Cover Page

Study title: Efficacy and safety of brodalumab in adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis; EMBRACE 1
LEO Pharma number: LP0160-1396
NCT number: NCT04305327
Date: 05-Oct-2021

Clinical Trial Protocol

LP0160-1396

Efficacy and safety of brodalumab in adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis; EMBRACE 1

Phase 3 – efficacy and safety trial including pharmacokinetics and vaccine response

A phase 3, randomised, double-blind, multi-centre trial to evaluate the efficacy, safety, and tolerability of brodalumab treatment compared to placebo (blinded) and ustekinumab (open-label) in adolescent subjects (12–17 years of age) with moderate-to-severe plaque psoriasis

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:**	**LP0160-1396**
	Date:	**05-Oct-2021**
	EudraCT no:	**2019-001868-30**
	Version:	**6.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within eTMF LEO 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:

[redacted]

[redacted]

Biostatistics lead, [redacted]

[redacted]

Medical lead, [redacted]

[redacted]

Clinical operations lead, [redacted]

[redacted]

Signatory investigator

Acknowledgement statement investigator(s)

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 2 (substantial)	05-Oct-2021	Global
Amendment 1 (substantial)	10-Jun-2020	Global
Original protocol	21-Jan-2020	Not applicable

Amendment 2 (05-Oct-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

This amendment was written to:

- Allow inactive or non-live vaccines, including COVID-19 vaccines, from Week 12.
- Add voluntary photography as trial procedure at selected trial sites.
- Update estimands strategy to account for COVID-19 pandemic restrictions impact on the trial conduct.

The changes included in the amendment and a brief scientific rationale for each item are presented in the table below.

Section no. and name	Description of change	Brief rationale
Section 4 Schedule of trial procedures	Visit window for Visit 3 and 4 changed from ±1 to ±3.	To allow more flexibility for the investigator and the subject.
	Added that visits outside the allowed visit window still need to be performed, taking into consideration that a minimum interval of 7 days must be kept between 2 administrations of brodalumab/placebo (except for Visit 3 and Visit 4, which are exempt from the 7-day gap requirement).	For clarity.

Section no. and name	Description of change	Brief rationale
	Footnotes f and g Panel 2 and footnote f Panel 3 deleted. New footnote e added to Panel 2 specifying that subjects must be randomised as soon as all inclusion and exclusion criteria are confirmed (including the central laboratory and ECG results from the screening visit).	To align with the updated text. For better guidance for the investigator.
Section 4 Schedule of trial procedures Section 7.1.2 Screening period (Week -4 to Week 0)	The 14 days minimum prior to initiation of the treatment requirement deleted.	To assure randomisation and initation of treatment as soon as subject´s eligibility is confirmed.
Section 4 Schedule of trial procedures Section 11.7.2 Photography (selected trial sites)	New voluntary trial procedure added.	The processing of photos is necessary for reasons of public interest in the area of public health, to ensure high standards of quality, and for scientific research purposes.
Section 5.2 Experience with investigational medicinal product Section 5.5 Benefit/risk assessment	List of countries where brodalumab is approved updated.	To have an up-to-date country list.
Section 5.5 Benefit/risk assessment	Sentence regarding the need for subjects to be up-to-date with the vaccination program of their country of residence deleted.	To align with inclusion criteria.
Section 5.5 Benefit/risk assessment Section 8.3 Exclusion criteria Section 9.7 Prohibited medication and procedures	Specified that inactivated or non-live vaccine will be allowed from Week 12.	To avoid putting subjects in an unjustified risk, the restriction for not allowing access to inactive and non-live vaccines including COVID-19 vaccines are limited to a minimum.
Section 7.1.1 Overview of the trial design	Added that it will be recorded in the eCRF if a visit was missed and whether the reason for the missed visit was related to pandemic restrictions.	In order to perform the specified statistical analyses, data that is missing due to pandemic restrictions and data that is missing for other reasons need to be distinguished.

Section no. and name	Description of change	Brief rationale
Section 8.2 Inclusion criteria	´As determined by the investigator' added to inclusion criterion 2. Inclusion criterion 7 deleted. Inclusion criteria 9, 10, 11, and 12 deleted and replaced by new inclusion criterion ´Subject has no evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment'.	For clarity. Exclusion criterion 4 is sufficient as the period for prohibited administration of inactivated and non-live vaccine is reduced from 52 weeks to 12 weeks for placebo and brodalumab arms. To allow for more operational flexibility at site.
Section 8.2 Inclusion criteria Throughout the document	Definition of childbearing potential deleted as all female subjects will be considered of childbearing potential when entering the trial. Inclusion criterion 13 deleted accordingly and replaced by ´Female subjects must have a negative pregnancy test at screening and at baseline'.	To make the trial more operationally flexible.
Section 8.3 Exclusion criteria	Specified in exclusion criterion 18 that subjects with treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma can be enrolled in the trial.	For clarity.
Section 9.1 Trial product description	Panel 9 ´Source' column changed to [redacted] Name of the IMP corrected.	For correctness and to clarify who is responsible for batch release.
Section 9.2.1 Administration of brodalumab, placebo, and ustekinumab	Sentence ´Further details on IMP administration are provided in a trial product handling manual; the IMP administration must be carried out according to these instructions.´deleted.	Details on the IMP administration are given in the protocol.
Section 9.2.3 Reporting of IMP administration in eCRF	Time of IMP administration will be recorded only at selected visits.	Time of administration only needed at selected visits to create PK profiles.

Section no. and name	Description of change	Brief rationale
Section 9.2.1.1 Conditions requiring rescheduling of administration of brodalumab, placebo, or ustekinumab	Specified that the 7-day gap requirement between administration of brodalumab/placebo does not apply to Visit 3 and Visit 4.	Due to the change of the visit window for Visit 3 and 4.
Section 9.7 Prohibited medications and procedures	Specified how to record prohibited medications and when a prohibited medication constitutes a protocol deviation.	For clarity.
Section 9.10 Reporting product complaints	Specified that the product complaint must be immediately reported to the CRA by the site and that the CRA must contact Global Safety at LEO Pharma.	To be in alignment with LEO Pharma´s procedures.
Section 10.2.2 Reasons for temporary discontinuiation of IMP	Specified that the IMP may be temporarily suspended in case of infection and other intercurrent illness and that it must be temporarily suspended in case of ANC ≥0.50x103/µL – ≤1.5x103/µL and fever or positive urine pregnancy test.	For clarity.
Section 11.1 Overview	Sentence added explaining that the laboratory assessments can be completed anytime prior to ´Patient-reported outcomes for safety assessments´.	To make the trial more operationally flexible.
Section 11.1 Overview Section 13.2 Collection of adverse event reports Appendix 3D	Text regarding assessment of AEs updated. AEs will be assessed by a physician.	To clarify responsibilities.
Section 11.4.3 Electrocardiogram	Added that subjects should not be randomised before the evaluation report from the ECG service company of the ECG performed at Visit 1 is received at site.	For better guidance.
Section 11.4.5.1 Overview of all laboratory tests	PPD test and QuantiFERON® test replaced by ´Tuberculosis (only if applicable)' in Panel 18.	To align with new inclusion criterion 8.
Section 11.4.5.1 Overview of all laboratory tests Section 11.6.2 Blood sampling for analysis of IL-17 and other blood biomarkers	Blood biomarkers changed to interleukin (IL)-17, IL-10, IL-6, CXCL9, CCL20, S100-A12, and Caspase-8.	To match the serum biomarkers mentioned in the CTPs with the offerings of the preferred assay lab partner.

