.
  - Failure to meet eligibility criteria (specify which).
  - Lost to follow-up.
  - Withdrawal by subject.
  - Other (specification is required).
- Date of screen failure.
- Any AEs and serious AEs (SAEs).

In case of any SAEs, these must be followed-up as described in Section 13.7.

8.4.2.1 Re-sampling

If a subject fails any eligibility criteria related to laboratory parameters, a re-sampling of failed parameter(s) is allowed within 28 days after the screening sampling date. If the laboratory parameter(s) normalises, the subject is allowed to be randomised and enter the trial. The subject will keep the assigned subject ID.

8.4.2.2 Re-screening

Re-screening of screening failures is allowed only once within the limits of the trial's recruitment period. However, re-screening is not allowed if the subject fails screening due to exclusion criteria no. 11, 12. 13, or 14. In the event of re-screening, a new informed consent must be obtained, and a new subject ID assigned. For re-screened subjects, the subject ID from the first screening will be recorded in the eCRF. All screening and laboratory assessments must be repeated except tuberculosis test, if negative at first screening.

9 Treatments

9.1 Trial product description

All IMP will be packaged in individually numbered kits. Each pre-filled syringe is for single use only. Refer to Panel 6 for further details.

Panel 6: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size	Source
Brodalumab Trade name: Kyntheum®	Solution for subcutaneous injection	Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: • Proline • Glutamate • Polysorbate 20 • Water for injection	Pre-filled syringe with 210 mg brodalumab in 1.5 mL solution	CCI Commercially available
Guselkumab Trade name: Tremfya®	Solution for subcutaneous injection	Guselkumab formulated at a nominal concentration of 100 mg/mL including the following excipients: • Histidine • Histidine monohydrochloride monohydrate • Polysorbate 80 • Sucrose • Water for injection	Pre-filled syringe with 100 mg guselkumab in 1 mL solution	Janssen Biologics B.V. Commercially available; supplied by CMO
Placebo 1.0 mL (dummy 1 to mimic guselkumab)	Solution for subcutaneous injection	The placebo solution is similar to the active brodalumab solution except that it does not contain any active substance	Pre-filled syringe with 1.0 mL solution	CCI San Diego, USA
Placebo 1.5 mL (dummy 2 to mimic brodalumab)	Solution for subcutaneous injection	The placebo solution is similar to the active brodalumab solution except that it does not contain any active substance	Pre-filled syringe with 1.5 mL solution	CCI San Diego, USA

Abbreviation: CMO = contract manufacturing organisation.

9.2 Administration of investigational medicinal product

An IRT system will assign the required kit number- for each subject at each IMP administration visit.

IMP administration visits are shown in the schedule of trial procedures (Section 4). The first day of administration is considered Day 1 (Week 0, Visit 2). On administration visits, all other visit activities must be handled prior to administration of active IMP and/or dummy. The last

administration of active IMP under this protocol will occur at Week 26 for Arm 1 (brodalumab) and Week 20 for Arm 2 (guselkumab).

The IMPs and the dummies must be injected subcutaneously in the upper legs (thighs), stomach area (abdomen) or in the upper, outer arm by an unblinded healthcare professional (HCP). Injections should not be given into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. It is recommended that subsequent injections should be given on a different area or body region. It will be captured in the eCRF which region each injection is given and if it was on the right or left side. At Weeks 0, 4, 12, and 20, subjects will be injected with an active IMP and a dummy; it is recommended that these injections are given in the same area, at least 3 cm away from each other.

Guselkumab must be administered according to the instructions for administration provided in the current EU SmPC Tremfya®(5).

Instructions for use of the pre-filled syringes are provided in the investigator trial file; the IMP administration must be carried out according to these instructions.

9.3 Treatment assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised centrally at Week 0 (Visit 2) to receive either brodalumab or guselkumab treatment (see Section 3). Randomisation will be stratified by baseline (Visit 2) body weight (≤100 kg and >100 kg). Treatment assignment occurs based on a computer-generated randomisation scheme in a 1:1 ratio.

The IRT system will be used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking. The IRT system will assign the required kit number for each subject.

Each investigator site will be supplied with sufficient IMP for the trial on an ongoing basis controlled by the IRT system.

9.3.1 Blinding

This is a subject- and assessor-blinded trial, in which the 2 active IMPs (brodalumab and guselkumab) are to be administered at different frequencies and in pre-filled syringes that are visually distinct from each other and contain different volumes of solution. They will be packaged open label. To obtain blinding, 2 dummies (both brodalumab placebo solutions) will be used to cover the different injection timepoints. Dummy 1 will be used in Arm 1

(brodalumab arm) to match guselkumab in Arm 2 (guselkumab arm). Dummy 1 is a brodalumab placebo solution and is matched for volume, but is not matched for viscosity, colour, or syringe to guselkumab. Dummy 2 will be used in Arm 2 (guselkumab arm) to match brodalumab in Arm 1 (brodalumab arm). Dummy 2 is matched for volume, viscosity, colour, and syringe to brodalumab. Furthermore, to ensure subjects stay blinded to treatment allocation, site staff should ensure that subjects are blindfolded during the administration of IMP.

Neither the subjects nor any of the assessors will be aware of the treatment received. As the IMPs are packaged open-label, IMPs must be handled and administered by a qualified, unblinded HCP who is a member of site staff, not involved in any safety or efficacy assessments. The efficacy assessments will be performed by a designated assessor (see Section 11.1) who is blinded to the treatment allocation and not involved in the administration of IMP.

The trial site will maintain a signature and delegation log detailing which staff members are unblinded or blinded and which staff members are maintaining and administering the IMPs.

9.3.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigators, HCPs who are not members of the trial staff, or authorised LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator can unblind a subject's treatment in the IRT system. For a requester who is not a member of the trial staff and who does not have access to the IRT system (e.g. a physician at an emergency room), a local contact number for the emergency unblinding contract research organisation (CRO) is provided on the subject card (see Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. The requester will provide the trial ID and subject ID to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation. Should the requester wish to discuss whether unblinding is necessary, the emergency unblinding CRO will provide the requester with the LEO Pharma 24/7 contact which will be diverted to the medical cover.

9.4 Background treatment

Not applicable.

9.5 Rescue treatment

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

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives throughout the trial (including screening period) must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name.
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose, unit, and frequency.
- Route of administration.

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded:

- Procedure.
- Body location (if relevant).
- Indication.
- Start and stop date (it will also be recorded if the procedure is ongoing).

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

The following concomitant medications related to psoriasis treatment are permitted throughout the trial (including the screening period):

- Upper mid-strength or lower potency topical steroids on the face, axillae, and groin only.
- Shampoos without steroids.
- Bland emollients without urea or beta or alpha hydroxy acids.

9.7 Prohibited medications and procedures

The medications listed in Panel 7 are prohibited during the trial. In the case that any prohibited treatments are used during the trial, it must be recorded as a protocol deviation.

The following circumstances require permanent discontinuation of IMP:

- Use of any other biologic immunomodulating agent than IMPs.
- Use of any prohibited medication that in combination with IMP results in a significant risk to the subject's safety (as assessed by the investigator).
- Administration of a live vaccine.

If the prohibited medication does not require permanent discontinuation of IMP, then the investigator and the sponsor's medical expert should discuss and consider to either discontinue the prohibited medication or discontinue the IMP.

Panel 7: Prohibited medications and procedures

Prohibited medication/procedure	Prohibited from	Prohibited to
Etanercept[1]	2 weeks prior to first administration of IMP	Week 28
Adalimumab[1]	4 weeks prior to first administration of IMP	Week 28
Infliximab[1]	8 weeks prior to first administration of IMP	Week 28
Certolizumab pegol[1]	10 weeks prior to first administration of IMP	Week 28
Ustekinumab[1]	First administration of IMP	Week 28
Any other approved or experimental anti-IL-17 or anti-IL-23[1]	Not allowed at any time	Week 28
Other experimental or commercially available biologic immunomodulator(s)	4 weeks or 5 half-lives, whichever is longer, prior to first administration of IMP	Week 28
Any other non-marketed drug substance	4 weeks or 5 half-lives, whichever is longer, prior to screening	Week 28
Ultraviolet A light therapy (with or without psoralen), ultraviolet B light therapy, excimer laser	4 weeks prior to first administration of IMP	Week 28
Oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; fumarates; apremilast; or oral or parenteral corticosteroids including intramuscular and intraarticular administration (with the exception that: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses are permitted).	4 weeks prior to first administration of IMP	Week 28
Topical therapies for psoriasis (e.g. calcineurin inhibitors and vitamin D analogues, super-potent or potent topical steroids) with the following exceptions: Upper mid-strength or lower potency topical steroids on the face, axillae, and groin only. Shampoos without steroids. Bland emollients without urea or beta or alpha hydroxy acids.	7 days prior to first administration of IMP	Week 28
Use of live vaccines[1]	4 weeks prior to first administration of IMP	Week 28

Abbreviations: IL = interleukin; IMP = investigational medicinal product.
1) Use requires permanent discontinuation of IMP.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMP will be packaged in individually numbered kits.

The labelling of IMPs will be in accordance with the EU Guidelines for good manufacturing practices for medicinal products for human and veterinary use, Annex 13 (19), local regulations, and trial requirements. Label text will be translated into local languages, as required.

9.8.2 Storage of trial products

All LEO Pharma supplied IMPs (Section 9.1) must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

The IMPs must be stored at 2–8°C (and protected from light) at the trial site. Do not freeze the IMPs. The pre-filled syringes must not be shaken or heated.

The temperature during storage should be monitored by a calibrated, stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer. A temperature log must be kept to document the storage within the right temperature interval, unless the temperature recorder has back-up of data. Storage facilities should be checked at least every working day.

Storage of IMP may be delegated, e.g. to a hospital pharmacy, as locally applicable.

Note that in the cases listed below, site staff should not use the affected IMP and should immediately quarantine the IMP (also change the status in the IRT system), and contact their clinical research associate (CRA) for further guidance:

- Temperature excursion upon receipt or during storage at the trial site.
- Damaged syringe or kit.

Damaged IMP should be documented in the IRT system and reported as a product complaint to Global Safety, LEO Pharma (see Section 9.10). Damaged IMP may not be used.

Further details regarding IMP storage (including handling of temperature excursions upon receipt or during storage at the trial site) and handling of damaged IMP (including kits damaged upon receipt) are provided in the trial product handling manual.

9.8.3 Drug accountability

The investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

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

An individual drug accountability form must be kept of the IMP dispensed/administered to each subject randomised in the trial. This individual drug accountability form must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMP. Drug accountability information will be entered in the IRT system, where also inventory status of all IMP at the trial site will be maintained. Refer to the IRT manual for information on how to update the kit status in the IRT system.

The trial site will maintain trial kit cartons from used kits until reconciliation has been checked by the CRA. Subsequently, the trial kit cartons from used kits may be discarded.

All unused IMP (including packaging material) supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO. Prior to return, the IMP must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMP. Accountability must be documented in the IRT system. Please refer to the trial product handling manual for further details.

9.8.4 Treatment compliance

IMP injections will be performed by site staff. Site staff will also keep the accountability records up to date. Treatment compliance will be assessed by the site staff at the time points specified in Section 4. Any non-compliance (subject received partial dose; subject received no dose) and the reason for it must be recorded in the eCRF.

9.8.5 Trial product destruction

Used syringes can be destroyed at the trial site provided the trial site has procedures in place for such IMP destruction. Trial sites that do not have such IMP destruction procedures in place will dispose used IMP in sharps bins that will be returned to the CMO. For more information, see the trial product handling manual.

Unused IMP and disposal containers with used syringes returned to the CMO will be destroyed by the CMO according to approved procedures and any local requirements.

9.9 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.

9.10 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 Safety at LEO Pharma on the trial-specific complaint form (paper) within 3 days of first knowledge.

Critical complaints (defined as any defect, issue, or device deficiency that has or potentially could have a serious impact for the subject, such as SAE or large particles in the syringe) must be reported to Global Safety, LEO Pharma 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 Sections 13.3 and 13.4.

Refer to the trial product handling manual for information on how to update the kit status in the IRT system.

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

Global Safety, LEO Pharma contact information for reporting product complaints:

Fax number: +45 6910 2468

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

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (prior to first dose or during the treatment period) or permanently discontinue trial treatment at any time if the subject, the investigator, or LEO Pharma considers that it is not in the subject's best interest to continue.

To obtain the most representative efficacy and safety evaluation of brodalumab in the target population, the subject will be asked to remain in the trial and complete all the remaining visits and assessments after permanent discontinuation of IMP. It is key to assess the efficacy status of each subject at the planned primary endpoint visit (Week 16, see Section 4) irrespective of whether the subject has discontinued IMP or not. Therefore, the permanent discontinuation of IMP is evaluated as a separate occurrence that does not necessitate withdrawal from the trial.

Permanent discontinuation of IMP and withdrawal from trial are considered 2 (potentially) separate occurrences:

- Permanent discontinuation of IMP occurs when all **further trial treatment** is stopped. The subject will continue to participate in trial visit activities as outlined in Section 10.3.
- Withdrawal from trial occurs when all **further trial activities** are stopped before the final visit at Week 28. This can happen either at the same time as permanent discontinuation of IMP or later.

Medical reasons for discontinuation of IMP are given in Section 10.2.1.

Reason(s) for discontinuation from IMP and/or withdrawal from the trial must be recorded in the medical records and the eCRF (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, pregnancy, or other, Sections 10.2.1 and 11.6.2). For subjects randomised to IMP, but not attending any post-baseline visits, it will be recorded whether any safety evaluations were performed after exposure to IMP.

Subjects who withdraw from the trial and subjects who discontinue IMP will not be replaced.

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

10.2 IMP discontinuation rules

10.2.1 Reasons for permanent discontinuation of IMP

When discontinuing IMP, either at the scheduled end-of-treatment visit or IMP is discontinued prematurely, the subject should be treated at the discretion of the investigator (Section 9.9).

Subjects will permanently discontinue IMP prematurely in the event of:

- Having shown no response (efficacy) after 16 weeks of treatment.
- Anaphylactic reaction or other severe systemic reaction to IMP injection.
- An AE or deterioration of an AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further IMP administration (e.g. Crohn's disease).
- Some cases of use of prohibited medication and treatment, see Section 9.7 for further details.
- 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 (positive serum pregnancy test).
- Any infection that is opportunistic, such as active tuberculosis and other infections whose nature or course may suggest an immunocompromised status.
- Any suicidal behaviour or suicidal ideation of category 4 or 5 according to the C-SSRS (the subject must be referred to a mental health professional).
- A PHQ-8 score of ≥15 corresponding to moderately severe-to-severe depression (the subject must be referred to a mental health professional).
- Any single measurement of ANC $<0.50\times10^3/\mu L$.
- Severe laboratory abnormalities:
  - ALT and/or AST values >3×ULN with total bilirubin >2×ULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
  - Confirmed ALT and/or AST >5×ULN (for more than 2 weeks).

Refer to Section 10.3 for details on the handling of discontinuation of IMP or withdrawal of a subject, and to Section 4 for assessments to be performed in case of discontinuation of IMP.

Data to be recorded in the eCRF

The primary reason for permanent discontinuation of IMP must be recorded in the medical records and on the end-of-treatment form in the eCRF where the following options are available:

- Lack of efficacy.
- Adverse event.
- Withdrawal by subject.
- Lost to follow-up.
- Death.
- Pregnancy.
- Other.

If 'other' is selected, a specification must be provided in the eCRF. If 'adverse event' is selected, the AE in question will be linked to the IMP discontinuation.

'Lack of efficacy' should be assigned when a subject experiences aggravation/exacerbation/worsening of the trial disease, even when it is documented as an (S)AE according to Section 13.6.5.

10.2.2 Reasons for temporary discontinuation of IMP

Administration of IMP should be temporarily suspended in the event of:

- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents. The administration of the IMP should be withheld until the infection has resolved in the opinion of the investigator.
- Other major intercurrent illnesses or major surgery. The administration of the IMP should be withheld until the event has resolved in the opinion of the investigator.
- ANC $\geq 0.50\times10^3/\mu L$ to $\leq 1.5\times10^3/\mu L$ and fever. The administration of the IMP should be withheld until the infection has resolved in the opinion of the investigator and ANC is $>1.5\times10^3/\mu L$.
- Positive urine pregnancy test. The administration of the IMP should be withheld until confirmation by serum pregnancy test.

A decision to discontinue IMP temporarily or to reinstitute IMP treatment must be discussed with sponsor's medical expert. However, the investigator may suspend trial treatment at any time, even without consultation with sponsor's medical expert if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. In such cases, sponsor's medical expert should be informed as soon as possible. The schedule of planned visits should be maintained and all trial-related assessments should still be performed during the period of temporary discontinuation of IMP.