Section no. and name	Description of change	Brief rationale
Section 11.9.1 End of treatment form Section 11.9.2 End of trial form	Specification added to indicate that for subjects not completing the trial, it will be recorded if the reason for not completing the trial was related to pandemic restrictions.	This information is needed to fully assess and report the impact of COVID-19 on the trial.
Section 11.10 Storage of biological samples	Storage time for blood samples corrected.	For correctness.
Section 13.3 Reporting of adverse events	Specified that the duration of the AE must be reported by the start date and stop date of the event, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing.	For clarity.
Section 13.4.1 Investigator reporting responsibilities	A more detailed specification on the timing of reporting of SAEs added (i.e. immediately, without undue delay).	To align with updated text in the EU CT regulation on reporting of SAEs.
Section 13.4.2 LEO Pharma reporting responsibilities	Specified that edition 13 of the Investigator´s Brochure should be used.	To align with the newest edition of the Investigator´s Brochure.
Section 13.6.5 Aggravation of condition	Added that plaque psoriasis is a fluctuating disease with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by plaque psoriasis should be reported as an AE.	To provide better guidance to the investigator.
Section 13.7 Follow-up for final outcome of adverse events	Specified that the final outcome of SAEs that have stabilised and from which the subject cannot be expected to recover during the trial should be reported as ‘recovering/resolving’ or ‘not recovered/not resolved’ at the investigator´s discretion. In addition, a statement detailing why the subject cannot be expected to recover during the trial should be added to the narrative description of the SAE on the SAE form.	For clarity.
Section 14 Statistical methods	Estimands updated with strategies to handle occurrences of permanent discontinuation of IMP due to pandemic restrictions.	To provide estimand strategies in case COVID-19 pandemic restrictions impact the trial conduct.

Section no. and name	Description of change	Brief rationale
Section 14.3.6.1 Estimand strategy for binary endpoints	Sensitivity analysis 2 and 3 for primary estimand for binary endpoints removed.	The main analysis and the sensitivity analyses targeted different estimands. The sensitivity analyses were removed to follow the ICH E9 R1.
	Missing data for reasons other than pandemic restrictions in secondary estimand for binary endpoints imputed assuming missing at random instead of imputed based on 'control-based' pattern mixture model, which was added as a sensitivity analysis.	To align with other LP0160 protocols.
	Sensitivity analysis for secondary estimand for binary endpoints using 'retrieved-data' pattern mixture model removed.	It is expected that the rate of the intercurrent events will be low, and therefore there will not be sufficient retrieved data to inform this analysis.
	Supplemental estimand: "hypothetical" estimand moved to 14.3.6.3 Estimand strategy for vaccine-related endpoints.	No longer recommended to use a purely hypothetical strategy for the primary and secondary endpoint. This is now reserved for the vaccine-related endpoints.
Section 14.3.6.2 Estimand strategy for continuous endpoints	Primary analysis for primary estimand for continuous endpoints changed from MMRM to ANCOVA.	To align the inferential models.
	Sensitivity analysis for primary estimand for continuous endpoints removed.	Sensitivity analyses are reserved for primary and key secondary endpoints, which are all binary.
	Supplemental estimand: "hypothetical" strategy moved to 14.3.6.3 Estimand strategy for vaccine-related endpoints.	No longer recommended to use a purely hypothetical strategy for the primary and secondary endpoint. This is now reserved for the vaccine-related endpoints.
Section 14.3.6.3 Estimand strategy for vaccine-related endpoints	Primary analysis for the continuous vaccine-related endpoints changed from MMRM to ANCOVA.	To align the inferential models.

Section no. and name	Description of change	Brief rationale
Section 14.3.9 Analysis of other endpoints	Description of analysis of vaccine-related endpoints moved to section 14.3.6.3 Estimand strategy for vaccine-related endpoints. Exploratory analysis of itch based on the reversible illness-death model removed.	For clarity. The main analysis of the itch data is considered sufficient to assess the effect of treatment.
Section 14.3.10.6 Patient Health Questionnaire-A (PHQ-A)	Exploratory analysis removed.	The main analysis of the PHQ-A data is considered sufficient to summarise the observed data.
Appendix 1	Hospitalisation definition clarified.	For clarity
Appendix 6	New appendix added containing the summary of the previous protocol amendment.	To document the protocol amendment history, and to keep only the most recent amendment summary at the start of the protocol.
Throughout the document	Changed designated assessor to investigator.	For consistency within the protocol.
Throughout the document	Removed Australia.	Australia will not be participating in this trial.
Throughout the document	Minor editorial revisions.	Minor, have therefore not been summarised.

Table of contents

List of panels

List of abbreviations

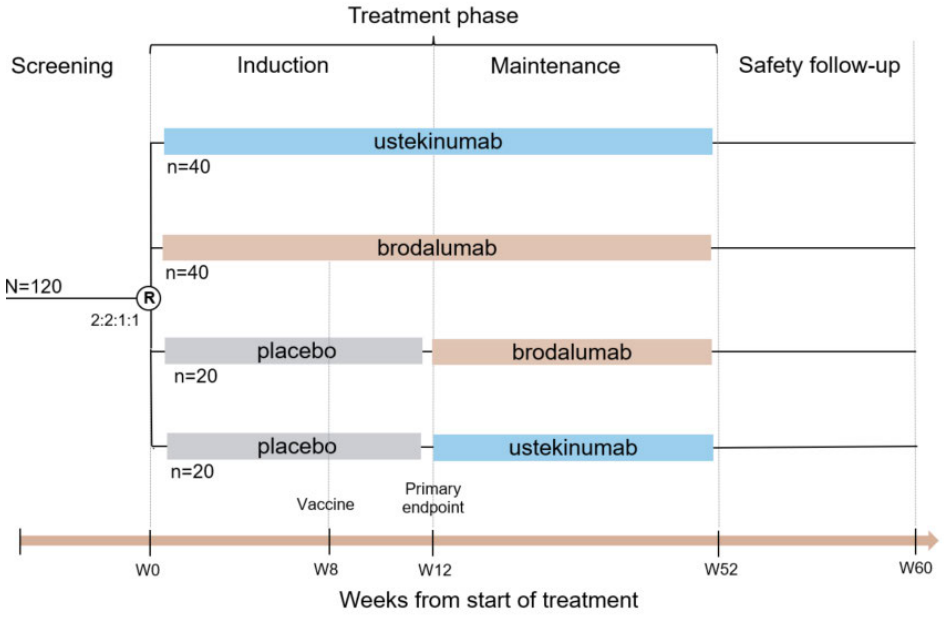
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AS	area score
AST	aspartate aminotransferase
aTTA	anti-tetanus toxoid antibodies
AUC	area under the curve
AUC_{W10-12}	area under the serum concentration-time curve at Week 10-12
BCG	Bacillus Calmette-Guérin
BSA	body surface area
C_{trough}	trough (pre-dose) serum concentrations
C_{W10}	serum concentration sampled during Week 10
CDISC	clinical data interchange standards consortium
CDLQI	Children Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
CI	confidence interval
CMO	contract manufacturing organisation
CONSORT	consolidated standards of reporting trials
COVID-19	coronavirus disease 19
CRA	clinical research associate
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency

ePRO	electronic patient-reported outcome
EU	European Union
FAS	full analysis set
FDA	United States Food and Drug Administration
FDLQI	Family Dermatology Life Quality Index
GCP	Good Clinical Practice
GEE	generalised estimating equation
HPV	human papillomavirus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IgG	immunoglobulin G
IL	interleukin
IMP	investigational medicinal product
IRT	interactive response technology
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	least squares
MACE	major adverse cardiac events
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
MSM	multi-state model
NRI	non-responder imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI 75	at least 75% improvement in PASI score
PDCO	paediatric committee
PHQ-A	Patient Health Questionnaire-9 modified for adolescents, without question number 9
PK	pharmacokinetics

PPD	purified protein derivative
PT	preferred term
Q2W+1	Weeks 0, 1, 2, and every 2 weeks thereafter
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	standard data tabulation model
SIB	suicidal ideation and behaviour
SmPC	summary of product characteristics
SMQ	standardised MedDRA queries
SOC	system organ class
SS	severity score
SSS	sum of severity scores
sPGA	static Physician's Global Assessment
Td	combined tetanus toxoid and diphtheria toxoid vaccine
Tdap	combined tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
TEAE	treatment-emergent adverse event
Th	T-helper
TT	tetanus toxoid
UK	United Kingdom
ULN	upper limit of normal
UAE	United Arab Emirates
USA	United States of America
WBC	white blood cell
WHO	World Health Organization

1 Protocol synopsis

Trial ID EudraCT no.	LP0160-1396 2019-001868-30
Title of trial	A phase 3, randomised, double-blind, multi-centre trial to evaluate the efficacy, safety, and tolerability of brodalumab treatment compared to placebo (blinded) and ustekinumab (open-label) in adolescent subjects (12–17 years of age) with moderate-to-severe plaque psoriasis
Short title of trial	Efficacy and safety of brodalumab in adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis; EMBRACE 1
Primary objective	To determine the efficacy of subcutaneous administration of brodalumab compared with placebo in treating adolescents with moderate-to-severe plaque psoriasis.
Primary endpoint, key secondary endpoints, and secondary endpoint for the primary objective	*Primary endpoint:* • Having at least 75% improvement in Psoriasis Area and Severity Index (PASI) score from baseline (PASI 75 response), assessed at Week 12. *Key secondary endpoints:* • Static Physician's Global Assessment (sPGA) score of 0 or 1, assessed at Week 12. • sPGA score of 0, assessed at Week 12. • PASI 90 response, assessed at Week 12. • PASI 100 response, assessed at Week 12. • Children's Dermatology Life Quality Index (CDLQI) total score of 0 or 1, assessed at Week 12. *Secondary endpoint:* • Family Dermatology Life Quality Index (FDLQI) total score of 0 or 1, assessed at Week 12.
Final collection of data for the primary endpoint	Week 12.
Trial design	This trial is designed as a clinical phase 3, multi-centre, randomised, placebo-controlled (double-blind until Week 12) and comparator-controlled (open-label ustekinumab) trial in which adolescents with moderate-to-severe plaque psoriasis will be treated with brodalumab, ustekinumab, placebo followed by brodalumab, or placebo followed by ustekinumab. The brodalumab arm and the 2 placebo arms will be double-blinded until Week 12 and the ustekinumab arm will be open-label throughout the entire trial. The trial will be unblinded after Week 12, but the efficacy assessments will be performed by an investigator who is blinded to the treatment allocation of all arms throughout the entire trial.



Abbreviations: N, total number of subjects in the trial; n, number of subjects in each treatment arm; R, randomisation; W, weeks.

The trial consists of a screening period of 2 to 4 weeks (Week -4/-2 to Week 0), an induction period of 12 weeks (Week 0 to Week 12), a maintenance period of 40 weeks (Week 12 to Week 52), and a safety follow-up period of 8 weeks (Week 52 to Week 60).

Induction period from Week 0 to Week 12

Subjects randomised at Week 0 to brodalumab or any of the 2 placebo arms will receive injections at Weeks 0, 1, 2, 4, 6, 8, and 10. The dose will be determined by the subject's body weight at Week 0 (Day 1):

- Subjects weighing 30 to <70 kg will receive 140 mg brodalumab (in a 1.0 mL syringe) or 1.0 mL brodalumab placebo.
- Subjects weighing ≥70 kg will receive 210 mg brodalumab (in a 1.5 mL syringe) or 1.5 mL brodalumab placebo.

Subjects randomised at Week 0 to ustekinumab will receive injections at Weeks 0 and 4. The ustekinumab dose will be determined by the subject's body weight at each dosing visit:

- Subjects weighing 30 to <60 kg will receive 0.75 mg ustekinumab per kg body weight.
- Subjects weighing ≥60 and ≤100 kg will receive 45 mg ustekinumab.
- Subjects weighing >100 kg will receive 90 mg ustekinumab.

Vaccination

Subjects randomised at Week 0 to brodalumab or any of the 2 placebo arms will receive 1 dose of 0.5 mL of non-live T-cell-dependent tetanus toxoid (TT)-containing vaccine at Week 8. The vaccine response will be evaluated at Week 12 and vaccine-related safety assessments will be evaluated throughout