If all assessments were performed prior to IMP administration, but a decision was made to temporarily discontinue IMP, the IMP should be administered at a rescheduled visit, which should be reported in the eCRF as an unscheduled visit. The subsequent IMP administration should be scheduled according to the schedule of the trial procedures with a minimum of 7 days to the subsequent administration of the respective IMP (visits 3 and 4 are exempt from the 7-day gap requirement). When IMP is temporarily discontinued on a visit where 2 injections are required, the 2 injections can be rescheduled independently due to the difference in administration frequencies (brodalumab/dummy 2: Q2W, guselkumab/dummy 1: Q8W). If the trial visit cannot be rescheduled to maintain a minimum of 7 days to the subsequent scheduled dose, the sponsor's medical expert should be contacted.

10.3 Early termination assessments

Permanent discontinuation of IMP

Unless the subject discontinues IMP due to withdrawal of consent, lost to follow-up, or death, subjects will be encouraged to continue in the trial for collection of scheduled efficacy and safety assessments, or at least attend an early termination visit and primary endpoint visit as indicated below (see Section 4 for data to be collected at these visits). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Subjects who permanently discontinue IMP prior to Week 16 (Visit 11) will be asked to attend at least:

- Early termination visit, as soon as possible and within 2 weeks of the last IMP administration.
- Primary endpoint assessment visit at nominal Week 16 (Visit 11).

Subjects who permanently discontinue IMP at Week 16 (Visit 11) or hereafter will be asked to attend at least:

- Early termination visit, as soon as possible and within 2 weeks of the last IMP administration.

Withdrawal from trial

Subjects who withdraw from the trial for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP. See the schedule of trial procedures (Section 4) for data to be collected. The investigator will review any AEs which will be followed-up according to Section 13.7, if the subject agrees.

10.4 Lost to follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and if the trial site is not able to get in contact with the subject. The following actions must be taken if a subject fails 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 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, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

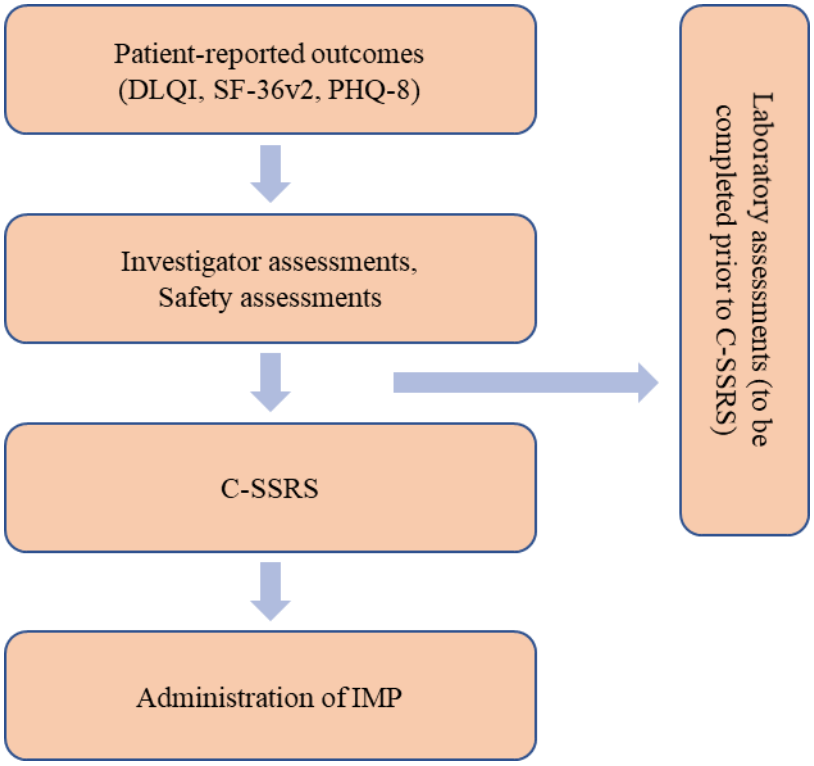
11 Trial assessments and procedures

11.1 Overview

Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4. Refer to Section 7.1 for further details on the trial design.

Assessments and procedures at each trial visit should be performed as shown in Panel 8.

Panel 8: Sequence of assessments



Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; IMP = investigational medicinal product; PHQ-8 = Patient Health Questionnaire-8; SF-36v2 = 36-Item Short Form Health Survey version 2.

Subjects participating in the trial will be under careful supervision of a principal investigator who must be a medically qualified physician. Investigators must be experienced in treating psoriasis and have documented experience and/or training in use of the assessments required by the protocol. The investigators performing the assessments must not be involved in the administration of IMP (Section 9.3.1).

Site staff assessing PASI, IGA, palmoplantar IGA (PP-IGA), and static Physician's Global Assessment of genitalia (sPGA-G) or reviewing the C-SSRS and PHQ-8 must be medically qualified physicians trained in the assessments. If adequately trained, other site staff may be

responsible for conducting the C-SSRS interview. The training certificate must be archived in the investigator trial file before any assessments.

To reduce inter-rater variability, the same assessor should perform all the evaluations for a given subject throughout the entire trial period, if feasible.

The site staff handling the IMP administration must not be involved in the efficacy assessments (Section 9.3.1).

AEs must be assessed by medically qualified personnel (Section 13.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Date of birth (date, month, and year). If full date of birth is not allowed to be recorded, month and year of birth or only year of birth should be collected as per local legislation. In these cases, the subject's age in years will also be recorded.
- Sex: female, male.
- Race: American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific islander, White, other ('other' requires a specification to be provided).
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.

11.2.2 Trial diseases (psoriasis, psoriatic arthritis or arthropathy, and other immunoinflammatory diseases)

The duration of psoriasis will be recorded (to the nearest whole year). For subjects with 'current or previous psoriatic arthritis or psoriatic arthropathy', the duration will be recorded (to the nearest whole year) together with the duration of any other immunoinflammatory diseases the subjects might have.

11.2.3 Trial disease treatment history

The subject's psoriasis- and psoriatic arthritis-specific medication, and medication for other immunoinflammatory diseases, including biologic and non-biologic systemic therapy, phototherapy, and/or topical therapy at any time in the subject's history will be recorded. For

these medications, the reason for discontinuation should be specified. If a treatment was given for both psoriasis and psoriatic arthritis, only the primary treatment indication should be recorded. It must be recorded if the subject has a contraindication to methotrexate, cyclosporine, phosphodiesterase-4 (PDE-4) inhibitors, Janus kinase (JAK) inhibitors, fumaric acid, or psoralen and ultraviolet A treatment (PUVA).

11.2.4 Medical history

Other relevant past and concurrent medical illnesses, based on subject interview, will be recorded in the eCRF. For each condition, diagnosis, treatment, start date, and stop date will be recorded; it will also be recorded if the condition, diagnosis, or treatment is ongoing. Please refer to Section 9.6 for recording of prior and concomitant medications. Relevant medical history also includes diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

11.2.5 Substance use: tobacco and alcohol

The subject's tobacco consumption will be recorded in the eCRF. It will be recorded if the subject has ever consumed tobacco, the type and amount of tobacco consumed, and the duration and frequency of the subject's consumption will be recorded.

The subject's alcohol consumption will be recorded in the eCRF. It will be recorded if the subject consumes alcohol. If applicable, the average number of drinks and frequency of the consumption will be recorded.

11.3 Efficacy assessments

11.3.1 Psoriasis Area and Severity Index

11.3.1.1 Psoriasis Area and Severity Index

The PASI is the most widely used tool in clinical practice and clinical trials to assess the severity and extent of psoriasis (20). The PASI score will be assessed according to the schedule of trial procedures (Section 4). 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.

The PASI is a composite index with scores ranging from 0 to 72, with higher values indicating a more severe or more extensive condition.

The investigator will assess the severity of 3 psoriasis disease characteristics (redness, thickness, and scaliness) on each of the 4 body regions (head/neck, trunk, upper extremities, and lower extremities) according to the severity scale shown in Panel 10. It should be noted

that ‘upper extremities’ include arms and hands, ‘trunk’ includes the axillae and groin, and ‘lower extremities’ include legs, buttocks, and feet.

The investigator will assess the extent of psoriasis within each of the 4 body regions according to the area score scale shown in Panel 11. The assessment of extent is the percentage of the body region affected and not the percentage of the total body surface area (BSA) affected. For example, if one arm and hand are completely affected, and the other arm and hand are completely unaffected, the extent assessment for the upper extremities will be 50%.

For each body region, a combined score is calculated from the sum of severity scores multiplied by the area score and the weighting factor pertaining to that body region. The PASI score equals the sum of the combined scores for each body region (Panel 9).

The investigator must evaluate subject eligibility in relation to inclusion criterion no. 4 for the PASI score at screening and baseline. The evaluation will be captured in the eCRF.

Panel 9: Calculation of the PASI score

Body region	Redness (erythema)	Thickness (induration)	Scaliness (desquamation)	Sum of severity scores	Area score	Weighting factor	Body region score
Head and neck	(SS +	SS +	SS) =	SSS	x AS	x 0.1	
Trunk	(SS +	SS +	SS) =	SSS	x AS	x 0.3	
Upper extremities	(SS +	SS +	SS) =	SSS	x AS	x 0.2	
Lower extremities	(SS +	SS +	SS) =	SSS	x AS	x 0.4	
The PASI score is the sum of the 4 body region scores (head, trunk, arms, and legs) (each calculated as SSS ($SS_{redness}$ + $SS_{thickness}$ + $SS_{scaliness}$) x AS x weighting factor)							(range 0-72)

Abbreviations: AS = area score; PASI = Psoriasis Area and Severity Index; SS = severity score; SSS = sum of severity scores.

Modified from (20).

Panel 10: PASI severity score scale

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)

Abbreviation: PASI = Psoriasis Area and Severity Index.
Modified from (20).

Panel 11: PASI area score scale

0	0% affected area
1	1% to 9% affected area
2	10% to 29% affected area
3	30% to 49% affected area
4	50% to 69% affected area
5	70% to 89% affected area
6	90% to 100% affected area

Abbreviation: PASI = Psoriasis Area and Severity Index.
Modified from (20).

11.3.1.2 Palmoplantar Psoriasis Area and Severity Index

The palmoplantar PASI (PP-PASI) is a point-based system quantifying the area and severity of palmoplantar psoriasis. The PP-PASI measures erythema, induration, and desquamation on a scale of 0-4, with 4 being the most severe (Panel 12). The weighting factor for each palm is

20%, while that of each sole is 30%. The PP-PASI tool is widely used as a measure of improvement of palmoplantar psoriasis in clinical trials.

Only subjects with palmoplantar psoriasis at baseline will be followed post randomisation using the PP-PASI tool.

Panel 12: PP-PASI score scale

Score	Erythema (E)	Induration (I)	Desquamation (D)	Area involved (%)
0	None	None	None	0
1	Slight	Slight	Slight	1-9
2	Moderate	Moderate	Moderate	10-29
3	Severe	Severe	Severe	30-49
4	Very severe	Very severe	Very severe	50-69
5	--__	__	__	70-89
6	__	__	__	90-100
The PP-PASI score is calculated as follows: [(E+I+D) × area × 0.2 – right palm] + [(E+I+D) × area × 0.2 – left palm] + [(E+I+D) × area × 0.3 – right sole] + [(E+I+D) × area × 0.3 – left sole]				

Abbreviation: PP-PASI = palmoplantar PASI.
Modified from (21).

11.3.2 Investigator's Global Assessment

11.3.2.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of psoriasis and is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Panel 13). The IGA score will be assessed according to the schedule of trial procedures (Section 4). 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. The disease severity assessment score will be recorded in the eCRF.

Panel 13: Investigator's Global Assessment

Score	Disease severity	IGA morphological descriptors
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink colouration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red colouration; 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 thickening with hard edges; bright to deep dark red colouration; severe/coarse scaling covering almost all or all lesions

Modified from (22).

11.3.2.2 Palmoplantar Investigator's Global Assessment

The PP-IGA tool assesses a combination of erythema and secondary features (plaque elevation and/or scaling); it is based on the above-mentioned IGA (22) specifically applied to the palms and soles. For the analysis of responses, the subject's palmoplantar psoriasis is assessed as follows: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe.

Only subjects with palmoplantar psoriasis at baseline (Week 0; Visit 2) will be followed post randomisation using the PP-IGA tool.

11.3.3 Static Physician's Global Assessment of genitalia

The sPGA-G score is based on a combination of erythema and secondary features (plaque elevation and/or scaling). For the analysis of responses, the subject's genital psoriasis is assessed as follows: 0 = clear, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe.

Panel 14: Static Physician's Global Assessment of genitalia

Score	Category	Category description[1]
0	Clear	Erythema: residual or no erythema. Plaque elevation: no elevation. Scaling: no scale.
1	Minimal	Erythema: faint, light pink erythema. Plaque elevation: elevation is very slight and difficult to confirm. Scaling: some fine, white surface dryness.
2	Mild	Erythema: mild, pink erythema. Plaque elevation: slight elevation with sloped edges. Scaling: fine scale on some or most lesions.
3	Moderate	Erythema: moderate, red erythema. Plaque elevation: slight elevation with sloped edges. Scaling: coarse scale on most lesions.
4	Severe	Erythema: severe, bright red erythema. Plaque elevation: substantial elevation, hard or sharp edges. Scaling: coarse, non-adherent scale on most or all lesions.
5	Very severe	Erythema: very severe, deep red erythema. Plaque elevation: very significant elevation with hard and sharp edges. Scaling: very coarse, thick, and adherent scale completely or nearly completely covering most or all lesions.

1) Severity is determined by a combination of 3 plaque characteristics (erythema, elevation, and scaling) based on descriptions of each characteristic. Erythema is the primary characteristic that should influence the rating, with plaque elevation and scaling considered as secondary. Assessment does not require all 3 characteristics to be present.

Modified from (23).

Only subjects with genital psoriasis at baseline (Week 0; Visit 2) will be followed post randomisation using the sPGA-G tool.

11.3.4 Patient-reported outcomes

The subjects will receive an electronic diary (eDiary) device and eDiary training at screening (Visit 1). The subject should bring the device once at baseline (Week 0, Visit 2). The eDiary should be returned at the last visit at the latest.

Each subject will make individual assessments relating to their perception of the disease and quality of life. These assessments will be performed prior to the investigator performing any efficacy assessments. The investigator should not question the subject's answers for any of the patient-reported outcomes (PROs). The investigator must review the data for timeliness and completeness.

Symptoms reported in the PROs 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?” or as per the instructions given for C-SSRS and PHQ-8 (Section 11.5).

The PROs will be completed according to the schedule of trial procedures (Section 4).

11.3.4.1 Dermatology Life Quality Index

The DLQI is a validated questionnaire with content specific to those with dermatology conditions. 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 (24). 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 questionnaire will be filled out on a separate device.

11.3.4.2 36-Item Short Form Health Survey

The 36-Item Short Form Health Survey version 2 (SF-36v2; acute recall) is a 36-item general health status assessment. Subjects will be asked to answer each question by selecting 1 of 3 to 6 categorical response options. The instrument instructions do not state a specific recall period; however, a recall period is defined within most items. The acute recall version, which asks subjects about the last week, will be used in this trial (25).

The SF-36v2 (acute recall) yields scores for 8 health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and 2 psychometrically derived summary scores (a physical component summary and a mental component summary).

The SF-36v2 questionnaire will be filled out on a separate device.

11.3.4.3 Pruritus Numeric Rating Scale

The pruritus NRS renders a quantitative symbolisation of itch. This validated scale is used by presenting the respondent with an ordered set from which to choose. Subjects will assess their worst itch over the past 24 hours using an 11-point NRS with 0 indicating ‘no itch’ and 10 indicating ‘worst possible itch’.

The pruritus NRS will be completed daily by the subject at home on eDiary from screening onwards.

11.3.4.4 Pain Numeric Rating Scale

The pain NRS renders a quantitative symbolisation of pain. This validated scale is used by presenting the respondent with an ordered set from which to choose. Subjects will assess their worst pain over the past 24 hours using an 11-point NRS with 0 indicating ‘no pain’ and 10 indicating ‘worst possible pain’.

The pain NRS will be completed daily by the subject at home on eDiary from screening onwards.

11.4 Safety assessments

11.4.1 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed according to the schedule of trial procedures (Section 4). The subjects must relax in a supine position for >5 minutes before the measurements are done.

If an abnormal vital sign at screening is considered to be clinically significant by the investigator, it will be at the discretion of the investigator to decide if the subject should be randomised into the trial.

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false. If the third measurement confirms the first measurement (abnormal), the second measurement will be considered false. Only the last value measured and considered correct will be recorded in the eCRF.