	the trial. Subjects randomised to ustekinumab only will not receive the vaccination. *Maintenance period from Week 12 to Week 52* Subjects randomised at Week 0 to either brodalumab or ustekinumab will continue on the allocated treatment until Week 52: • Subjects on brodalumab treatment will receive injections every 2 weeks from Week 12 to Week 50. • Subjects on ustekinumab treatment will receive injections at Weeks 16, 28, and 40. Subjects randomised to placebo followed by brodalumab will switch to brodalumab treatment during the maintenance period and receive brodalumab injections at Weeks 12, 13, 14, and then every 2 weeks until Week 50. The brodalumab dose will be determined by the subject's body weight at Week 0: • Subjects weighing 30 to <70 kg at Week 0 will receive 140 mg brodalumab. • Subjects weighing ≥70 kg at Week 0 will receive 210 mg brodalumab. Subjects randomised to placebo followed by ustekinumab will switch to ustekinumab treatment during the maintenance period and will receive ustekinumab injections at Weeks 12, 16, 28, and 40. The ustekinumab dose will be determined by the subject's body weight at each dosing visit: • Subjects weighing 30 to <60 kg will receive 0.75 mg ustekinumab per kg body weight. • Subjects weighing ≥60 and ≤100 kg will receive 45 mg ustekinumab. • Subjects weighing >100 kg will receive 90 mg ustekinumab. *Rescue treatment* From Week 4 and after, rescue treatment with topical corticosteroids (class I to IV, according to World Health Organization [WHO] classification of topical corticosteroids, as deemed appropriate by the investigator) is allowed in all 4 treatment arms in subjects with an increase of ≥25% in PASI score from baseline (Week 0). *Safety follow-up period from Week 52 to Week 60* The subjects will be followed until Week 60. The 8-week follow-up period covers 5 half-lives of brodalumab and is appropriate for short-term safety evaluation after the treatment is completed.
Main assessments	*Investigator efficacy assessments* • PASI score. • sPGA score. *Patient-reported outcomes for efficacy* • CDLQI score. • FDLQI score.

Main criteria for inclusion	• Subject was diagnosed with chronic plaque psoriasis at least 6 months before randomisation. • Subject has a diagnosis of moderate-to-severe plaque psoriasis as defined by PASI ≥12, sPGA ≥3, and body surface area ≥10% at screening and at baseline. • Subject, in whom topical therapy is not adequate, and who is a candidate for systemic therapy. • Subject's immunisations are up-to-date according to national immunisation programme schedule as specified by country-specific paediatric health authorities. Missing an adolescent dose of combined tetanus, diphtheria, and pertussis (Tdap) or combined tetanus and diphtheria (Td) vaccine is accepted. • Subject has no evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment.
Main criteria for exclusion	• Subject is diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g., eczema). • Subject has been vaccinated with a TT-containing vaccine ≤18 months prior to first dose of investigational medicinal product (IMP). Subject has been vaccinated with a TT-containing vaccine within 5 years prior to the first dose of IMP - applicable for countries in EU + UK. • Subject has developed or experienced either Guillian-Barre syndrome, encephalopathy, Arthus-type hypersensitivity, or severe allergic reactions in connection with previous Tdap or Td vaccine. • Subject with chronic or recurrent infections, or active infection, systemically treated within 4 weeks prior to first dose of IMP. • Subject has a known history of Crohn's disease. • Subject has any active malignancy or a history of any malignancy within 5 years. • Subject has a history of suicidal behaviour and has suicidal ideation with some intent to act or specific plan and intent. • Subject has a history of depressive disorder with severe episode(s) within the last 2 years. • Subject has received anti-IL-12/23p40 for less than 12 months prior to the first dose of IMP or has previously no response to anti-IL-12/23p40 therapy. • Subject has previously received anti-IL-17 therapy.
Investigational medicinal products	*Brodalumab* • Brodalumab is a recombinant fully human monoclonal immunoglobulin G (IgG)2 antibody that binds with high affinity to the human interleukin-17 receptor A (IL-17RA) and blocks the interaction with IL-17A, IL-17E, and IL-17F.

	• Active substance and concentration: brodalumab, 140 mg/mL. • Dosage form: solution for injection. • Method of administration: subcutaneous administration. *Placebo* • The brodalumab placebo solutions are similar to the active brodalumab solutions except that they do not contain any active substance. *Ustekinumab* • Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. • Active substance and concentration: ustekinumab, 90 mg/mL. • Dosage form: solution for injection. • Method of administration: subcutaneous administration. *Tdap; vaccine including pertussis* • A combined TT, diphtheria toxoid, and acellular pertussis vaccine (adsorbed, reduced antigen content). Each 0.5 mL dose is formulated to contain TT ≥20 IU, diphtheria toxoid ≥2 IU, pertussis toxoid 20 µg. • Dosage form: suspension for injection. • Method of administration: intramuscular administration. *Td; vaccine not including pertussis* • A combined TT and diphtheria toxoid vaccine (adsorbed, reduced antigen content). Each 0.5 mL dose is formulated to contain TT ≥20 IU and diphtheria toxoid ≥2 IU. • Dosage form: suspension for injection. • Method of administration: intramuscular administration.
Duration of treatment	The duration of the treatment phase for each subject is planned for 52 weeks including a 12-week induction period and a 40-week maintenance period.
Number of subjects	A total of 120 eligible subjects randomised in a 2:2:1:1 ratio to brodalumab (52 weeks of treatment), ustekinumab (52 weeks of treatment), placebo followed by brodalumab (brodalumab placebo the first 12 weeks of treatment and brodalumab the last 40 weeks), or placebo followed by ustekinumab (brodalumab placebo the first 12 weeks of treatment and ustekinumab the last 40 weeks).
Number and distribution of trial sites	Approximately 75 sites mainly in Europe and Russia.
Statistical methods	*Primary and key secondary endpoints* The difference in response rates at Week 12 between the brodalumab arm and the pooled placebo arms will be analysed based on the Cochran-Mantel-Haenszel (CMH) test stratified by baseline body weight (<70 kg, ≥70 kg). Missing data at Week 12 will be imputed using non-responder imputation. Additionally, subjects satisfying the requirements for rescue treatment prior to Week 12, will be defined as non-responders. Inference will be based on the p-

	value obtained from the CMH test. In order to quantify the difference in response rates, the common risk difference and associated 95% confidence interval, based on the CMH test, will also be reported. In order to control the familywise error rate, a hierarchical testing procedure, indictaing the order in which the primary and key secondary endpoints are to be tested, has been pre-specified.
Signatory investigator	[redacted]
Sponsor	LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