Reporting in eCRF
Vital signs will be recorded in the eCRF. If vital signs were not assessed, a reason should be given. Clinically significant abnormal vital signs at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.4.2 Physical examination

An abbreviated physical examination will be performed by the investigator according to the schedule of trial procedures (Section 4) and must include:

- General appearance.
- Lymph nodes.
- Dermatologic examination of the skin.

If an abnormal finding at screening or baseline is considered to be clinically significant by the investigator, it will be at the discretion of the investigator to decide if the subject should be randomised into the trial.

Reporting in eCRF
It will be recorded in the eCRF if a physical examination was performed and, if applicable, the investigator's evaluation ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'); if a physical examination was not performed, a reason should be given.

Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.4.3 Body measurements

As part of the physical examination, the following must be measured and collected in the eCRF at the visits specified in the schedule of trial procedures (Section 4):

- The subject's height without shoes (only measured at screening).
- The subject's weight (in indoor clothing and without shoes).

11.4.4 Laboratory testing

11.4.4.1 Overview

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4). The tests shown in Panel 15 will be performed.

Panel 15: Clinical laboratory tests

Biochemistry	Haematology and differential	Urine analysis
Sodium Potassium Calcium Bicarbonate Albumin Blood urea nitrogen Creatinine Uric acid Total bilirubin[1] Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase C-reactive protein Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose eGFR (only at screening)	Red blood cell count Haemoglobin Haematocrit Platelets White blood cell count Differential (absolute count and %): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Urine dipstick[2]: • Specific gravity • pH • Occult blood • Protein • Glucose • Leucocyte esterase • Ketones Urine pregnancy test[3] Albumin-to-creatinine ratio[4] **Other** Serum beta hCG[3] Tuberculosis test (if applicable) HIV, HBV, HCV (only at screening)

Abbreviations: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; hCG = human chorionic gonadotropin; HDL = high density lipoprotein; HIV = human immunodeficiency virus; LDL = low density lipoprotein.

1) If total bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Urine samples will be tested at the trial site (dipstick). In case of abnormal dipstick results, a urine sample will be sent to the central laboratory.
3) Only women of childbearing potential. Urine pregnancy tests will be performed at the trial sites. If a urine pregnancy test is positive, a serum pregnancy test must be done to confirm the result. At screening, a serum pregnancy test is always performed.
4) Only at screening, in case of abnormal dipstick result.

11.4.4.2 Investigator evaluation of laboratory samples

Central laboratory
Chemistry, haematology, urinalysis (if applicable), serology, and serum pregnancy tests will be analysed by a central laboratory which will provide results to the trial sites. The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date the report for documentation of the review. The signed and dated version will be filed with the investigator's trial documentation. Clinically significant abnormal tests must be repeated as soon as possible to confirm the abnormality. Subjects with clinically significant abnormal test results should be followed up at the discretion of the investigator.

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial. However, subjects meeting exclusion criterion no.16 (laboratory abnormalities) must not be randomised into the trial.

A laboratory manual will be provided to the trial sites specifying the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this trial.

Tests performed at the trial site
Urine samples will be tested with a dipstick according to the schedule of trial procedures (Section 4). If a dipstick shows any abnormal reading, a urine sample must always be collected and sent to the central laboratory for further analysis, regardless of causality or investigator's assessment of significance.

Women of childbearing potential will have a urine pregnancy test performed at the trial site at baseline prior to randomisation. The test will be repeated every 4 weeks as shown in the schedule of trial procedures in Section 4.

Reporting in eCRF

At each visit where samples must be taken, the site staff will record in the eCRF if a sample (urine/blood) was taken and the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant').

It will be recorded in the eCRF if the subject is a woman of childbearing potential and if a urine pregnancy test was performed, if not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition will be reported as an AE. Any new clinically significant abnormal laboratory values, sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.5 Other assessments: Patient-reported outcomes

11.5.1 Overview

The C-SSRS must be completed after all other assessments have been performed at the trial visit, but prior to IMP administration. The investigator should not question the subject's answers. The investigator must review the data for eligibility (at screening and at baseline), timeliness, and completeness, and take appropriate action (see below) before the subject leaves the trial site.

11.5.2 Columbia-Suicide Severity Rating Scale

The C-SSRS is a rater-administered, standardised, and validated instrument developed for the assessment of the severity and frequency of SIB (26, 27).

The C-SSRS is divided into suicidal ideation (category 1 to 5), suicidal behaviour (category 6 to 9), completed suicide (category 10), and non-suicidal self-injurious behaviour:

Suicidal ideation

- Category 1: Wish to be dead.
- Category 2: Non-specific active suicidal thoughts.
- Category 3: Active suicidal ideation with any methods (not plan) without intent to act.
- Category 4: Active suicidal ideation with some intent to act, without specific plan.

- Category 5: Active suicidal ideation with specific plan and intent.

Suicidal behaviour

- Category 6: Preparatory acts or behaviour.
- Category 7: Aborted attempts.
- Category 8: Interrupted attempts.
- Category 9: Actual attempts (non-fatal).

Completed suicide

- Category 10: Completed suicide.

Non-suicidal self-injurious behaviour

- Non-suicidal self-injurious behaviours.

At all visits where the C-SSRS interview must be performed (see Section 4), it must be done after all other visit activities have been completed. However, the C-SSRS interview must be performed and the answers reviewed before the IMP administration. The C-SSRS takes approximately 3 to 10 minutes to complete.

The investigator must evaluate the subject's eligibility in relation to exclusion criteria no. 11 and 12 for the C-SSRS components 'history of suicidal behaviour' and 'suicidal ideation' at screening (Visit 1) and baseline (Visit 2; Week 0).

The 'baseline' paper version of the C-SRSS will be used at screening and the 'since last visit' paper version will be used at all subsequent visits. The C-SSRS assessments will be transcribed into the eCRF.

Subjects with suicidal ideation of category 4 or 5 or any suicidal behaviour must be referred to a mental health professional and be discontinued from IMP. In addition, the event must be reported as an AE.

11.5.3 Patient Health Questionnaire-8

The PHQ-8 is a validated and widely used 8-item version of the Patient Health Questionnaire depression scale designed to clinically assess subjects for symptoms and signs of depression (16).

At all visits where the PHQ-8 must be completed (see Section 4), the answers must be reviewed by the investigator before the IMP administration. The PHQ-8 questionnaire will be filled out on a separate device and takes approximately 3 minutes to complete.

For PHQ-8 scores ≥10, the subject must be referred to a mental health professional (score ≥10 is cut-point for defining current depression), and the event must be reported as an AE (16). Subjects scoring ≥15 must in addition be discontinued from IMP.

11.6 End of trial

Both an end-of-treatment form and an end-of-trial form will be completed in the eCRF for all randomised subjects.

11.6.1 End-of-treatment form

An end-of-treatment form will be completed in the eCRF for all randomised subjects when they have had their last administration of IMP. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (see Section 10.3 for early termination assessments).

It will be recorded on the end-of-treatment form if the subject completed the treatment. If not, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

11.6.2 End-of-trial form

An end-of-trial form must be completed in the eCRF for all randomised subjects. The following data will be collected:

- Did the subject complete the trial. If not, the primary reason for early termination must be recorded.
- Date of last contact.
- Primary reason for withdrawal from trial (lack of efficacy, adverse event, withdrawal by subject, lost to follow-up, death, pregnancy, other). ‘Lack of efficacy’ should be assigned when a subject experiences aggravation/exacerbation/worsening of the trial disease, even when it is documented as an (S)AE according to Section 13.6.5. If ‘other’ is selected, a specification must be provided in the eCRF.

The end-of-trial form will be completed when the subject has had his/her last visit (that is, the final visit at Week 28, or earlier in case of early termination [see Section 10]).

11.7 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, and serology. The total volume of blood to be drawn is approximately 60 mL, which is significantly less than the total volume of blood drawn during a blood donation (approximately 500 mL).

11.8 Storage of biological samples

Blood and urine samples are collected only for clinical laboratory tests in the trial (haematology, biochemistry, serology, and urinalysis). The storage of these biological samples will therefore follow the standard operating procedures at the sites and laboratories where the tests are conducted. Typically, samples are stored for no more than a few days after sample collection.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This is a phase 4, randomised, blinded (subject and assessor), parallel-group, multi-site, clinical trial. The parallel-group design is chosen as it is the only appropriate design to evaluate the trial objectives. Furthermore, randomisation provides the most reliable method removing selection bias between 2 groups of subjects. Additionally, the randomisation will be stratified by body weight to further ensure comparability of the treatment groups. The subjects and the assessors will be blinded, as it is the only design that can provide strong clinical evidence compared with the alternative designs, e.g. assessor-blinded only. Additionally, a blinded design is also expected to be a requirement from regulatory authorities.

The duration of the trial is approximately 32 weeks including a screening period of 2 to 4 weeks, and the primary endpoint is assessed at Week 16, ensuring a treatment duration long enough for efficacy and safety evaluations for both treatments during the induction period. Moreover, from the clinical perspective, it is also important to investigate if the treatment differences are sustained for a longer period. Therefore, an additional 12 weeks of active treatment are included, resulting in a total of 28 weeks of therapy, providing enough time to evaluate if efficacy is sustained for both treatments.

The eligible trial population is described in detail in Section 8. Most criteria are defined according to the approved IB of Kyntheum® and EU SmPC of Tremfya®. Inadequate response to ustekinumab is defined as IGA ≥2 after at least 3 doses at or higher than the approved dose or frequency, and this correlates well with the currently acceptable treatment goals.

This trial will provide a direct comparison of brodalumab and guselkumab on regimens according to the approved IB/SmPC. The data generated could support evidence-based decisions on sequencing and switching biologic treatments within psoriasis in the clinical setting.

12.2 Appropriateness of assessments

12.2.1 Rationale for primary endpoint

PASI is the most thoroughly validated and the most extensively studied psoriasis clinical severity scoring tool, which assesses the extent of psoriasis at 4 anatomical regions with the signs of erythema, scale, and elevation (28). The efficacy endpoint, PASI 75, together with static Physician's Global Assessment (sPGA) score of 1 or 0, are recommended by the European Medicines Agency (EMA) for assessment of clinical efficacy (29) and recognised

as important endpoints in clinical trials in psoriasis by regulatory authorities in the EU. However, with more effective treatments emerging, patients and physicians are increasingly looking for more ambitious response parameters. As this trial aims to compare 2 highly efficacious drugs, it is considered that PASI 100 is the most reliable and relevant response criterion to identify the differences in efficacy among the 2 treatments.

12.2.2 Rationale for assessment of palmoplantar psoriasis

Palmoplantar psoriasis is a variant of plaque psoriasis that develops on the palms and soles. It can be seen with or without psoriasis elsewhere on the body and affects approximately 3–4% of all psoriasis patients (30, 31).

Treatment for palmoplantar psoriasis is often challenging, as the thick epidermal layers of the palms and soles prevent local action of topical treatments (32). However, randomised controlled trials on the efficacy and safety of biologics for treatment of palmoplantar psoriasis are still limited, because palmoplantar psoriasis patients usually do not have sufficiently high BSA involvement to meet the inclusion criteria (32-34).

Less than 5% BSA is involved in palmoplantar psoriasis without involvement of other body areas. Despite this relatively small BSA involvement, subjects with palmoplantar psoriasis suffer from substantial impairment of health-related quality of life, having difficulty with daily activities involving hands and feet (34, 35).

Therefore, palmoplantar psoriasis is a disease with significant quality-of-life issues, where more data from clinical trials are needed. The psoriasis patients with predominantly hands and/or feet involvement are able to participate in this trial due to lack of a BSA inclusion criterion. Hence, the PP-IGA and PP-PASI are included in this trial, as they are validated, reliable, and responsive assessments of palmoplantar psoriasis, which have been used in previous clinical trials (36-38).

12.2.3 Rationale for assessment of genital psoriasis

Traditionally, the genitals have been acknowledged as a vulnerable and difficult-to-treat area with topicals. Thus, there is an unmet need for effective and proven treatments of genital psoriasis.

Questionnaire-based studies have shown a high prevalence of genital psoriasis among patients with plaque psoriasis (28.6–46%) (39, 40). A clinical observational study showed that the current prevalence of genital psoriasis was 38% and the lifetime prevalence of genital psoriasis was as high as 63% (41). While psoriasis in the genital area is often overlooked and

left untreated, it has been shown to have a significant impact on health-related quality of life and it is associated with a high disease burden (42).

Previous tools for assessing genital psoriasis have not been widely accepted or used in clinical trials or in clinical practice. Recently, the sPGA-G was developed and validated for the assessment of genital psoriasis in clinical trials (23, 43). The tool has been accepted by the United States Food and Drug Administration (FDA).

Taken together, genital psoriasis is an important and often overlooked manifestation of psoriasis in which data from clinical trials are needed. The sPGA-G is considered a relevant and feasible tool for the assessment of genital psoriasis and is therefore included as a clinical assessment in this trial.

13 Adverse events

13.1 Definition and classification of adverse events

AEs and SAEs are defined in Appendix 1.

Classification of AEs in terms of severity, causality, and outcome is defined in Appendix 2. Causality assessment will be made for all IMPs (brodalumab, guselkumab, and dummies).

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject has signed the ICF until completion of the clinical trial (Section 7.3).

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, for example: “How have you felt since I saw you last?” No specific symptoms should be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

Refer to Sections 11.4.1 to 11.4.4 for principles of data entry in the eCRF with regard to vital signs and laboratory results (e.g. abnormal findings).

13.3 Reporting of adverse events

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

The *AE term* must be in precise English medical terminology (that is, 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 (if the event is ongoing, it will also be recorded). In addition, it will be recorded if the AE started prior to first administration of IMP.

AEs must be classified in terms of severity, causality, and outcome according to the definitions in Appendix 2.

Action taken with IMP: any action taken with IMP as a consequence of the AE must be recorded (dose not changed, temporary discontinuation of IMP, permanent discontinuation of IMP, not applicable, unknown).

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

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

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1. SAE criteria are also listed on the SAE form.

13.4.1 Investigator reporting responsibilities

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

By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE.

The actual reporter, if not the investigator, should also sign and date the SAE report.

The completed SAE form must be faxed or scanned and e-mailed to Global Safety at LEO Pharma using the e-mail address or fax number below:

Global Safety at LEO Pharma

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

Fax number: +45 6910 2468

If relevant, the investigator will enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

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

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

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO Pharma reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether or not an SAE is expected. The relevant reference safety information documents for this clinical trial are:

- For brodalumab, the IB Section 7.2, edition 13.0 and subsequent updates must be used.
- For Tremfya® (guselkumab) the current SmPC in the EU must be used.

Global Safety at LEO Pharma will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned countries.

The IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned countries.

All SAEs which are assessed as causally related to the IMP(s) **by either the investigator or LEO Pharma (44)**, 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 the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or termination

and final outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Section 13.4.1.

Pregnant subjects must immediately discontinue IMP permanently (Sections 10.2.1 and 10.3).

13.5.2 Adverse events of special interest

The following AEs of special interest (AESIs) have been defined: SIB, serious infections (i.e. infections meeting the criteria of being an SAE), malignancy diagnosed after randomisation (except basal cell carcinoma, squamous cell carcinoma of the skin, and cervical carcinoma in situ), and major adverse cardiac events (MACE) defined as stroke, myocardial infarction, or cardiovascular death. These AESIs 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 immunomodulating biologics used for psoriasis. AESIs must be reported to LEO Pharma as described in Panel 16.

Panel 16: Adverse events of special interest

AESI	Additional data to be collected
SIB	Any SIB event must be reported to LEO Pharma Global Safety (Section 13.4.1) on a specific SIB AE form within 24 hours of first knowledge, no matter whether the event is considered serious or non-serious. For SIB events, the specific SIB AE form replaces the standard LEO Pharma SAE form.
Serious infections	Any serious infection must be reported to LEO Pharma Global Safety (Section 13.4.1) on the standard LEO Pharma SAE form within 24 hours of first knowledge.
MACE	Any MACE must be reported to LEO Pharma Global Safety (Section 13.4.1) on the standard LEO Pharma SAE form within 24 hours of first knowledge.
Malignancy diagnosed after randomisation (except basal cell carcinoma, squamous cell carcinoma of the skin, and cervical carcinoma in situ)	Any malignancy events that meet the criteria of being serious must be reported to LEO Pharma Global Safety (Section 13.4.1) on the standard LEO Pharma SAE form within 24 hours of first knowledge. The following should be included, if available: • Histology report. • Oncology assessment. • Treatment (surgery, radiation, chemotherapy, other). If a malignancy event does not meet the criteria of being serious, it should only be reported on the AE form in the eCRF as described in Section 13.3 and reporting within 24 hours is not required.

Abbreviations: AE = adverse event; eCRF = electronic case report form; MACE = major adverse cardiac events; SAE = serious adverse event; SIB = suicidal ideation and behaviour.

13.6 Reporting of other events

13.6.1 Overdose

An overdose is defined as a subject receiving a quantity of IMP which is in excess of that specified in this protocol. An overdose is either accidental or intentional. An accidental overdose must be documented in the eCRF as a medication error as described in Section 13.6.2. An intentional overdose should be documented as misuse or abuse (see Sections 13.6.3 and 13.6.4).

If the overdose is accidental and due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 9.10.

LEO Pharma does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat any overdose if necessary.

13.6.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP while in the control of the investigator or subject. Broadly, medication errors fall into 3 categories: wrong medication, wrong dose (including overdose, form, concentration, amount), wrong route of administration.

The medication error category must be documented on the other event form in the eCRF. In addition, AEs originating from a medication error must be recorded on the AE form as separate events. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (Section 13.4).

If the medication error is due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 9.10.

13.6.3 Misuse

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

The term ‘misuse’ must be recorded on the other event form in the eCRF. In addition, AEs originating from misuse must be recorded on AE form as separate events. If the AE originating from misuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.4 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 recorded on the other event form in the eCRF. In addition, AEs originating from abuse must be recorded on the AE form as separate events. If the AE originating from abuse qualifies as an SAE, expedited reporting is required (Section 13.4).

13.6.5 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared to screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.

In case the aggravation/exacerbation/worsening of the trial disease leads to permanent discontinuation of IMP or withdrawal from the trial, 'lack of efficacy' should be chosen as the primary reason for discontinuation of IMP / withdrawal from the trial in accordance with Section 10.2.1 and Section 11.6.2.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). SAEs must be followed up until a final outcome has been established, that is, the follow up may continue beyond the end of the clinical trial. For SAEs which have stabilised and cannot be expected to recover during the trial, for example chronic or stabilised conditions, 'not recovered' is accepted as a final outcome. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

13.8 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 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.*" (45).

If the investigator becomes aware of information that requires an immediate change in a clinical trial procedure or a temporary halt of the clinical trial to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO Pharma, regulatory authorities, or IECs.

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

LEO Pharma must act immediately upon receipt of the urgent safety measure notification in accordance with internal procedures and local legislation.

14 Statistical methods

14.1 Sample size

The primary and key secondary endpoints for this trial are having PASI 100 response at Week 16 and the time from randomisation to PASI 100 response. Denoting the Week 16 response rates by π and the sub-distribution hazard rates for having PASI 100 response at time t, measured in weeks, by $\lambda(t)$, the null hypothesis for the primary endpoint,

$$H_0: \pi_{broda} - \pi_{gus} \leq 0,$$

will be tested versus the 1-sided alternative,

$$H_1: \pi_{broda} - \pi_{gus} > 0,$$

while, for the key secondary endpoint, the null hypothesis,

$$H_0: \lambda_{broda}(t) = \lambda_{gus}(t),$$

will be tested versus the alternative,

$$H_1: \lambda_{broda}(t) \neq \lambda_{gus}(t).$$

Panel 17 provides the estimated PASI 100 response rates based on an assessment of the 124 subjects initially randomised to ustekinumab in the AMAGINE-2 and -3 trials, who received brodalumab 210 mg Q2W as rescue therapy starting at Week 16. To qualify for rescue medication in the AMAGINE-2 and -3 trials at Week 16, subjects must have had an sPGA ≥3 at Week 16 or an sPGA =2 for at least 4 weeks up to and including Week 16. In order to derive the estimates presented in Panel 17, missing data was imputed using non-responder imputation (NRI).

Panel 17: PASI response rates after the initiation of brodalumab 210 mg Q2W as rescue therapy among subjects initially randomised to ustekinumab in the AMAGINE-2 and -3 trials

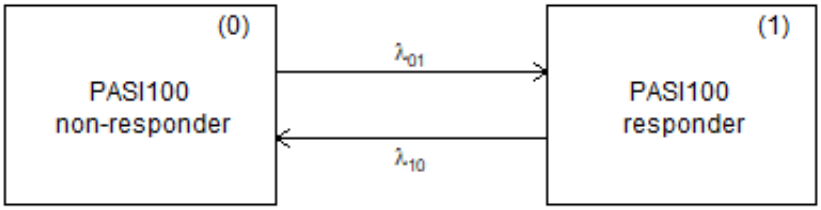
Week	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)	# Imputed by NRI
0	23.4	4.8	0.0	0
2	53.2	19.4	4.8	2
4	67.7	37.1	13.7	3
8	71.0	52.4	29.8	1
12	73.4	58.1	35.5	4
16	78.2	61.3	34.7	9
20	79.0	62.1	42.7	12
24	83.9	62.9	41.1	11
28	79.8	62.9	41.1	14
32	76.6	63.7	38.7	15
36	71.8	57.3	35.5	20

Abbreviations: NRI = non-responder imputation; PASI = the Psoriasis Area and Severity Index; Q2W = every 2 weeks.

In order to power this trial, data were simulated from the two-state alternating continuous-time Markov process displayed in Panel 18. The 'two-state alternating model' assumes that the transition intensity functions are constant over time. The benefit of the multi-state framework is that it naturally captures the correlation between the time from randomisation to PASI 100 response and the PASI 100 response status at Week 16. Estimates of the transition intensities for brodalumab were obtained by fitting the 'two-state alternating model' based on data from the AMAGINE-2 and -3 trials, among subjects receiving brodalumab 210 mg Q2W as rescue therapy after initially being randomised to ustekinumab. The model was fitted using the multi-state model (MSM) package in R, which accounts for the non-informative intermittent inspection process used to obtain the data. For guselkumab, the expected PASI 100 response rates, based on the 'two-state alternating model', were derived from the Chapman-Kolmogorov equation,

$$\pi_{PASI100}(t)=1 - \left[\frac{\lambda_{10}}{\lambda_{10}+\lambda_{01}}+\frac{\lambda_{01}}{\lambda_{10}+\lambda_{01}}e^{-(\lambda_{01}+\lambda_{10})t}\right]$$

Panel 18: Two-state alternating model used to simulate patient-level data, in order to power the trial



The estimated transition intensities for the guselkumab arm were then derived by minimising the mean squared error, based on the approximate observed rates extracted from the NAVIGATE trial shown in Panel 19.

Panel 19: Approximate PASI 100 response rates for the guselkumab arm, reported in the NAVIGATE trial

Week	PASI 100 (%)
0	0.0
4	3.2
8	7.6
12	11.3
16	18.0
20	23.2
24	21.0
28	22.4
36	20.3

Abbreviations: PASI 100 = 100% improvement from baseline in the Psoriasis Area and Severity Index.
Source: (4).

Panel 20 provides the estimated marginal power for the primary and key secondary endpoints and the conjunctive power for rejecting the null hypotheses associated with the primary and key secondary endpoints, while controlling the familywise error rate (FWER) at the 5% significance level (for 2-sided Fisher's Exact and Gray's tests). The power analysis is based on 100,000 simulations, from the alternating two-state model illustrated in Panel 18, assuming the underlying transition intensities for the brodalumab arm were,

e) $\lambda_{\text{broda},0,1} = 1.00 \cdot \hat{\lambda}_{\text{broda},0,1} = 0.0333$ and $\lambda_{\text{broda},1,0} = 1.00 \cdot \hat{\lambda}_{\text{broda},1,0} = 0.0272$,

l) $\lambda_{\text{broda},0,1} = 0.98 \cdot \hat{\lambda}_{\text{broda},0,1} = 0.0326$ and $\lambda_{\text{broda},1,0} = 1.02 \cdot \hat{\lambda}_{\text{broda},1,0} = 0.0277$ or

u) $\lambda_{\text{broda},0,1} = 1.02 \cdot \hat{\lambda}_{\text{broda},0,1} = 0.0340$ and $\lambda_{\text{broda},1,0} = 0.98 \cdot \hat{\lambda}_{\text{broda},1,0} = 0.0266$,

and assuming the underlying transition intensities for the guselkumab arm were

e') $\lambda_{\text{gus},0,1} = 1.00 \cdot \hat{\lambda}_{\text{gus},0,1} = 0.0158$ and $\lambda_{\text{gus},1,0} = 1.00 \cdot \hat{\lambda}_{\text{gus},1,0} = 0.0435$,

l') $\lambda_{\text{gus},0,1} = 0.98 \cdot \hat{\lambda}_{\text{gus},0,1} = 0.0155$ and $\lambda_{\text{gus},1,0} = 1.02 \cdot \hat{\lambda}_{\text{gus},1,0} = 0.0444$ or

u') $\lambda_{\text{gus},0,1} = 1.02 \cdot \hat{\lambda}_{\text{gus},0,1} = 0.0162$ and $\lambda_{\text{gus},1,0} = 0.98 \cdot \hat{\lambda}_{\text{gus},1,0} = 0.0427$.

The scenarios described in bullet points l), u), l') and u') have been introduced for robustness of the resulting sample size with respect to small perturbations of the transition intensities.

Panel 20: Estimated conjunctive power for rejecting the hypotheses associated with the primary and key secondary endpoints

Sample size per arm	Scenario for transition intensities						Power for the primary endpoint	Power for the key secondary endpoint	Conjunctive power
		$\lambda_{broda,0,1}$	$\lambda_{broda,1,0}$		$\lambda_{gus,0,1}$	$\lambda_{gus,1,0}$			
N=110	e)	0.0333	0.0272	e')	0.0158	0.0435	83.3%	96.8%	82.5%
N=110	e)	0.0333	0.0272	l')	0.0155	0.0444	85.3%	97.4%	84.6%
N=110	e)	0.0333	0.0272	u')	0.0162	0.0427	80.9%	95.8%	79.9%
N=110	l)	0.0326	0.0277	e')	0.0158	0.0435	80.7%	95.8%	79.7%
N=110	l)	0.0326	0.0277	l')	0.0155	0.0444	82.5%	96.4%	81.6%
N=110	l)	0.0326	0.0277	u')	0.0162	0.0427	78.0%	94.7%	76.8%
N=110	u)	0.0340	0.0266	e')	0.0158	0.0435	85.8%	97.5%	85.1%
N=110	u)	0.0340	0.0266	l')	0.0155	0.0444	87.5%	98.0%	86.9%
N=110	u)	0.0340	0.0266	u')	0.0162	0.0427	83.8%	96.9%	83.0%
N=120	e)	0.0333	0.0272	e')	0.0158	0.0435	87.0%	97.8%	86.4%
N=120	e)	0.0333	0.0272	l')	0.0155	0.0444	88.5%	98.3%	88.0%
N=120	e)	0.0333	0.0272	u')	0.0162	0.0427	84.7%	97.1%	84.0%
N=120	l)	0.0326	0.0277	e')	0.0158	0.0435	84.1%	96.9%	83.3%
N=120	l)	0.0326	0.0277	l')	0.0155	0.0444	86.0%	97.6%	85.3%
N=120	l)	0.0326	0.0277	u')	0.0162	0.0427	81.9%	96.2%	81.0%
N=120	u)	0.0340	0.0266	e')	0.0158	0.0435	89.3%	98.4%	88.8%
N=120	u)	0.0340	0.0266	l')	0.0155	0.0444	90.6%	98.7%	90.2%
N=120	u)	0.0340	0.0266	u')	0.0162	0.0427	87.2%	97.9%	86.6%

Abbreviation: N = number of subjects.

Based on the above assumptions and results, a sample size of 240 subjects would ensure a conjunctive power of at least 80% in order to reject the null hypotheses for both the primary and key secondary endpoints for all of the illustrated scenarios.

14.2 Trial analysis sets

All screened subjects will be accounted for in the clinical trial report (CTR).

All randomised subjects will be included in the intention-to-treat (ITT) analysis set and will be analysed based on the planned (randomised) treatment allocation. The full analysis set (FAS) will consist of all randomised subjects with at least 1 post-baseline PASI assessment and be analysed based on the planned (randomised) treatment allocation.

A safety analysis set will be defined as all subjects who received IMP and will be analysed according to the actual treatment received.

14.3 Statistical analysis

14.3.1 General principles

Unless otherwise stated, significance tests will be 2-sided with a significance level of 5%; CIs will be presented with 95% degree of confidence; efficacy analyses will be based on FAS; safety analyses will be based on the safety analysis set; the presentation of supplementary estimands will be reserved for primary and key secondary endpoints only; and least square (LS)-mean estimates will be based on the observed margins.

Inference based on multiple imputation methods will consist of n=1,000 imputed datasets to ensure that the between-imputation variance is estimated with adequate precision. For the analysis of binary endpoints relying on multiple imputation methods to address missing data, the risk differences and log odds ratios along with the associated standard errors will be pooled directly based on Rubin’s rules to quantify the potential treatment benefit. For the analysis of multiply-imputed datasets using analysis of covariance (ANCOVA), the estimated regression coefficients and associated standard errors will be pooled directly using Rubin’s rules.

Tabulations of data by visit will explicitly account for missing data. Categorical data will be summarised by treatment arm, using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, median, standard deviation (SD), minimum, and maximum values.

Any changes from the statistical analyses planned in this clinical trial protocol will be described and justified in either a protocol amendment, the SAP, and/or in the CTR depending on the ramifications of the proposed changes.

14.3.2 Handling of missing values and imputation

Likelihood methods, as well as single and multiple imputation methods will be implemented to account for the presence of missing data and to address occurrences of intercurrent events by 'hypothetical' strategies in the statistical analysis of the primary and secondary endpoints. For imputation-based methods, non-monotone missing data will be imputed based on a Markov Chain Monte Carlo method, assuming an underlying multi-variate normal distribution for continuous endpoints and the fully-conditional specification method for binary or ordinal endpoints. For imputation-based methods, monotone missing data will be imputed based on a monotone regression method for continuous endpoints and a fully-conditional specification logistic regression method for binary or ordinal endpoints. The variables used in the analysis model will be included in the imputation model. Here, the categorization into non-monotone and monotone missing data-patterns is based on all scheduled visits.

Multiple imputation methods that will be implemented as part of the analyses of the primary and key secondary endpoints include the 'delta-adjusted' pattern-mixture model and the 'retrieved-data' pattern-mixture model. The missing data methods are designed to assess the robustness of the results of the primary analysis, with respect to the assumptions made regarding missing data.

The 'delta-adjusted' pattern-mixture model provides a convenient framework for assessing the impact of departures from the missing at random (MAR) assumption in instances where the 'control-based' pattern-mixture model is not reasonable, e.g. when comparing 2 active treatments. For continuous endpoints, the 'delta-adjusted' pattern-mixture model assumes that within a given treatment arm, the mean response value among subjects no longer receiving treatment differs from the mean response among subjects remaining on treatment by a specified margin, denoted by Δ. For a given treatment arm at a specific timepoint, missing data are imputed based on the distribution of the conditional mean fitted to the observed data adjusted by the specified margin, Δ. When imputing missing binary data in the context of a logistic regression model, Δ is interpreted as the odds ratio of responding for withdrawals vs. completers. Similarly, for the imputation of missing time-to-event data based on a proportional hazards model, Δ is interpreted as the hazard ratio comparing withdrawals vs. completers.

The ‘retrieved-data’ pattern-mixture model assumes that within a given randomised treatment arm, the mean response value among subjects who withdraw from the trial, is given by the mean response among subjects who discontinue IMP but remain in the trial. Separate imputation models are therefore required for the trial populations defined by the randomised treatment allocation, along with discontinuation status.

Endpoint-specific considerations regarding the implementation of multiple imputation algorithms will be specified in the SAP.

14.3.3 Disposition of subjects

An overall summary of subject disposition will be presented. The disposition summary will include information on the number of subjects screened, randomised, exposed, included in the FAS, permanently discontinuing IMP, and withdrawing from the trial by treatment arm and overall.

Stacked cumulative incidence plots of the time to permanent discontinuation of IMP and withdrawal from trial will be presented separately for the ITT analysis set by treatment arm and reason.

14.3.4 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for the ITT analysis set by treatment arm and overall.

Demographics include age, sex, race, and ethnicity. Baseline characteristics include height, weight, body mass index, smoking status, alcohol use, duration of psoriasis, and previous psoriasis therapy including prior biologic use. In addition to the above specified baseline characteristics, the following baseline measures of disease severity will be presented: PASI, IGA, PP-PASI, PP-IGA, sPGA-G, DLQI, SF-36v2, and the baseline weekly average pruritus and pain as assessed by the NRS. See Section 14.3.1 for further details of the presentation of categorical and continuous variables.

14.3.5 Exposure and treatment compliance

The cumulated dose administered to each subject will be determined and summarised descriptively. For subjects who withdraw from the trial, are lost to follow-up, or permanently discontinue IMP, their cumulated dose will be calculated up until the time of withdrawal/permanent discontinuation of IMP/loss to follow-up.

Treatment compliance will be presented from data listings. Subjects not receiving the scheduled dose will be listed by sites, sorted by treatment group, subject number, and visit. Subjects being administered IMP via remote visits will be listed by sites, sorted by treatment group, subject number, and visit.