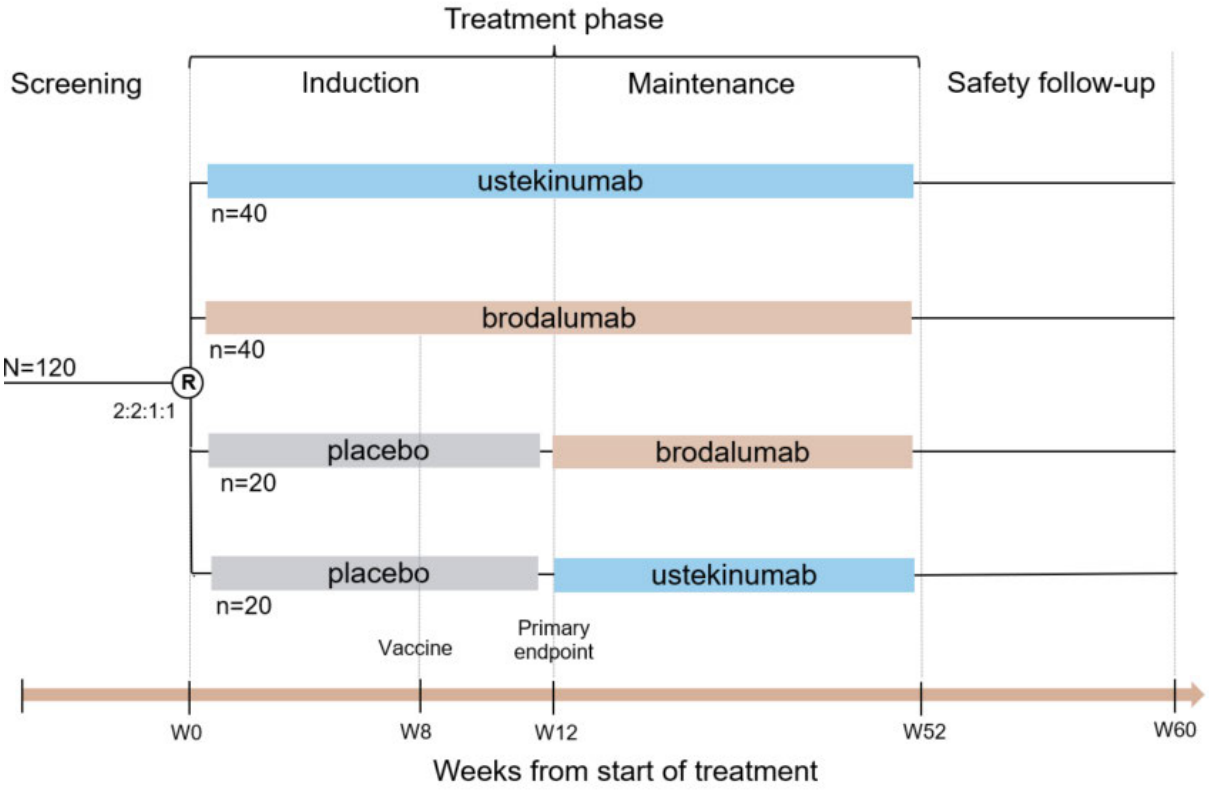
2 Trial identification

EudraCT number: 2019-001868-30.

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: N, total number of subjects in the trial; n, number of subjects in each treatment arm; R, randomisation; W, weeks.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures for screening and induction period

	Screening	Treatment phase – induction period								Only applicable if early stop of IMP[b]		Unscheduled visit, if applicable[c]	References (protocol section)
Visit (V)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early termination visit**	**Safety follow-up visit**		
Week	**Up to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**10+4 days**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**Up to -28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**V8+4**				
Visit window (days)[a]	-	-	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+2**				
Trial population and eligibility													
Informed consent/assent[d]	X												8.4.1
Subject eligibility	X	X[e]											8.1
Investigator assessments at screening 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
Subject assessments of efficacy													
eDiary hand out and training	X												11.3.4
Adolescent Pruritus NRS[f]	<========== daily eDiary completion ==========>									X			11.3.4.3
Itch-related Sleep NRS[f]	<========== daily eDiary completion ==========>									X			11.3.4.4
eDiary return[e]										(X)	(X)		11.3.4

	Screening	Treatment phase – induction period								Only applicable if early stop of IMP[b]		Unscheduled visit, if applicable[c]	References (protocol section)
Visit (V)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early termination visit**	**Safety follow-up visit**		
Week	**Up to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**10+4 days**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**Up to -28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**V8+4**				
Visit window (days)[a]	-	-	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+2**				
Health-related quality of life assessments													
CDLQI		X			X					X		(X)	11.3.4.1
FDLQI		X			X					X		(X)	11.3.4.2
Investigator assessments of efficacy													
PASI	X	X	X	X	X	X	X	X		X		(X)	11.3.1
sPGA	X	X	X	X	X	X	X	X		X		(X)	11.3.2
BSA	X	X	X	X	X	X	X	X		X		(X)	11.3.3
Investigator assessments of safety													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	(X)	13
Concomitant medication, concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	(X)	9.6
ECG	X	X								X		(X)	11.4.3
Vital signs	X	X	X	X	X	X	X	X		X	X	(X)	11.4.1
Physical examination	X	X								X		(X)	11.4.2
Body measurements: height, weight	X	X			X					X		(X)	11.4.4

	Screening	Treatment phase – induction period								Only applicable if early stop of IMP[b]		Unscheduled visit, if applicable[c]	References (protocol section)
Visit (V)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early termination visit**	**Safety follow-up visit**		
Week	**Up to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**10+4 days**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**Up to -28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**V8+4**				
Visit window (days)[a]	-	-	±3	±3	±3	±3	±3	±3	+2				
Laboratory - blood samples													
Haematology	X	X		X	X		X			X		(X)	11.4.5
Chemistry	X	X			X		X			X		(X)	11.4.5
Serology	X											(X)	11.4.5
Tuberculosis test	X												11.4.5
ADA		X[g]			X[g]					X		(X)	11.4.7
PK		X[g]			X[g]		X[g]		X[g]	X		(X)	11.5.1
Blood biomarkers		X[g]					X[g]			X		(X)	11.6.2
Lymphocyte subsets		X[g]					X[g]			X		(X)	11.6.3
Vaccine antibodies		X[g]					X[g]			X		(X)	11.4.6
Serum pregnancy test[h]	X											(X)	11.4.5
Urine samples													
Urine pregnancy test and remind about proper birth control, as needed[i]	X	X			X		X			X	X	(X)	11.4.5
Urinalysis (urine dipstick)[j]	X	X			X		X			X		(X)	11.4.5
Subject assessments of safety													
C-SSRS	X	X	X	X	X	X	X	X		X	X	(X)	11.7.1.1
PHQ-A	X	X	X	X	X	X	X	X		X	X	(X)	11.7.1.2

	Screening	Treatment phase – induction period								Only applicable if early stop of IMP[b]		Unscheduled visit, if applicable[c]	References (protocol section)
Visit (V)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Early termination visit**	**Safety follow-up visit**		
Week	**Up to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**10+4 days**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**Up to -28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**V8+4**				
Visit window (days)[a]	-	-	±3	±3	±3	±3	±3	±3	+2				
Trial products including randomisation													
Randomisation		X											9.3
On-site administration of **blinded trial product**, if randomised to the brodalumab or the placebo arms		X	X	X	X	X	X	X				(X)	9.2.1
On-site administration of Td or Tdap **vaccine**, if randomised to the brodalumab or the placebo arms							X					(X)	9.2.2
On-site administration of **ustekinumab**, if randomised to the ustekinumab arm		X			X							(X)	9.2.1
Treatment compliance		X	X[h]	X[h]	X	X[h]	X[h]	X[h]				(X)	9.8.4
Other assessments													
Photography (selected trial sites)[k]		X		X									11.7.2
Concluding forms in the eCRF													
End of treatment form[l]										X			11.9.1
End of trial form[m]										(X)	(X)		11.9.2

Abbreviations: ADA, anti-drug antibodies; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; eCRF, electronic case report form; FDLQI, Family Dermatology Life Quality Index; IMP, investigational medicinal product; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PHQ-A, Patient Health Questionnaire-9 modified for adolescents, without question number 9; PK, pharmacokinetics; PPD, purified protein derivative (tuberculosis diagnostic test); sPGA, static Physicians's Global Assessment; Td, combined tetanus toxoid and diphtheria vaccine; Tdap, combined tetanus, diphtheria, and acellular pertussis vaccine; V, visit.