14.3.6 Estimand strategy

14.3.6.1 Overview

For each endpoint associated with a trial objective, a primary estimand will be pre-specified. Additional supplementary estimands will be used to further aid in the interpretation of the results.

For each estimand, pre-specified sensitivity analyses will be conducted to assess the robustness of the results with respect to departures from the statistical assumptions supporting the associated models/estimators.

Description of intercurrent events

An intercurrent event refers to a post-randomisation event that either precludes the existence of or affects the interpretation of the measurements of an endpoint. For the purposes of this trial, we define the following 3 intercurrent events:

Permanent discontinuation of IMP independent of pandemic restrictions: This event occurs when a subject permanently discontinues IMP for reasons not related to COVID-19 pandemic restrictions. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP independent of pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator's or sponsor's discretion. The timing of the event will be taken as the date of permanent discontinuation of IMP recorded in the eCRF.

Permanent discontinuation of IMP due to pandemic restrictions: This event occurs when a subject permanently discontinues IMP for reasons related to COVID-19 pandemic restrictions. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to COVID-19 pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines, travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff, and interruptions to supply chain of IMP. The timing of the event will be taken as the date of permanent discontinuation of IMP recorded in the eCRF.

Unblinding of subject: This event occurs at the first instance of either

a) Subject self-injecting IMP at home as part of the COVID-19 pandemic contingency plan (Appendix 6), or

b) Subject becoming accidentally unblinded

Here, a) will be assumed to have occurred at the first instance, where a remote visit including dispensation of IMP is performed and b) will be taken to have occurred when accidental unblinding of a subject is reported in a protocol deviation. The timing of the intercurrent event will be taken as whichever comes first of the visit date of the first remote visit including dispensation of IMP as recorded in the eCRF or the date of accidental unblinding as reported for the subject in a protocol deviation.

Note, there is a distinction between permanent discontinuation of IMP (an intercurrent event) and withdrawal from trial and/or loss to follow-up. Withdrawal from trial and loss to follow-up, which are not intercurrent events, will be addressed when specifying methods and/or assumptions for handling missing data. The death of a subject has not been described above as an intercurrent event since occurrences of this event are considered unlikely in the setting of this trial. Should it happen that a subject die, then analyses will handle this using the same strategy as described below for addressing permanent discontinuation of IMP due to pandemic restrictions.

Strategies for handling intercurrent events
The 'hypothetical' strategy attempts to quantify the effect of treatment, in the hypothetical situation, where intercurrent events do not occur.

The 'treatment-policy' strategy attempts to quantify the effect of the decision to treat subjects with the randomised treatment, thus ignoring the occurrence of intercurrent events.

A 'composite' strategy accounts for the occurrence of intercurrent events, through the definition of a suitable composite endpoint, whose components include the aforementioned intercurrent events, as well as the endpoint of interest.

A fourth strategy, for addressing intercurrent events, is the 'while on treatment' strategy. This strategy will be implemented to handle intercurrent events for time-to-event endpoints. Under the 'while on treatment' strategy, interest lies in assessing the treatment response prior to the occurrence of intercurrent events. The occurrence of intercurrent events can then be accounted for through the formulation of a competing risks model.

Depending on the strategy selected, the occurrence of an intercurrent event may lead to the exclusion of data observed after the occurrence of the event, be ignored, be accounted for in the definition of a composite endpoint, or restrict the relevant observation window to the time prior to the occurrence of the intercurrent event. Panel 21 provides an overview of the estimand strategies that will be used to address occurrences of the intercurrent events described above.

Panel 21 Estimand strategies for addressing intercurrent events

Type of endpoint	Estimand	Strategy for addressing IE		
		Permanent discontinuation of IMP independent of pandemic restrictions	**Permanent discontinuation of IMP due to pandemic restrictions**	**Unblinding of subject**
Binary based on investigator assessments	Primary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Treatment-policy': Occurrences of the IE will be ignored
Binary based on subject assessments	Primary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm
Binary based on investigator assessments	First supplementary	'Treatment-policy': Occurrences of the IE will be ignored	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Treatment-policy': Occurrences of the IE will be ignored
Binary based on investigator assessments	Second supplementary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm
Time-to-event	Primary	'While on treatment': The IE is accounted for as a competing risk in a competing risks model	'Hypothetical': Occurrences of the IE will lead to right censoring, assumed to be non-informative, in a competing risks model	'Treatment-policy': Occurrences of the IE will be ignored

Type of endpoint	Estimand	Strategy for addressing IE		
		Permanent discontinuation of IMP independent of pandemic restrictions	**Permanent discontinuation of IMP due to pandemic restrictions**	**Unblinding of subject**
Continuous based on investigator assessments	Primary	'Treatment-policy': Occurrences of the IE will be ignored	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a multiple imputation algorithm based on the assumption of MAR within treatment arms	'Treatment-policy': Occurrences of the IE will be ignored
Continuous based on subject assessments	Primary	'Treatment-policy': Occurrences of the IE will be ignored	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a multiple imputation algorithm based on the assumption of MAR within treatment arms	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a multiple imputation algorithm based on the assumption of MAR within treatment arms

Abbreviations: IE = intercurrent event, MAR = missing at random.

As seen in Panel 21 the strategy for addressing unblinding of subjects will depend on whether the endpoint of interest is based on subject assessments or investigator assessments. Unblinding of a subject will be considered as specifically having the potential to affect the interpretation of PROs and associated endpoints for that subject. Primary estimands for endpoints based on subject assessments will use a 'hypothetical' strategy for addressing unblinding of subjects.

It is expected that unblinding of subjects will not affect the interpretation of those endpoints which are based on investigator assessments, since these assessments will be performed by investigators/assessors that are blinded to treatment allocation. Primary estimands for endpoints based on investigator assessments will use the 'treatment-policy' strategy for addressing unblinding of subjects.

14.3.6.2 Estimand strategy for binary endpoints

Primary estimand for binary endpoints

For ease of explanation, we consider a specific binary endpoint based on investigator assessments, namely the primary endpoint of the trial:

- Having PASI 100 response at Week 16

The primary estimand associated with this endpoint can be seen to assess the difference in the rate of achieving PASI 100 response at Week 16 without permanently discontinuing IMP regardless of subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur. In the following, we elaborate on the estimand strategy specified in Panel 21 for this estimand, specifically the strategies for addressing the two intercurrent events related to permanent discontinuation of IMP.

To elaborate on the 'composite' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions, we specify the composite variable to be used for analysis. This variable can take the values:

- "1" if the subject is a PASI 100 responder at Week 16 and has not permanently discontinued IMP independently of pandemic restrictions by Week 16.
- "0" if the subject is a PASI 100 non-responder or has permanently discontinued IMP independently of pandemic restrictions prior to Week 16.

We now elaborate on the 'hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions. For subjects who have permanently discontinued IMP due

to pandemic restrictions prior to Week 16, data collected after permanent discontinuation of IMP will be excluded from analysis and replaced by model-based predictions. The purpose is to predict what value the estimand's variable would take if the given subject would not permanently discontinue IMP due to pandemic restrictions. With this purpose in mind, two questions naturally arise because of the 'composite' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions:

a) Would the subject still have been on treatment at Week 16 as opposed to having permanently discontinued IMP independently of pandemic restrictions beforehand?

b) If yes, would the subject have been a PASI 100 responder at Week 16?

In practice, both of these hypothetical questions will be addressed, although in reverse order, by carrying out the steps in Panel 22, each of which will be elaborated on further below. The steps are based on the envisaged hypothetical scenario where permanent discontinuation of IMP due to pandemic restrictions would not occur and subjects who have experienced this event would respond like similar subjects who have not experienced it. In addition to outlining the 'hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions, Panel 22 specifies the handling of missing data in the main analysis of the primary estimand.

Panel 22 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the primary estimand for the primary endpoint

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute PASI 100 response at Week 16 under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 16	'Hypothetical' strategy
		Subjects who have not permanently discontinued IMP prior to Week 16 and whose PASI score at Week 16 is missing	Handling of missing data
2	Impute treatment adherence status at Week 16	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 16	'Hypothetical' strategy

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; PASI = Psoriasis Area and Severity Index.

When performing Step no. 1 in Panel 22, data collected after permanent discontinuation of IMP will be excluded from the imputation models, regardless of the reason for treatment discontinuation. This is well aligned with the 'composite' strategy described above for addressing permanent discontinuation of IMP independent of pandemic restrictions, where data collected after permanent discontinuation of IMP is irrelevant for the value of the estimand's variable.

For subjects who prior to Week 16 have permanently discontinued IMP due to pandemic restrictions, the values imputed in Step no. 1 may be thought of as PASI 100 responses at Week 16, conditional on treatment adherence, thereby addressing the hypothetical question b) stated above. Similarly, Step no. 2 in Panel 22 may be thought of as addressing the hypothetical question a) for these subjects.

Impute PASI 100 response at Week 16 under MAR assumptions

Imputation of missing binary PASI 100 data at Week 16 will be done using multiple imputations of the underlying PASI scores Pwithin the 2 groups defined according to randomised treatment arm, assuming that data is missing at random within each group. The following will be done for each group:

1. In each group, intermittent missing values will be imputed based on a Markov Chain Monte Carlo method, assuming an underlying multi-variate normal distribution, to obtain 1000 copies of the dataset with a monotone missing data pattern (seed=645659, unless otherwise specified).
2. An ANCOVA model will be fitted to the PASI score at Week 2. This is to be done in the context of a proper imputation model as implemented in PROC MI using the monotone regression method. The model will include effects of baseline body weight (≤100 kg, >100 kg), prior TNF-α inhibitor use at baseline (≤1, >1), and baseline PASI score. The estimated parameters, and their variances, will be used to impute missing PASI scores at Week 2 in each of the 1000 copies of the dataset generated above (seed=246673, unless otherwise specified). Negative imputed values will be replaced by 0, and imputed values larger than 72 will be replaced by 72, thereby ensuring that imputed PASI scores are within the range from 0 to 72.
3. For each of the 1000 copies of the dataset, missing PASI scores at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on an ANCOVA model with effects of baseline body weight (≤100 kg, >100 kg) and prior TNF-α inhibitor use at baseline (≤1, >1) together with the PASI scores at baseline and Week 2. The estimated parameters, and their variances, will be used to impute missing values at Week 4. Again, negative imputed values will be replaced by 0, and imputed values larger than 72 will be replaced by 72.
4. This stepwise procedure will then be repeated sequentially for Weeks 6, 8, 10, 12, 14 and 16 with the modification that only the PASI scores from the 2 preceding visits will be included as covariates, in addition to the effects of baseline body weight (≤100 kg, >100 kg) and prior TNF-α inhibitor use at baseline (≤1, >1). The missing binary PASI 100 response at Week 16 will be derived from the corresponding underlying imputed PASI score.

If the model does not converge, variables will be dropped one by one in the following order:

- Prior TNF-α inhibitor use at baseline.
- Baseline body weight.

Impute treatment adherence status at Week 16

For each treatment arm, a Cox proportional hazards regression model will be fitted for the hazard rate of permanent discontinuation of IMP independent of pandemic restrictions. The models will be stratified by baseline body weight (≤100 kg, >100 kg) and will include prior TNF-α inhibitor use at baseline (≤1, >1) as a factor and baseline PASI score as a continuous covariate. The time to permanent discontinuation of IMP independent of pandemic restrictions will be measured in weeks and is assumed to not depend on the observed post-baseline PASI scores. Occurrences of permanent discontinuation of IMP due to pandemic restrictions will in this context be considered as right censorings assumed to be non-informative. For subjects experiencing such a censoring event prior to Week 16, say at time t, the model will provide an estimated probability

$$\hat{p}(t, \text{treatment arm, baseline body weight, prior TNF-}\alpha\text{ inhibitor use, baseline PASI score})$$

of being on treatment at Week 16 conditional on being on treatment at the earlier time t in the scenario, where permanent discontinuation of IMP due to pandemic restrictions would not occur. The conditional probability $\hat{p}$ will be calculated as the estimated survival function evaluated at Week 16 divided by the same function evaluated at time t.

For each subject having permanently discontinued IMP prior to Week 16 due to pandemic restrictions and each of the 1000 copies of the dataset, a Bernoulli trial with the subject-specific success probability

$$\hat{p}(t, \text{treatment arm, baseline body weight, prior TNF-}\alpha\text{ inhibitor use, baseline PASI score}).$$

will be performed (seed=221576, unless otherwise specified) with t denoting the time of treatment discontinuation due to pandemic restrictions. The results of the Bernoulli trials can be thought of as addressing the hypothetical question a).

The imputed value of the estimand's variable will be derived from the PASI 100 response at Week 16, conditional on treatment adherence, from Step no. 1 in Panel 22 and the result of the Bernoulli trial described above, in accordance with the 'composite' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions.

The elaborations above are based on the primary endpoint, but the same principles will be applied for the primary estimand associated with other binary endpoints based on investigator assessments. Note here, that the PASI scale is considered as continuous when carrying out Step no. 1 in Panel 22. For e.g. the binary endpoint,

- having IGA of 0 at Week 16

the underlying IGA score will be considered as ordinal rather than continuous, so Step no. 1 in Panel 22 will instead be carried out as outlined below for such an endpoint.

Impute 'having IGA of 0' response at Week 16 under MAR assumptions
Imputation of missing binary 'having IGA of 0' data at Week 16 will be done using multiple imputations of the underlying 5-point IGA values within the 2 groups defined according to randomised treatment arm, assuming that data is missing at random within each group. The following will be done for each group:

1. In each group, intermittent missing values will be imputed based on fully conditional specification logistic regression to obtain 1000 copies of the dataset with a monotone missing data pattern (seed=151308, unless otherwise specified).
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 2. This is to be done in the context of a proper imputation model as implemented in PROC MI using the monotone logistic method with the cumulative logit link function. The model will include effects of baseline body weight (≤100 kg, >100 kg), prior TNF-α inhibitor use at baseline (≤1, >1) and baseline IGA. The estimated parameters, and their variances, will be used to impute missing IGA values at Week 2 in each of the 1000 copies of the dataset generated above (seed=404677, unless otherwise specified). The imputations will be done based on the predicted probabilities associated with each of the values on the IGA scale at Week 2.
3. For each of the 1000 copies of the dataset, missing values at Week 4 will be imputed in the same way as for Week 2. The imputations will be based on a proportional odds logistic regression model with effects of baseline body weight (≤100 kg, >100 kg) and prior TNF-α inhibitor use at baseline (≤1, >1) together with the IGA values at baseline and Week 2. The estimated parameters, and their variances, will be used to impute missing values at Week 4.
4. This stepwise procedure will then be repeated sequentially for Weeks 6, 8, 10, 12, 14 and 16 with the modification that only the IGA values from the 2 preceding visits will be included as covariates, in addition to the effects of baseline body weight (≤100 kg, >100 kg) and prior TNF-α inhibitor use at baseline (≤1, >1). The missing binary 'having IGA of 0' response at Week 16 will be derived from the corresponding underlying imputed IGA value.

The primary estimand for binary endpoints based on subject assessments can be seen to assess the difference in rate of achieving response without permanently discontinuing IMP, if permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects would not occur. In accordance with Panel 21, this estimand will address unblinding of subjects by the same 'hypothetical' strategy as used for addressing permanent discontinuation of IMP due to pandemic restrictions. This means that the above elaboration on estimand strategy also applies to the primary estimand for binary endpoints based on subject assessments with the exception that unblinding of subjects will be handled just as permanent discontinuation of IMP due to pandemic restrictions.

Main analysis

For each of the 1000 complete datasets, the treatment effect will be estimated, along with the associated standard error, from a logistic regression model, adjusted for baseline body weight (≤100 kg, >100 kg), prior TNF-α inhibitor use at baseline (≤1, >1) and the baseline value of the underlying response variable. Based on Rubin's rules, a combined estimate and standard error for the treatment effect will be calculated and the associated t statistic will be used for testing the null hypothesis that the response rate for the brodalumab arm is less than or equal to the rate for the guselkumab arm, against the alternative that brodalumab is superior to guselkumab. In practice, the t test will be carried out as a two-sided test at the 5% significance level, where the null hypothesis will only be rejected in favour of the stated alternative if the treatment effect estimate is in favour of brodalumab. This corresponds to a one-sided test at the 2.5% significance level.

To quantify the magnitude of the potential treatment effect, estimates of the LS-mean risk difference and odds ratio will be presented along with the associated 95% confidence intervals (CIs), based on combining estimates and associated standard errors from the 1000 analyses using Rubin's rules.

Sensitivity analyses

The following sensitivity analyses will be conducted based on the logistic regression model specified for the main analysis.

- Sensitivity analysis 1
  These sensitivity analyses will assess the robustness of the results of the main analysis with respect to the MAR assumption. For subjects experiencing intercurrent events to be addressed by 'composite' or 'hypothetical' strategies cf. Panel 21, the data observed after the occurrence of such events will be excluded from the imputation models for

the following sensitivity analyses. Missing data will be imputed in separate sensitivity analyses based on each of the following imputation algorithms:

- NRI.
- 'Delta-adjusted' pattern-mixture model.

Missing data arising after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies cf. Panel 21 will not be imputed by the algorithms mentioned above, as the value of the estimand's variable will be determined by the strategy for addressing the intercurrent event.

- Sensitivity analysis 2
  This sensitivity analysis will assess the robustness of the results of the main analysis with respect to the assumption that the effect of treatment does not depend on baseline body weight or prior TNF-α inhibitor use at baseline. To carry out this sensitivity analysis, an interaction term between baseline body weight (≤100 kg, >100 kg) and treatment arm, as well as an interaction term between prior TNF-α inhibitor use at baseline (≤1, >1) and treatment arm, will be included in the logistic regression model described in the main analysis. Backward elimination of the interaction terms will be used. The least significant interaction term that is not significant at the 5% significance level will be removed. Once an interaction term is removed from the model, it remains excluded. The process is repeated until all interaction terms in the model, if any, are significant at the 5% level. If the full model does not converge, the two separate models obtained by removing one of the interactions terms and keeping the other will be fitted.

- Sensitivity analysis 3
  These sensitivity analyses will assess the robustness of the results of the main analysis with respect to the assumption that use of prohibited medication and procedures has no influence on the endpoint of interest among subjects not discontinuing IMP. This will be done by excluding data collected after use of prohibited medication and procedures. Missing data resulting from such exclusions will be imputed in separate sensitivity analyses based on each of the following imputation algorithms:

  - NRI.
  - 'Delta-adjusted' pattern-mixture model.

  Missing data arising after use of prohibited medication and procedures that have happened after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies cf. Panel 21 will not be imputed by the algorithms mentioned

above, as the value of the estimand's variable will be determined by the strategy for addressing the intercurrent event.

For subjects using prohibited medication and procedures or experiencing intercurrent events to be addressed by 'composite' or 'hypothetical' strategies cf. Panel 21 the data observed after the occurrence of such events will be excluded from the imputation models.

Supplementary analysis

To carry out this supplementary analysis, the main analysis will be performed only using investigator and subject assessments performed at on-site visits.

First supplementary estimand

The first supplementary estimand can be seen to assess the difference in response rates achieved regardless of permanent discontinuation of IMP and subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur.

In accordance with Panel 21, permanent discontinuation of IMP independent of pandemic restrictions will be addressed using the 'treatment-policy' strategy. Specifically, permanent discontinuation of IMP independent of pandemic restrictions will be ignored. The same strategies for addressing permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects will be used, and missing data will be handled in the same way as for the main analysis of the primary estimand, with the exceptions that:

- Data collected from subjects who have permanently discontinued IMP independently of pandemic restrictions prior to Week 16 will be included when performing Step no. 1 of the multiple imputation method.
- Step no. 2 of the multiple imputation method will not be carried out.

These exceptions are introduced to align with the 'treatment policy' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions, which simply ignores treatment discontinuations of that nature. Panel 23 summarises the procedure.

Panel 23 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the first supplementary estimand for the primary endpoint

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute PASI 100 response at Week 16 under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 16	'Hypothetical' strategy
		Subjects who have not permanently discontinued IMP due to pandemic restrictions prior to Week 16 and whose PASI score at Week 16 is missing	Handling of missing data

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; PASI = Psoriasis Area and Severity Index.

Inference will be based on the logistic regression model described in the main analysis of the primary estimand under the same assumptions.

Additional sensitivity analyses of this estimand will assess the robustness of the imputation method for subjects with missing data. Imputation methods to be used for these analyses include:

- 'Retrieved-data' pattern-mixture model (if sufficient data exist).
- 'Delta-adjusted' pattern-mixture model.
- NRI.

Second supplementary estimand

The second supplementary estimand can be seen to assess the difference in the rate of achieving response without permanently discontinuing IMP, if permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects would not occur.

The second supplementary estimand associated with the primary endpoint will use the same strategies for addressing intercurrent events as the primary estimand for binary endpoints based on subject assessments.

Inference will be based on the logistic regression model described in the main analysis of the primary estimand under the same assumptions.

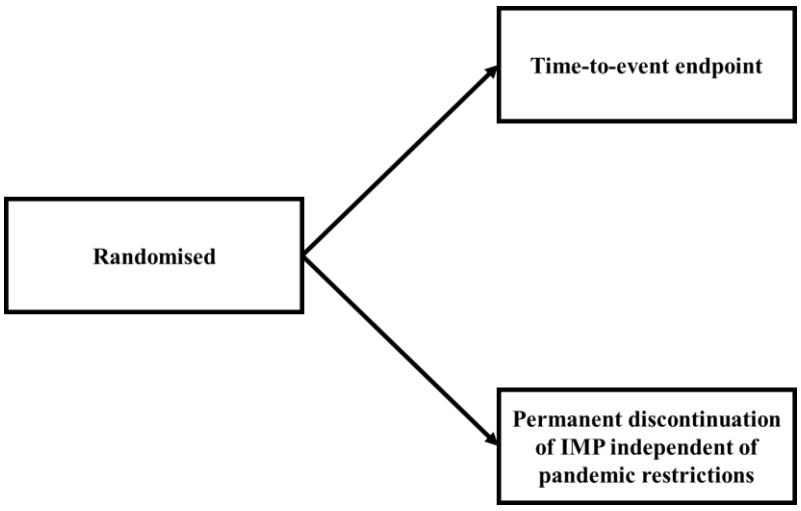
14.3.6.3 Estimand strategy for time-to-event endpoints

Primary estimand for time-to-event endpoints

The primary estimand for time-to-event endpoints can be seen to assess the treatment response prior to permanent discontinuation of IMP regardless of subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur.

Panel 24 describes the competing risks model mentioned in Panel 21 as part of the strategy for addressing the two intercurrent events related to permanent discontinuation of IMP. Permanent discontinuation of IMP due to pandemic restrictions will be interpreted as right censoring, assumed to be non-informative, in the application of this model and data collected after the occurrence of such a censoring event will be excluded from analysis. This is thought of as a 'hypothetical' strategy, the envisaged scenario being that permanent discontinuation of IMP due to pandemic restrictions would not occur and that subjects who have experienced this event would respond like similar subjects who have not experienced it.

Panel 24: Competing risks model describing the primary estimand for time-to-event endpoints



Abbreviations: IMP = investigational medicinal product.

Main analysis
The null hypothesis,

$$H_0{:}\lambda_{broda}(t) = \lambda_{gus}(t), \forall\, t \in (0{,}28),$$

where $\lambda(t)$ denotes the sub-distribution hazard rate associated with the time-to-event endpoint at time *t,* measured in weeks, will be tested against the alternative,

$$H_1{:}\lambda_{broda}(t) \neq \lambda_{gus}(t)$$

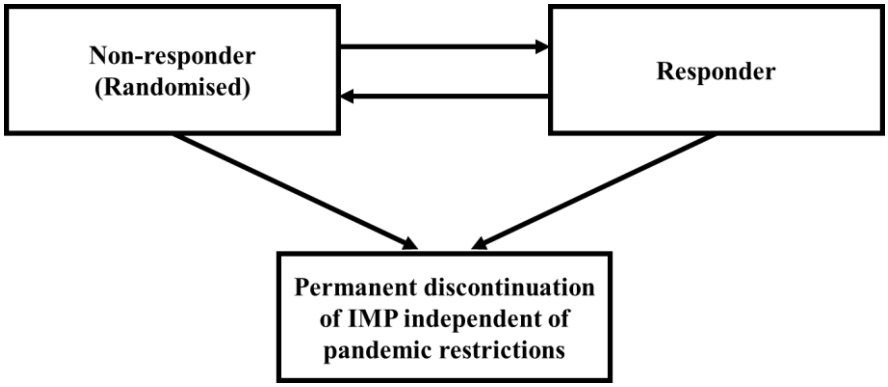
based on Gray's test, stratified by baseline body weight (≤100 kg, >100 kg).

To quantify the magnitude of the potential treatment effect, the estimated cumulative incidence functions for the competing risks model displayed in Panel 24 will be presented for the groups defined by treatment arm and randomisation strata, based on the Aalen-Johansen estimator, along with 95% confidence bands. Additionally, the estimated sub-distributional hazard ratios comparing treatment arms and corresponding 95% CIs for the 2 competing risks based on fitting Fine and Gray models, stratified by baseline body weight (≤100 kg, >100 kg) and adjusted for prior TNF-α inhibitor use at baseline (≤1, >1) and the baseline PASI score will be presented.

It is important to note that for endpoints that are only assessed at trial visits, e.g. PASI score, the above specified analysis implicitly ignores the intermittent inspection process. The time to achieving the endpoint, e.g. PASI 100 response, is imputed based on the trial visit where the response is first observed.

Sensitivity analysis assessing the robustness with respect to the intermittent follow-up
For a given subject in the main analysis, the time to response while remaining on treatment – interpreting permanent discontinuation of IMP due to pandemic restrictions as right censoring – is imputed using the scheduled timing of the visit where the desired response is first observed. In order to assess the robustness of the results of the primary analysis with respect to this imputation strategy, the probability of achieving a response prior to discontinuation of IMP independent of pandemic restrictions will be estimated based on the MSM illustrated in Panel 25. For this analysis, the intermittent nature of the follow-up will be taken into account by formulating the individual contributions to the likelihood with respect to the transition probability matrix, as in Kalbfleisch and Lawless, 1985 (46). The estimated state occupation probabilities and expected duration of time spent in the response state will also be estimated.

Panel 25: Multi-state model for the sensitivity analysis accounting for the intermittent nature of the observation process



Abbreviations: IMP = investigational medicinal product.

Proportional transition intensity regression models, assuming the baseline transition intensities are piecewise constant, will also be fit to the MSM in Panel 25. The models will adjust for baseline PASI score, prior TNF-α inhibitor use at baseline (≤1, >1), and baseline body weight (≤100 kg, >100 kg) to quantify the magnitude of the potential treatment effect, while accounting for the intermittent nature of the inspection process.

Sensitivity analysis with respect to the assumption of non-informative censoring

In addition to ignoring the intermittent nature of the observation process, the primary analysis assumes non-informative censoring, i.e. the censoring and event processes are independent. In order to assess the sensitivity of the results of the primary analysis with respect to the assumption of non-informative censoring, the piecewise constant proportional hazards 'delta-adjusted' pattern-mixture model of Lipkovich et al., 2016 (47)**,** will be generalised to the competing risks setting in order to impute censored event times, for causes other than administrative censoring.

Details regarding the formulation, specification, and estimation for the models that will be fit as a part of the sensitivity analyses will be provided in the SAP.

Supplementary analysis

Proportional hazard regression models will be fit for the cause-specific hazard rates of achieving a PASI 100 response and permanent discontinuation of IMP independent of pandemic restrictions. The models will be stratified by body weight (≤100 kg, >100 kg) and will include prior TNF-α inhibitor use at baseline (≤1, >1) and baseline PASI score as

covariates. The estimated cause-specific hazard ratios comparing treatment arms will be presented along with 95% CIs.

14.3.6.4 Estimand strategy for continuous endpoints

Primary estimand for continuous endpoints

For ease of explanation, we consider a specific continuous endpoint based on investigator assessments:

- Absolute PASI at Week 16

The primary estimand associated with this endpoint can be seen to assess the LS-mean difference in absolute PASI at Week 16 regardless of permanent discontinuation of IMP and subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur. In the following, we elaborate on the estimand strategy specified in Panel 21 for this estimand, specifically the 'hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions.

The hypothetical scenario envisaged is that permanent discontinuation of IMP due to pandemic restrictions would not occur and that subjects who have experienced this event would respond like similar subjects who have not experienced it. Data collected after permanent discontinuation of IMP due to pandemic restrictions will be excluded. The 'hypothetical' strategy and the handling of missing data in the main analysis are outlined in Panel 26.

Panel 26 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the primary estimand for 'Absolute PASI at Week 16'

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute PASI score at Week 16 under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 16	'Hypothetical' strategy
		Subjects who have not permanently discontinued IMP due to pandemic restrictions prior to Week 16 and whose score at Week 16 is missing	Handling of missing data

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; PASI = Psoriasis Area and Severity Index.

The imputation of PASI scores at Week 16 will be carried out as specified for the primary estimand for the primary endpoint. The elaborations above are based on the endpoint 'Absolute PASI at Week 16', but the same principles will be applied for the primary estimand associated with other continuous endpoints based on investigator assessments.

The primary estimand for continuous endpoints based on subject assessments can be seen to assess the LS-mean difference in the continuous endpoint regardless of permanent discontinuation of IMP, if permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects would not occur. In accordance with Panel 21, this estimand will address unblinding of subjects by the same 'hypothetical' strategy as used for addressing permanent discontinuation of IMP due to pandemic restrictions. This means that the above elaboration on estimand strategy also applies to the primary estimand for continuous endpoints based on subject assessments with the exception that unblinding of subjects will be handled just as permanent discontinuation of IMP due to pandemic restrictions.

Main analysis

Each of the 1000 imputed datasets will be analysed based on an ANCOVA model, including baseline body weight (≤100 kg and >100 kg), prior TNF-α inhibitor use at baseline (≤1, >1) and treatment arm as factors and adjusting for the baseline value of the endpoint as a covariate. The pooled estimate of the difference in the LS-mean between the brodalumab and guselkumab arms, along with the associated 95% CIs and nominal p-values, will be presented based on applying Rubin's rules to the estimates and standard errors from the aforementioned ANCOVA analysis of the imputed datasets.

Sensitivity analyses

Rather than assuming missing data are MAR, the sensitivity analyses will impute missing data based on the following algorithms:

- 'Delta-adjusted' pattern-mixture model.
- 'Retrieved-data' pattern-mixture model (if sufficient data exist).

Missing data arising after the occurrence of intercurrent events to be addressed by a 'hypothetical' strategy cf. Panel 21 will not be imputed by the algorithms mentioned above, as the value of the estimand's variable will be determined by the strategy for addressing the intercurrent event.

14.3.7 Analysis of efficacy endpoints

Panel 27 provides an overview of the statistical analysis of the primary, key secondary, secondary, and exploratory efficacy endpoints. As stated in Section 14.3.1, the analysis of efficacy endpoints will be based on the FAS.

Panel 27: Overview of the statistical analysis of efficacy endpoints

Endpoint	Type of endpoint	Primary estimand
Primary endpoint		
PASI 100 response at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Key secondary endpoint(s)		
Time to PASI 100 response	TTE	Primary estimand for TTE endpoints
Secondary and exploratory endpoints		
Time to PASI 90 response	TTE	Primary estimand for TTE endpoints
Having PASI 100 response at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having IGA of 0 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 or 1 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 or 1 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having DLQI total score of 0 or 1 at Week 4	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 8	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 12	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 16	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 20	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 24	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 28	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having IGA of 0 or 1 and at least a 2-grade improvement from baseline at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments

Endpoint	Type of endpoint	Primary estimand
Having IGA of 0 or 1 and at least a 2-grade improvement from baseline at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Change in SF-36v2 from baseline at Week 4	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 from baseline at Week 8	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 from baseline at Week 16	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 from baseline at Week 28	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in the weekly average pruritus NRS at Week 4	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in the weekly average pruritus NRS at Week 8	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in the weekly average pruritus NRS at Week 16	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in the weekly average pruritus NRS at Week 28	Continuous	Primary estimand for continuous endpoints based on subject assessments
Improvement of at least 4 units in the weekly average pruritus NRS at Week 4	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Improvement of at least 4 units in the weekly average pruritus NRS at Week 8	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Improvement of at least 4 units in the weekly average pruritus NRS at Week 16	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Improvement of at least 4 units in the weekly average pruritus NRS at Week 28	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Change from baseline in weekly average pain NRS at Week 4	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in weekly average pain NRS at Week 8	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in weekly average pain NRS at Week 16	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change from baseline in weekly average pain NRS at Week 28	Continuous	Primary estimand for continuous endpoints based on subject assessments
Having absolute PASI ≤1 at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤1 at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤1 at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤1 at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤2 at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤2 at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≤2 at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments

Endpoint	Type of endpoint	Primary estimand
Having absolute PASI ≤2 at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥3 at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥3 at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥3 at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥3 at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥5 at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥5 at Week 8	Binary	Primary estimand for binary endpoints based in continuous investigator assessments
Having absolute PASI ≥5 at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having absolute PASI ≥5 at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Absolute PASI at Week 4	Continuous	Primary estimand for continuous endpoints based on investigator assessments
Absolute PASI at Week 8	Continuous	Primary estimand for continuous endpoints based on investigator assessments
Absolute PASI at Week 16	Continuous	Primary estimand for continuous endpoints based on investigator assessments
Absolute PASI at Week 28	Continuous	Primary estimand for continuous endpoints based on investigator assessments
Having PP-PASI 100 response at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PP-PASI 100 response at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PP-PASI 100 response at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PP-PASI 100 response at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PP-IGA 0/1 at Week 4	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 8	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 4	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 8	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments

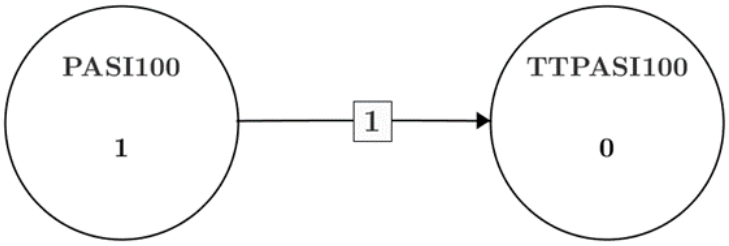
Endpoint	Type of endpoint	Primary estimand
Having sPGA-G 0/1 response at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments

Abbreviations: DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement in PASI score; PASI 90 = 90% improvement in PASI score; PP-PASI = palmoplantar PASI; PP-IGA = palmoplantar IGA; SF-36v2 = 36-Item Short Form Health Survey version 2; sPGA-G = static Physician's Global Assessment of genitalia; TTE = time-to-event.