a) 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 randomisation/baseline at Day 1. Visits outside the allowed visit window still need to be performed, taking into consideration that a minimum interval of 7 days must be kept between 2 administrations of brodalumab/placebo (except for Visit 3 and Visit 4, which are exempt from the 7-day gap requirement).
b) All subjects who permanently discontinue IMP prematurely will be asked to attend an early termination visit, a safety follow-up visit (8 weeks after last IMP), and the subsequent primary and secondary endpoints visits (at Week 12, Week 16, and Week 52). The subjects will also be asked to continue in the trial and attend other than primary and secondary endpoints visits, if the subjects wish. Refer to Section 10 for further information.
c) Unscheduled visit(s) may occur if subjects need to make a visit in between the scheduled visit dates e.g., due to an adverse event, difficulty complying with the trial protocol requirements, or a significant change in their disease state.
d) The informed consent/assent form(s) must be signed prior to performing any protocol-related procedures. If the subject reaches legal age during the trial, the subject will be consented to the most current version of the informed consent form if required by national laws or regulations.
e) Subjects must be randomised as soon as all inclusion and exclusion criteria are confirmed (including the central laboratory and ECG results from the screening visit).
f) Assessed daily by the subject. Completion of the eDiary will be initiated at the latest 1 week prior to baseline at Day 1. The eDiary will be returned at the last visit.
g) Only subjects randomised to either brodalumab or placebo.
h) Only female subjects.
i) Only female subjects. If a urine pregnancy test (human chorionic gonadotropin) is positive, a serum pregnancy test has to be done to confirm the result. At screening, a serum pregnancy test is always performed regardless of the urine pregnancy result.
j) In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts).
k) Photography will require additional informed consent. If deemed necessary (e.g. in case of poor quality), photographs can be retaken.
l) An end of treatment form must be completed in the electronic case report form (eCRF) for all randomised subjects, including subjects who permanently discontinue IMP treatment prematurely.
m) An end of trial form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP treatment prematurely or withdraw from the trial, at their last trial visit.

Panel 3: Schedule of trial procedures for maintenance and safety follow-up periods

	Treatment phase – maintenance period													Safety follow-up period	Only applicable if early stop of IMP[c]		Unscheduled visit, if applicable[d]	References (protocol section)
Visit (V)	**10**	**11**	**12**	**13**	**14**	**15[b]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**Early termination visit**	**Safety follow-up visit**		
Week	**12**	**13**	**14**	**16**	**20**	**22+4 days**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**85**	**V10+7**	**99**	**113**	**141**	**V14+18**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**421**				
Visit window (days)[a]	**±3**	**±1**	**±1**	**±3**	**±3**	**+2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Subject assessment of efficacy																		
Adolescent Pruritus NRS[e]	<========== daily eDiary completion ==========>														X			11.3.4.3
Itch-related Sleep NRS[e]	<========== daily eDiary completion ==========>														X			11.3.4.4
Return of eDiary[e]													X		(X)	(X)		11.3.4
Health-related quality of life assessments																		
CDLQI	X			X		X			X				X		X		(X)	11.3.4.1
FDLQI	X			X		X			X				X		X		(X)	11.3.4.2
Investigator assessments of efficacy																		
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X		X		(X)	11.3.1
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X		X		(X)	11.3.2
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X		X		(X)	11.3.3
Investigator assessments of safety																		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	13
Concomitant medication / concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	9.6
ECG	X					X							X		X		(X)	11.4.3
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.4.1

	Treatment phase – maintenance period													Safety follow-up period	Only applicable if early stop of IMP[c]		Unscheduled visit, if applicable[d]	References (protocol section)
Visit (V)	**10**	**11**	**12**	**13**	**14**	**15[b]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**Early termination visit**	**Safety follow-up visit**		
Week	**12**	**13**	**14**	**16**	**20**	**22+4 days**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**85**	**V10+7**	**99**	**113**	**141**	**V14+18**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**421**				
Visit window (days)[a]	**±3**	**±1**	**±1**	**±3**	**±3**	**+2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Investigator assessments of safety																		
Physical examination	X					X			X				X		X		(X)	11.4.2
Body measurement: height	X					X			X				X		X		(X)	11.4.4
Body measurement: weight	X			X		X	X		X	X			X		X		(X)	11.4.4
Laboratory - blood samples																		
Haematology	X			X		X	X		X		X		X		X		(X)	11.4.5
Chemistry	X			X		X	X		X		X		X		X		(X)	11.4.5
ADA				X[f]		X[f]							X[f]		X		(X)	11.4.7
PK	X[g]			X[f]		X[f]							X[f]		X		(X)	11.5.1
Blood biomarkers	X[g]												X[f]		X		(X)	11.6.2
Lymphocyte subsets	X[g]												X[f]		X		(X)	11.6.3
Vaccine antibodies	X[g]														X		(X)	11.4.6
Urine samples																		
Urine pregnancy test and remind about use of highly effective methods of contraception, as needed[h]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.4.5
Urinalysis (urine dipstick)[i]	X			X		X							X		X		(X)	11.4.5
Subject assessments of safety																		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.7.1.1
PHQ-A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)	11.7.1.2

	Treatment phase – maintenance period													Safety follow-up period	Only applicable if early stop of IMP[c]		Unscheduled visit, if applicable[d]	References (protocol section)
Visit (V)	**10**	**11**	**12**	**13**	**14**	**15[b]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**Early termination visit**	**Safety follow-up visit**		
Week	**12**	**13**	**14**	**16**	**20**	**22+4 days**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**85**	**V10+7**	**99**	**113**	**141**	**V14+18**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**421**				
Visit window (days)[a]	**±3**	**±1**	**±1**	**±3**	**±3**	**+2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Trial products																		
Dispense IMP for home-based administration[j]				X	X	X	X	X	X	X	X	X						9.2.1.2, 9.8.3
Return of IMP for home-based administration[j]					X	X	X	X	X	X	X	X	X		(X)			9.8.3
On-site administration of **brodalumab**, if randomised to the 'brodalumab' arm	X		X	X	X		X	X	X	X	X	X					(X)	9.2.1
On-site administration of **brodalumab**, if randomised to the 'placebo followed by brodalumab' arm	X	X	X	X	X		X	X	X	X	X	X					(X)	9.2.1
On-site administration of **ustekinumab**, if randomised to the 'ustekinumab' arm				X			X			X							(X)	9.2.1
On-site administration of **ustekinumab**, if randomised to the 'placebo followed by ustekinumab' arm	X			X			X			X							(X)	9.2.1
Treatment compliance	X	X	X	X	X	X	X	X	X	X	X	X	X		X			9.8.4
Other assessments																		
Photography (selected trial sites)[k]	X												X					11.7.2