14.3.8 Testing strategy

To control the FWER of the analysis of the pre-specified primary and key secondary endpoints, the hierarchical testing procedure illustrated in Panel 28 has been defined. The test of the null hypotheses will be based on the pre-specified main analysis of the primary estimands. The initial weight allocated to each hypothesis test is specified in Panel 28. Initially, 100% of the weight is allocated to the hypothesis test of the primary endpoint. If the null hypothesis associated with the primary endpoint is rejected, the key secondary endpoint will be assessed.

Panel 28: Hierarchical testing procedure to control the FWER for the pre-specified primary and key secondary endpoints



Abbreviations: FWER = familywise error rate; PASI = Psoriasis Area and Severity Index; TTPASI100 = time to PASI 100.

14.3.9 Analysis of safety

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

14.3.9.1 Adverse events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term and primary system organ class (SOC).

For AEs, missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of AEs. A worst-case approach will be used: if causality is missing, the AE will be regarded as related to the IMP; if the intensity of an AE is missing, the AE will be regarded as severe; if seriousness is missing, the AE will be regarded as serious; if onset date is missing, it will be assumed to be the first day of administration of IMP; if outcome is missing, and no date of outcome is present, the outcome is regarded as 'not recovered'.

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An event will be considered treatment-emergent if the onset occurred after the first administration of IMP or if the event started prior to the first administration of IMP and worsened in severity after the first administration of IMP. The tabulations described in the following will only include the treatment-emergent events reported prior to or at the Week 28 visit. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC. Tabulations of treatment-emergent AEs will be presented for the following 2 scenarios:

- 'While exposed to IMP', defined as AEs occurring within 5 half-lives after the most recent date of IMP administration.
- 'While in trial', defined as all AEs observed during the duration of the trial.

An overall summary of the number and percentage of subjects reporting the event, along with the number of events and the event rate per 100 subject-years for any treatment-emergent AEs, deaths, SAEs, AEs leading to permanent discontinuation of IMP or withdrawal from trial, treatment-related AEs, and severe AEs will be presented.

The severity for each type of AE will be tabulated by treatment arm.

The causal relationship to IMP for each type of AE will be tabulated by treatment arm. Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of events, subjects and the event rate per 100 subject-years for each type of related AE will be tabulated and presented.

SAEs will be evaluated separately and a narrative for each will be given. AEs leading to withdrawal from trial or permanent discontinuation of IMP will be tabulated and listed.

14.3.9.2 Adverse events of special interest

The AESIs for the trial are classified as important identified and important potential risks (Section 13.5.2). The AESI will be tabulated and listed by treatment arm according to the

safety analysis set for the ‘while exposed to IMP’ and ‘while on trial’ scenarios. The search criteria for AESIs will be specified in the SAP.

14.3.9.3 Vital signs

The change in vital signs (resting blood pressure, pulse, and body temperature) from baseline will be summarised by visit and treatment arm as mean, SD, median, minimum, and maximum values for the safety analysis set.

14.3.9.4 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline will be summarised by visit and treatment arm as mean, SD, median, minimum, and maximum values for the safety analysis set.

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 the end of treatment. Subjects with laboratory parameters outside the reference range will be listed. Reference ranges will be listed in the SAP.

14.3.9.5 Columbia-Suicide Severity Rating Scale

The most severe C-SSRS response observed for each subject over the relevant time periods will be summarised by the number and percentage of subjects, as well as by treatment arm based on the safety analysis set. This includes the time periods ‘while exposed to IMP’, ‘while in trial’, ‘while exposed to IMP and blinded’, and ‘while in trial and blinded’. The severity of the response will be ranked in the following order, from least to most severe:

1. Wish to be dead.
2. Non-specific active suicidal thoughts.
3. Active suicidal ideation with any methods (not plan) without intent to act.
4. Active suicidal ideation with some intent to act, without specific plan.
5. Active suicidal ideation with specific plan and intent.
6. Preparatory acts or behaviour.
7. Aborted attempt.
8. Interrupted attempt.

9. Actual attempt (non-fatal).

10. Completed suicide.

Additionally, the number and percentage of subjects reporting the following composite events will be presented by treatment arm:

- Any suicidal ideation or behaviour during the trial.
- Suicidal ideation with intent to act (4-5).
- Suicidal behaviour.
- Suicidal ideation (4-5) and suicidal behaviour.
- Suicidal ideation (4-5) or suicidal behaviour.
- Self-injurious behaviour without suicidal intent.

14.3.9.6 Patient Health Questionnaire-8

The most severe PHQ-8 total score observed for each subject over the relevant time periods will be summarised by the number and percentage of subjects, as well as by treatment arm for the safety analysis set. This includes the time periods ‘while exposed to IMP’, ‘while in trial’, ‘while exposed to IMP and blinded’, and ‘while in trial and blinded’. The summaries will be based on the following categories:

- 0-4 (none - minimal).
- 5-9 (mild).
- 10-14 (moderate).
- 15-19 (moderately severe).
- 20-24 (severe).

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49. WMA. World Medical Association. Declaration of Helsinki – ethical principles for medical research involving human subjects. Amended by the 64th WMA General Assembly, Fortaleza, Brazil. 2013.

50. CIOMS. International Ethical Guidelines for Health-related Research Involving Humans. Council for International Organizations of Medical Sciences. 4th. Geneva. 2016.

Appendix 1: 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. (48)

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.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.4.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).

- 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.
- 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 bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.

AESIs are described in Section 13.5.2.

Appendix 2: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the 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.

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, or not related according to the investigator's clinical judgement.

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 according to the investigator's clinical judgement should be classified using the categories below.

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 investigator, e.g. subject lost to follow-up.

LEO Pharma definitions versus CDISC definitions

Note that as per the above definition, LEO Pharma uses "recovered/resolved" only if an event has actually stopped. According to the Clinical Data Interchange Standards Consortium (CDISC) definition, the category "recovered/resolved" also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as "not recovered/not resolved" or "recovering/resolving".

Similarly, it should be noted that as per the above definition, LEO Pharma uses "recovered/resolved with sequelae" only if an event has reached a state where the residual symptoms are assumed to persist. According to CDISC, an event is considered "with sequelae", if it has "retained pathological conditions". Consequently, it is likely that some of the events classified by LEO Pharma with the outcome "recovered/resolved with sequelae" could have been classified with the outcome "recovered/resolved" according to the CDISC definition.

In summary, the definitions used by LEO Pharma are more conservative than those used by CDISC.

Serious adverse events
For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic illnesses, the final outcome should be reported as 'not recovered'; in addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

Appendix 3: Trial governance considerations

Appendix 3A: 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 (49) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (50).
- Current version of applicable ICH GCP Guidelines (44).
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authorities must be notified of/approve the clinical trial as required.

Any documents that the IEC may need to fulfil its responsibilities (such as the trial protocol, protocol amendments, IB, subject information sheet and ICF, or advertisements) will be submitted to the IEC. These documents must be reviewed and approved by the IEC before the trial is initiated.

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

The principal investigator will be responsible for the following, if required by local legislation:

- 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 ensuring adherence to applicable national and international legislation.

Appendix 3B: Informed consent process

Subjects will 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 will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

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

A copy of the ICF(s) must be provided to the subject.

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 including the number for the investigator in case of emergency situations. The subject card also includes a local telephone number for the emergency unblinding CRO to be used if the investigator or delegated site staff cannot be reached or if unblinding in the IRT system cannot be performed.

Appendix 3C: 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 Pharma and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO Pharma 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.

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

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

Trial subjects must be informed and consent to that their medical records may be examined by clinical quality assurance auditors or other authorised personnel appointed by LEO Pharma, by appropriate IEC members, and by inspectors from regulatory authorities.

Trial subjects must be informed that LEO Pharma might keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research.

Processing of personal data
This protocol specifies the personal data on trial subjects (for example race, ethnicity, age, sex, health condition, 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 Pharma, and third parties acting on behalf of LEO Pharma.

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

Investigators and LEO Pharma must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

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

Appendix 3D: Record keeping, quality control, and data handling

Source data at trial sites

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 1 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 and dated 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:

- Subject ID.
- The fact that the subject is participating in a clinical trial in psoriasis including treatment with brodalumab or guselkumab for 28 weeks.
- Other relevant medical information.

Trial monitoring

During the course of the trial, CRA(s) will visit the trial site. These visits have the following objectives: (i) to continually verify source data to confirm that data entered into the eCRF 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.

A risk-based monitoring approach will be applied. The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH GCP. The level of source data verification, data checks, and visit intervals will be specified in the monitoring guideline.

In addition to on-site monitoring, pre-specified trial data will undergo central monitoring as specified in the trial's data review plan.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, for example, 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 Pharma and major deviations described in the CTR.

Sponsor audits, IEC review, and regulatory agency inspections
The clinical trial will be subject to audits conducted by LEO Pharma 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 Pharma 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 Pharma must be notified immediately.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into the eCRF. Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF 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 eCRF 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 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.

Subject data should be entered into the eCRF no later than 5 working days after each visit, unless a different deadline is stated in the clinical trial agreement. 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 eDiary data). By the use of an ePRO, data will be available immediately after data entry and available for CRAs and site personnel, including the investigator, with reader 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 Pharma will be transmitted and handled via a secure file transfer protocol site.

Transmissions of data are documented in more detail in a data flow plan which is part of the trial master file.

Software used
CDISC controlled terminology version 30-Mar-2018 was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. Standard data tabulation model (SDTM) version 3.2 will be used for data tabulations.

Archiving of trial documentation
The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file (44). Essential trial documents must be stored until LEO Pharma 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 documents may be destroyed during the retention period without the written approval of LEO Pharma. No documents may be transferred to another location or party without written acceptance from LEO Pharma.

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 an electronic copy of the eCRFs and ePRO data for all screened subjects 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 Pharma, from regulatory authorities and/or IECs.

Appendix 3E: Registration, reporting, and publication policy

Trial disclosure

LEO Pharma is committed to be transparent with respect to its clinical trials.

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 Pharma in accordance with our Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial 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.

LEO Pharma may also provide researchers access to anonymised patient-level data for further research. Publication and access will be in accordance with the Position on Public Access to Clinical Trials which can be found on the LEO Pharma website. Moreover, LEO Pharma may re-use the same patient-level data for other projects within the same purpose as the trial.

Publications

The investigator shall be entitled to make publications of the results generated by the investigator in accordance with the process described here.

A multi-site publication will be 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. After such multi-site publication is made public, or if no multi-site publication has been submitted with the above-described deadline, 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 submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO Pharma a copy of all such manuscripts and/or presentations.

LEO Pharma shall have rights to review and comment. The investigator shall consider comments provided by LEO Pharma but is not required to modify the manuscript and/or presentation based on such comments, provided, however, that the investigator upon the request of LEO Pharma 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 Pharma withhold the publication or presentation to allow LEO Pharma to protect its inventions and other intellectual property rights described in any such manuscripts.

In case no multi-site publication has been made public at the time of investigator's notification of an independent publication to LEO Pharma, LEO Pharma and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-site publication.

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

Any publication must comply with Good Publication Practice (GPP3) standards.

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies 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), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results, and authorship. LEO Pharma also follows the CONSORT reporting guidelines (18).

Appendix 3F: Insurance

LEO Pharma has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

Appendix 3G: Financial disclosure

Investigators will provide LEO Pharma with sufficient, accurate financial information as requested to allow LEO Pharma to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible

for providing information on financial interests and update this information, should any relevant change occur, during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 3H: Committee structure

No data monitoring committee or other trial committee is planned for in this trial.

Appendix 3I: Trial and trial site closure

Premature termination of trial or trial site

LEO Pharma, 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 Pharma 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 Pharma 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 Pharma procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Screening activities 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 Pharma 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 3J: Responsibilities

The signatory investigator is responsible for the approval of the clinical trial protocol and the CTR on behalf of all clinical trial investigators and as agreed to in a signatory investigator agreement.

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a national 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 4: Short version of eligibility criteria

Inclusion criteria	
No.	**Short version**
1	Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2	Subject is ≥18 years of age at the time of screening.
3	Subject has a diagnosis of plaque psoriasis for at least 6 months before the first administration of IMP as determined by the investigator.
4	Subject has inadequately controlled plaque psoriasis currently treated with ustekinumab, and fulfils the criteria specified in the protocol.
5	Subject has no evidence of active tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment. Subjects with adequately treated latent tuberculosis, according to local guidelines, are eligible.
6	Subject has a negative serum pregnancy test during screening and a negative urine pregnancy test at baseline (for women of childbearing potential).
7	Subject uses a highly effective form of birth control throughout the trial and at least for 12 weeks after last administration of IMP (for women of childbearing potential).

Abbreviations: IMP = investigational medicinal product; PASI = Psoriasis Area and Severity Index.

Exclusion criteria	
No.	**Short version**
1	Subject diagnosed with erythrodermic/pustular/guttate/medication-induced psoriasis, or other skin conditions (e.g. eczema) that would interfere with evaluations of the effect of IMP.
2	Subject has a planned surgery, which in the opinion of the investigator will interfere with the planned IMP treatment.
3	Subject has clinically important active infections or infestations, chronic, recurrent, or latent infections or infestations, or is immunocompromised (e.g. HIV).
4	Subject has a known history of hepatitis B, hepatitis C, or HIV. Positive hepatitis B, hepatitis C, or HIV test results at screening (hepatitis B vaccinated subjects are eligible).
5	Subject has any systemic disease (e.g. renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled.
6	Subject has a known history of Crohn's disease.
7	Subject had myocardial infarction, stroke, or unstable angina pectoris within the past 12 months prior to the first administration of IMP.
8	Subject has any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
9	Subject has a history of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
10	Subject has a known history of active tuberculosis.
11	Subject has a history of suicidal behaviour based on the C-SSRS questionnaire at screening or at baseline.
12	Subject has any suicidal ideation of severity 4 or 5 ('some intent to act, no plan' or 'specific plan and intent') based on the C-SSRS questionnaire at screening or baseline.
13	Subject has a PHQ-8 score of ≥10, corresponding to moderate-to-severe depression at screening or baseline.
14	Subject has a history of depressive disorder with severe episode(s) within the last 2 years.
15	Subject has any concurrent medical condition that, in the opinion of the investigator, could cause the trial to be detrimental to the subject.
16	Subject has laboratory abnormalities that, in the opinion of the investigator, will prevent the subject from completing the trial or interfere with the analysis of results.

17	Subject has used potent topical steroids, topical anthralin/dithranol, topical calcipotriol, or any formulation or potency of topical therapy within 7 days prior to first administration of IMP.
18	Subject has used any of the following treatments within 4 weeks prior to first administration of IMP (Ultraviolet A therapy, ultraviolet B light therapy, excimer laser, oral retinoids, etc.; the full list is available in the protocol).
19	Subject has received any of the following biologic immunomodulating therapies prior to first administration of IMP (within 2 weeks for etanercept, within 4 weeks for adalimumab, etc.; the full list is available in the protocol).
20	~~Subject has previously received more than 1 TNF-α inhibitor.~~ **NOTE**: This exclusion criterion is not applicable in this version of the protocol. It is kept to avoid re-numbering of the exclusion criteria.
21	Subject has previously been treated with any anti-IL-17A, anti-IL-17RA, or anti-IL-23 besides ustekinumab.
22	Subject received live vaccine(s) within 4 weeks of the first administration of IMP.
23	Subject has received treatment with any non-marketed drug substance within the 4 weeks or 5 half-lives of the substance, whichever is longer, prior to screening.
24	Subject is currently enrolled in another investigational device or drug trial or ended participation in one within 4 weeks or 5 half-lives of the IMP, whichever is longer, prior to screening.
25	Subject has known or suspected hypersensitivity to any component(s) of the IMPs.
26	Subjects is pregnant or lactating.
27	Subject has a history of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
28	Subject has previously been randomised in this clinical trial.
29	Subject has a language barrier, mental incapacity, unwillingness, or lack of ability to understand the trial-related procedures.
30	Subject is an employee of the trial site or any other individual directly involved with the planning or conduct of the trial, or immediate family member of such individual.
31	Subject is legally institutionalised.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; HIV = human immunodeficiency virus; IL = interleukin; IMP = investigational medicinal product; PHQ-8 = Patient Health Questionnaire-8 TNF-α = tumour necrosis factor-α.

Appendix 5: Contact list

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

Sponsor

LEO Pharma A/S (referred to as 'LEO Pharma' or 'the sponsor' in this clinical trial protocol) is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

Coordinating investigator

Signatory investigator:

PPD , MD, PhD
PPD
Germany
PPD

Appendix 6: COVID-19 pandemic contingency plan

In case local restrictions due to a COVID-19 pandemic outbreak prevents a subject from attending the site, the site must contact the CRA to allow for implementation of contingency measures mentioned in this appendix based on mutual agreement.

This contingency plan provides a possibility to perform minimum safety and efficacy assessments followed by self-injection of IMP. Assessments will be performed via the use of a trial-specific mobile application on the subject's own smartphone or via the use of other video software used by the trial site in their normal clinical practice and in agreement with the sponsor and following notification of the relevant ethics committee and by completing the PHQ-8 questionnaire via a webpage (hereafter termed 'video visits').

Both brodalumab and guselkumab are approved treatments in several countries worldwide and subjects may self-inject the IMPs when deemed appropriate by a health care professional. Therefore, no safety issues are expected regarding self-injection of IMP in this trial.

Separate informed consent forms (A and B) are available, and intended for:

- Conduct of trial assessments via video visits (form A).
- Delivery of IMP to the subject and self-injection (form B).

Consent must be obtained from the subject before the respective contingency activities are performed. Investigators are encouraged to inform subjects about the contingency plan and to obtain informed consent from the subject in advance of a potential COVID-19 outbreak.

Delivery of IMP to a subject is possible only if the subject consents to ICF form A. If a subject does not consent to ICF form A, treatment with IMP must be temporarily discontinued until on-site visits are possible. However, trial staff should remain in contact with the subject via phone to ensure subject safety. Delivery of IMP to a subject may also be performed by the subject's spouse or other relative or delegated person of trust who can pick up the IMP at the trial site and deliver to the subject.

1. Visits

- Screening (Week -4/-2 to 0) and baseline (Week 0) visits should be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new subjects at that site should be on hold until on-site visits are possible.

- Panel 29 indicates the minimum requirements for procedures that should be performed during a lockdown; but sites should always try to follow the procedures outlined in Panel 2 and Panel 3 (original schedules of trial procedures) to the extent possible.

- All minimum assessments and procedures of a visit do not need to be performed on the same day but should be completed within the time window of the visit.

- Without compromising the safety of subjects and site personnel, it is expected that all efforts are made to secure attendance at sites for the primary endpoint visit (Week 16) and the final visit (Week 28). If the visits at Week 16 and Week 28 cannot be performed either on-site or via a video visit within the given visit window, the visit window for the assessments can be extended for up to 10 days.

Remote completion of the PHQ-8 questionnaire

After site staff has activated the remote set up of the subject, using either the subject's e-mail address or phone number, the subject should complete the PHQ-8 questionnaire on a computer via a webpage.

Delivery of IMP to subjects and self-injection

After ensuring that the outcomes of the C-SSRS and PHQ-8 assessments do not indicate that IMP administration should be discontinued, the following procedures should be performed by unblinded site staff:

1. Allocation of IMP for the subject using IRT (can be performed by blinded staff).
2. Prepare and ship/hand out to subject's relative or delegated person of trust (refer to trial product handling manual for instructions):
   - IMPs allocated via the IRT including instruction for use and other supplies.
   - Urine pregnancy test kits, if applicable.

   Care should be taken to keep blinded site staff from becoming unblinded while preparing the shipment/package for hand out to subject's relative or delegated person of trust.
3. Site staff are responsible for establishing contact with the subject as soon as he/she receives the IMP. This is to ensure that:
   - The subject is reminded of IMP storage instructions.
   - The date for self-injection is agreed on keeping in mind that it should be performed at the earliest possible timepoint.

- If applicable, female subject is reminded to perform a urine pregnancy test prior to the date of IMP self-injection.
- The subject is instructed to not inform the site staff (except from unblinded site staff) about the identity of the IMPs received.

4. At the date of self-injection, the unblinded site staff contacts the subject via the video function in the trial-specific mobile application or other video software used by the trial site in their normal clinical practice and completes the following:
   i. Obtain result of the urine pregnancy test before self-injection, if applicable.
   ii. Instruct subject in self-injection.
   iii. Self-injection may be performed under supervision of the unblinded site staff.
   iv. Information about the kit numbers administrated, date of injection, injection site, and whether the doses were fully or partly injected is provided by the subject to the unblinded site staff, who records the information on the IMP administration checklist. If the subject is comfortable with handling the injections, the supervision can be omitted during future self-injections. In that case, the subject must be instructed in contacting the unblinded site staff at the earliest possible time after self-injection to provide the above-mentioned information.
5. The subject should be instructed to keep the IMP cartons, while the IMP syringes are disposed of in the sharp-bin container provided to the subject. The IMP cartons should be returned to the site in a non-transparent bag.

2. Trial procedures

- Local laboratories can be used for biochemistry, haematology, albumin-to-creatinine ratio, and serum pregnancy test, if deemed necessary by the investigator, if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 1) should be reported in the eCRF.

Panel 29 Schedule of minimum trial procedures to be performed under the COVID-19 pandemic-related lockdown

		Treatment period															Early termination visit[3]	Unscheduled visit, if applicable[4]	References (protocol section)
Visit		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**			
Week		**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16[2]**	**18**	**20**	**22**	**24**	**26**	**28[2]**			
Visit window (days)[1]		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Treatment via trial-specific mobile application, when needed																			
Arm 1	Administration of brodalumab	X	X	X	X	X	X	X	X	X	X	X	X	X	X				9.2
	Administration of dummy 1			X				X				X							9.2
Arm 2	Administration of guselkumab			X				X				X							9.2
	Administration of dummy 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X				9.2
Concomitant medication/procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	9.6
Treatment compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X			(X)	9.8.4
Investigator assessments of efficacy via trial-specific mobile application																			
PASI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.3.1.1
IGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.3.2.1
Subject assessments of efficacy and health-related quality of life																			
Pruritus NRS[5]		<=Daily at home during entire treatment period using an eDiary device =>															X[6]		11.3.4.3
Pain NRS[5]		<=Daily at home during entire treatment period using an eDiary device =>															X[6]		11.3.4.4
Investigator assessments of safety via trial-specific mobile application																			
Urine pregnancy test[7]				X		X		X		X		X		X		X	X	(X)	11.4.4
AEs and SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	13

	Treatment period															Early termination visit[3]	Unscheduled visit, if applicable[4]	References (protocol section)
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**			
Week	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16[2]**	**18**	**20**	**22**	**24**	**26**	**28[2]**			
Visit window (days)[1]	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Patient-reported outcomes of safety																		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.5.2
PHQ-8 (website)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.5.3
Concluding forms in the eCRF																		
End-of-treatment form[8]															X	X		11.6.1
End-of-trial form[9]															X	(X)[9]		11.6.2

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; C-SSRS = Columbia-Suicide Severity Rating Scale; eCRF = electronic case report form; eDiary = electronic diary; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PHQ-8 = Patient Health Questionnaire-8; SAE = serious adverse event.

1) If the date of a trial visit does not conform to the clinical trial protocol, subsequent visits should be planned to maintain the visit schedule relative to Visit 2 (Week 0, baseline).
2) The primary endpoint visit (Week 16) and the final visit (Week 28) are in grey as these visits are critical and should be conducted at the site, if possible.
3) Subjects who discontinue IMP for any reason should attend an early termination visit as soon as possible and within 2 weeks after the last IMP. If a subject discontinues IMP or withdraws from the trial at a scheduled visit, then all assessments for an early termination visit must be performed at this particular visit (see Sections 10.3 and 11.6 for further instructions). The subjects who discontinue IMP prior to Week 16 will be asked to attend at least the primary endpoint visit at Week 16. A virtual early termination visit can be conducted. However, a visit at site should be conducted once the restrictions related to COVID-19 pandemic are lifted.
4) An unscheduled visit can be performed by subject's needs or at the discretion of the investigator. Procedures are marked in brackets '(X)' since they are optional depending on the reason for the unscheduled visit.
5) To be completed daily by the subject.
6) Must be completed at the early termination visit, if not already done at home before the visit.
7) Only women of childbearing potential.
8) An end-of-treatment form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP.
9) An end-of-trial-form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP or withdraw from the trial, at their last trial visit.

3. Blinding

The 2 active IMPs (brodalumab and guselkumab) are packaged open-label and are visually distinct from each other, containing different volumes of solution. Therefore, the subject will be unblinded if the subject self-injects the IMPs.

The subject must be instructed to keep blinding for other staff, i.e. other site staff including the investigator.

To protect trial integrity, dummy injections must be self-administered as this will reduce the risk of unblinding the site staff.

4 eCRF recording

It must be recorded in the eCRF if the visit or given assessment was conducted remotely or not. If not conducted, it will be recorded in the comments log if this was due to the COVID-19 pandemic.

All IMP self-injections and missed doses must be documented in the eCRF with 'COVID-19 pandemic' written in the comments log for the visit in scope.

For all information pertaining to remote visits, assessments, and IMP related information to be recorded in the eCRF, please refer to the eCRF completion guidelines.

5 Statistical methods

Statistical considerations related to COVID-19 pandemic restrictions are presented in Section 14 of the main protocol.

Appendix 7: Protocol amendment history

The protocol amendment summary of changes table for the current amendment is located directly before the table of contents.

Amendment 2 (22-Jan-2021)

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 or subsequent regulation.

Overall rationale for the amendment:

The main reason for this amendment is to provide a possibility to perform minimum safety and efficacy assessments via the use of electronic communications followed by delivery of IMP to subjects for self-injections in case of emergency COVID-19 pandemic restrictions.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures	Visits outside of the allowed visit window still need to be performed, taking into consideration that an interval of minimum 7 days to the subsequent, respective IMP administration must be maintained **(visits 3 and 4 are exempt from the 7-day gap requirement**).	To clarify that a gap of 7 days between IMP administrations is not expected for visits 3 and 4.
	Footnote revised: 8) The DLQI and SF-36v2 questionnaires ~~must~~ should be completed by the subject prior to ~~any other visit-related trial procedures.~~ **the investigator, safety, and other assessments.**	To clarify that DLQI and SF-36v2 questionnaires should be completed prior to all other assessments except the laboratory assessments and to provide a visual

Section no. and name	Description of change	Brief rationale
	For the sequence of assessments to be performed at each visit, please see Panel 8.	presentation of the sequence to assessments to be performed during visits.
6 Trial objectives, endpoints, and estimands	Panel 5 updated with strategies to handle occurrences of permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects.	To provide estimand strategies in case of COVID-19 pandemic restrictions.
9.2 Administration of investigational medicinal product	Instructions for use of the pre-filled syringes are provided in ~~a trial product handling manual~~ **the investigator trial file**; the IMP administration must be carried out according to these instructions.	To correct the location where the instructions for use is provided.
9.3.1 Blinding	**Furthermore, to ensure subjects stay blinded to treatment allocation, site staff should ensure that subjects are blindfolded during the administration of IMP.**	To clarify the procedure for how IMP will be administered to subjects in order to maintain the blind.
10.2.2 Reasons for temporary discontinuation of IMP	The subsequent IMP administration should be scheduled according to the schedule of the trial procedures with a minimum of 7 days to the subsequent administration of the respective IMP **(visits 3 and 4 are exempt from the 7-day gap requirement)**.	To clarify that a gap of 7 days between IMP administrations is not expected for visits 3 and 4.

Section no. and name	Description of change	Brief rationale
11.1 Overview	Sequence of assessments reordered to indicate that laboratory assessments could be performed at any time during the visit but should be completed prior to performing 'Other assessments'. Also, the investigator and safety assessments were merged in one box.	To enable the trial to be operationally more flexible.
13.4.2 LEO reporting responsibilies	For brodalumab, the IB Section 7.2, edition ~~12.0~~ **13.0** and subsequent updates must be used.	To reflect the latest IB version.
14 Statistical methods	Updated to limit introduction of bias for evaluation of the treatment effect of brodalumab and guselkumab due to COVID-19 pandemic restrictions and unblinding of subjects.	To provide strategies in case of COVID-19 pandemic restrictions.
Appendix 6	COVID-19 pandemic contingency plan to provide an opportunity for remote assessments and delivery of IMP and pregnancy tests to subjects that are unable to attend site visits due to COVID-19 restrictions.	To ensure the possibility of continued treatment despite restricted site access caused by the COVID-19 pandemic.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Amendment 1 (19-Aug-2020)

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 or subsequent regulation.

Overall rationale for the amendment:

The main reasons for this amendment, based on input provided during the Voluntary Harmonisation Procedure in EU, are:

- to add the discontinuation criterion for subjects who show no response after 16 weeks of treatment.
- to add an evaluation by a specialist in case of a positive QuantiFERON® test.
- to add an additional sensitivity analysis to assess the robustness of the results of the primary analysis with respect to the use of prohibited medication and procedures among subjects not discontinuing IMP.

Furthermore, capturing of 'lack of efficacy' in case of aggravation/exacerbation/worsening of the trial disease has been clarified, and albumin-to-creatinine test at screening was changed to only be performed in case of abnormal urine dipstick test.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section no. and name	**Description of change**	**Brief rationale**
4 Schedule of trial procedures	The row for serum pregnancy test has been moved under Investigator assessments of safety and (X) has been added to the schedule.	To make the procedure visible in the panels to highlight the need of this test in case of positive urine pregnancy test.
	Albumin-to-creatinine ratio will only be performed for subjects with abnormal urine dipstick results. The row for albumin-to-creatinine ratio has been moved under Investigator assessments of safety and replaced with (X).	To minimise the unessential procedure.

Section no. and name	Description of change	Brief rationale
	This change has also been reflected in Section 11.4.4 Laboratory testing Panel 15.	
	(X) has been added to treatment administration for unscheduled visit.	To allow for administration of IMP on unscheduled visits.
8.2 Inclusion criteria	Revised bullet point: No evidence of active tuberculosis **based on documented assessment by a pulmonologist or a tuberculosis specialist (phthisiologist)** ~~on chest radiograph within 3 months prior to the first administration of IMP, if any chest radiograph is available~~.	To exclude active tuberculosis in patients who had a positive QuantiFERON® or PPD test result.
10.2.1 Reasons for permanent discontinuation of IMP	Added bullet point: **Having shown no response (efficacy) after 16 weeks of treatment.**	To discontinue IMP administration for subjects who show no response after 16 weeks of treatment.
	Added clarification: **'Lack of efficacy' should be assigned when a subject experiences aggravation/exacerbation/worsening of the trial disease, even when it is documented as an (S)AE according to Section 13.6.5.**	To consistently capture permanent discontinuation of IMP or withdrawal from trial due to 'lack of efficacy'.
11.6.2 End-of-trial form	Added clarification: **'Lack of efficacy' should be assigned when a subject experiences aggravation/exacerbation/worsening of the**	To consistently capture permanent discontinuation of IMP or withdrawal from trial

Section no. and name	Description of change	Brief rationale
	trial disease, even when it is documented as an (S)AE according to Section 13.6.5.	due to 'lack of efficacy'.
13.6.5 Aggravation of condition	Added clarification: **In case the aggravation/exacerbation/worsening of the trial disease leads to permanent discontinuation of IMP or withdrawal from the trial, 'lack of efficacy' should be chosen as the primary reason for discontinuation of IMP / withdrawal from the trial in accordance with Section 10.2.1 and Section 11.6.2.**	To consistently capture permanent discontinuation of IMP or withdrawal from trial due to 'lack of efficacy'.
14.3.6.2 Estimand strategy for binary endpoints	An additional sensitivity analysis (sensitivity analysis 3) was added.	To assess the robustness of the results of the primary analysis with respect to the use of prohibited medication and procedures among subjects not discontinuing IMP.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.