	Treatment phase – maintenance period													Safety follow-up period	Only applicable if early stop of IMP[c]		Unscheduled visit, if applicable[d]	References (protocol section)
Visit (V)	**10**	**11**	**12**	**13**	**14**	**15[b]**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**Early termination visit**	**Safety follow-up visit**		
Week	**12**	**13**	**14**	**16**	**20**	**22+4 days**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**	**As soon as possible within 2 weeks after last IMP**	**8 weeks after last IMP**		
Day	**85**	**V10+7**	**99**	**113**	**141**	**V14+18**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**421**				
Visit window (days)[a]	**±3**	**±1**	**±1**	**±3**	**±3**	**+2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**				
Concluding forms in the eCRF																		
End of treatment form[l]													X		X			11.9.1
End of trial form[m]														X	(X)	(X)		11.9.2

Abbreviations: ADA, anti-drug antibodies; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; eCRF, electronic case report form; FDLQI, Family Dermatology Life Quality Index; IMP, investigational medicinal product; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PHQ-A, Patient Health Questionnaire-8 modified for adolescents, without question number 9; PK, pharmacokinetics; sPGA, static Physicians's Global Assessment, V, visit.

a) 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 randomisation/baseline at Day 1. Visits outside the allowed visit window still need to be performed, taking into consideration that a minimum interval of 7 days must be kept between 2 administrations of brodalumab/placebo (except for Visit 3 and Visit 4, which are exempt from the 7-day gap requirement).

b) This visit is scheduled 4 days after the IMP administration at Week 22.

c) All subjects who permanently discontinue IMP prematurely will be asked to attend an early termination visit, a safety follow-up visit (8 weeks after last IMP), and the subsequent secondary endpoints visits (at Week 16 and Week 52). The subjects will also be asked to continue in the trial and attend other than secondary endpoints visits, if the subjects wish. Refer to Section 10 for further information.

d) Unscheduled visit(s) may occur if subjects need to make a visit in between the scheduled visit dates e.g., due to an adverse event, difficulty complying with the trial protocol requirements, or a significant change in their disease state.

e) Assessed daily by the subject. The eDiary will be returned at the last visit.

f) Only subjects on brodalumab.

g) Only subjects randomised at Day 1 to either brodalumab or placebo.

h) Only female subjects. If a urine pregnancy test (human chorionic gonadotropin) is positive, a serum pregnancy test has to be done to confirm the result.

i) In case of abnormal dipstick results, a urine sample will be sent to the central laboratory for microscopic examination (leukocytes, erythrocytes, and casts).

j) Only applicable for home-based IMP administration; home-based administration of brodalumab is allowed (after proper training) at Week 18 (Day 127±3), Week 22 (Day 155±3), Week 24 (Day 169±3), Week 26 (Day 183±3), Week 30 (Day 211±3), Week 34 (Day 239±3), Week 38 (Day 267±3), Week 42 (Day 295±3), Week 46 (Day 323±3), and Week 50 (Day 351±3). Subjects who refuse to do home-based IMP administration can have the IMP administered at the trial site at these weeks.
k) Photography will require additional informed consent. If deemed necessary (e.g. in case of poor quality), photographs can be retaken.
l) An end of treatment form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP treatment prematurely.
m) An end of trial form must be completed in the eCRF for all randomised subjects, including subjects who permanently discontinue IMP treatment prematurely 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 disorder that occurs in approximately 2% of the population worldwide (1, 2), and it affects 0.7 to 1.2% of children younger than 18 years worldwide (3).

It has been demonstrated that the psoriasis prevalence in children correlates in a linear manner with age. The prevalence is low in the age range of 0 to 6 years (4), and increasing during adolescence. Approximately 30 to 40% of adults with psoriasis report signs and symptoms before the age of 16 years (5).

Psoriasis is a chronic polygenic inherited disease of uncontrolled cutaneous inflammation that manifests, in the majority of patients, as plaque psoriasis, clinically seen as sharply demarcated, elevated, scaly, erythematous plaques located predominantly on the scalp, extensor sides of elbows and knees, and the sacral region (6, 7, 8). The skin lesions can be painful, pruritic, and may cause significant emotional and physical discomfort (9). In general, childhood psoriasis presents in much the same way as in adults, typically with plaque-type lesions localised to the scalp, elbows, and knees (10). However, precipitating factors are more important in paediatric- than adult-onset psoriasis. For example, the appearance of psoriatic lesions may occur in uninvolved skin at sites of trauma (Koebner phenomenon), and psychological factors such as stress have also been reported to initiate paediatric psoriasis (11, 12). In addition to skin manifestations, paediatric psoriasis is associated with multiple comorbidities. Increased rates of hyperlipidaemia, obesity, hypertension, diabetes mellitus, metabolic syndrome, polycystic ovarian syndrome, Crohn's disease, and rheumatoid arthritis are found in adolescents with psoriasis (2, 13). Recently, a non-alcoholic fatty liver disease screening in children with psoriasis and excess adiposity has been proposed (14), acknowledging the fact of this comorbidity (13) and the importance of the early diagnose, when systemic treatment is indicated. Joint involvement with psoriatic arthritis is less common in younger psoriatic patients, but it does occur in 5-10% (15). When managing the paediatric psoriasis a significantly greater risk of anxiety and depression compared with the controls should be taken into consideration (16).

Treatment options are similar to those of adults, but many therapeutic agents are not approved for use in children and guidelines are generally lacking for this population. Topical therapy in childhood is the recommended first-line treatment for skin-related diseases, and most children can be managed effectively with topical agents (e.g., emollients, corticosteroids, calcipotriol,

and coal tar). Approximately 8% of adolescents require phototherapy or systemic psoriasis therapy, which is typically reserved for patients with severe disease (5).

5.2 Experience with investigational medicinal product

Brodalumab is a recombinant fully human monoclonal immunoglobulin G (IgG)2 antibody that binds with high affinity to human interleukin (IL)-17 receptor A (IL-17RA), thereby blocking the IL-17 pathway. Brodalumab is currently approved in the EU, UK, UAE, Japan, Taiwan, Thailand, Hongkong, China, Canada, and the USA for treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy.

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

The approved dose regimen for brodalumab for the treatment of moderate-to-severe plaque psoriasis in adults is 210 mg by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

The efficacy of brodalumab for treatment of psoriasis in adults has been confirmed in 3 placebo-controlled, clinical phase 3 trials, 2 of which also included an active comparator arm with ustekinumab. The overall benefit-risk profile of brodalumab was shown to be positive in the treatment of adults with moderate-to-severe plaque psoriasis regardless of baseline demographics and the subpopulations studied.

In a population pharmacokinetic (PK) analysis of brodalumab, body weight was found to be a significant predictor of systemic exposure of brodalumab (expressed as area under the serum concentration-time curve [AUC] at Week 10–12) in the body weight range tested (39–234 kg) (18). Simulated systemic exposure across observed body weight quintiles shows a decrease of exposure with increasing body weight (Panel 4).

Panel 4: Simulated systemic exposure (AUC at Week 10-12 dosing Q2W+1) across observed body weight quintiles by dosing regime

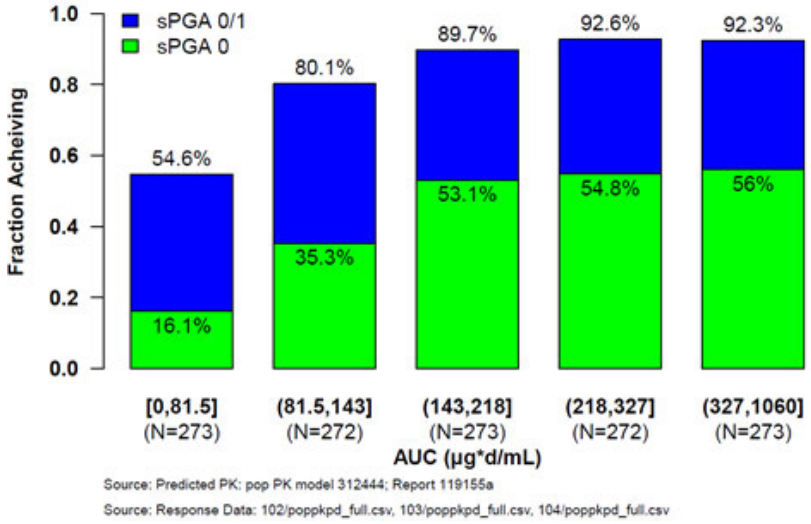
Dosage	Weight group	Median AUC (µg day/mL)	90% prediction interval
140 mg Q2W+1	39 - 72 kg	98.9	[34.6, 315.6]
	72 - 83 kg	57.8	[23.2, 169.7]
	83 - 93 kg	46.6	[17.6, 141.7]
	93 - 107 kg	34.9	[12.6, 106.7]
	107 - 234 kg	23.5	[6.8, 68.9]
210 mg Q2W+1	39 - 72 kg	293.3	[109.9, 682.4]
	72 - 83 kg	209.7	[83.5, 478.3]
	83 - 93 kg	171.6	[62.6, 379.8]
	93 - 107 kg	134.0	[47.7, 338.6]
	107 - 234 kg	91.5	[31.3, 238.1]

Abbreviation: AUC, area under the serum concentration-time curve; Q2W+1, dosing at Weeks 0, 1, 2, and every 2 weeks thereafter.

Based on the body weight distribution in the phase 3 trials, serum concentration-time profiles were simulated and systemic exposure (AUC at Week 10-12) was hereafter calculated. Summary statistics (median and 90% prediction interval) of the AUCs are provided for each body weight quintile. Source: 18.

A lower systemic exposure is apparently associated with a lower frequency of static Physician's Global Assessment (sPGA) response, both for sPGA 0/1 and sPGA 0 (Panel 5). Based on logistic regression, the AUC needed for 50% and 90% achievement of sPGA 0/1 at Week 12 are 34.8 and 159.8 µg*day/mL, respectively.

Panel 5: Week 12 sPGA response by quintiles of predicted $AUC_{week\ 10\text{-}12}$ for the phase 3 population studied for 210 mg Q2W+1 brodalumab



Abbreviations: AUC, area under the serum concentration-time curve; Q2W+1, dosing at Weeks 0, 1, 2, and every 2 weeks thereafter; PK, pharmacokinetics; sPGA, static Physician's Global Assessment.

Individual AUCs (Week 10-12) were calculated based on the individual population PK model parameter estimates and paired with the individual sPGA response. For each AUC quintile, the percentage of sPGA 0/1 and sPGA 0 were calculated.

Comparing the Psoriasis Area and Severity Index (PASI) improvement versus body weight and dose (Panel 6) also shows a relationship between body weight and response at both dose levels of brodalumab (140 mg and 210 mg). Furthermore, data show that increasing the dose from 140 mg to 210 mg at Weeks 0, 1, 2, and every 2 weeks thereafter results in an increased mean PASI response for all body weight groups above 70 kg. For patients with a body weight below 70 kg, no statistical significant difference was seen between the PASI response in the 140 mg and 210 mg dose groups.

Panel 6: Summary of mean PASI improvement from baseline (LOCF) at Week 12 by weight class and treatment (full analysis set)

	Brodalumab				
	140 mg Q2W (N = 1458)		210 mg Q2W (N = 1458)		p-value for comparing 210 mg Q2W and 140 mg Q2W
Weight Class	N1	Mean (SD)	N1	Mean (SD)	
With Lowest Weight Class as ≤ 60 kg					
≤ 60 kg	90	92.86 (15.63)	94	96.17 (15.14)	0.40
> 60 to 70 kg	150	92.39 (16.72)	167	91.79 (17.20)	0.84
> 70 to 80 kg	252	85.96 (24.29)	243	92.20 (18.28)	0.01
> 80 to 90 kg	303	79.27 (30.06)	294	90.78 (18.46)	<.001
> 90 to 100 kg	244	74.82 (31.13)	240	89.07 (18.89)	<.001
> 100 to 110 kg	171	61.34 (37.71)	172	86.15 (24.96)	<.001
> 110 to 120 kg	112	55.53 (46.41)	91	87.32 (22.03)	<.001
> 120 to 130 kg	64	55.25 (34.26)	55	77.73 (32.95)	<.001
> 130 kg	65	33.67 (43.17)	97	65.36 (36.42)	<.001

Abbreviations: LOCF, last observation carried forward; PASI, Psoriasis Area Severity Index.

Source: Module 5.3.5.3 Summary of weight-based dosing, Table 6.

5.3 Trial rationale and justification for dose

5.3.1 Trial rationale

Brodalumab is indicated for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic treatment. Brodalumab's mode of action is to bind to and block IL-17RA. It has been reported, that numbers of circulating Th17 cells in children with psoriasis are increased and positively correlated with the disease severity (19), indicating that brodalumab treatment might be as effective in the paediatric population as it is in adults.

This trial is part of the paediatric investigational plan agreed with the Paediatric Committee (PDCO) and the European Medicines Agency (EMA) to investigate whether brodalumab is efficacious and safe in treating adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis. The PK data from this trial will be used to determine the appropriate dose of brodalumab to be used in a planned future trial with subjects from 6 to 11 years of age.

Since vaccination programmes are an important part of health maintenance, the World Health Organization (WHO) as well as paediatric authorities worldwide recommend that infants, children, and adolescents follow a child vaccination schedule of the country of residence, it is therefore also relevant to investigate if brodalumab affects development of vaccination-induced immune responses. This trial will assess immunisation responses against tetanus toxoid (TT)-containing vaccine (a combined tetanus, diphtheria, and acellular pertussis [hereinafter referred to as 'Tdap'] vaccine or a combined tetanus, diphtheria vaccine [hereinafter referred to as 'Td'] in adolescents with moderate-to-severe plaque psoriasis. The

selected types of T-cell-dependent vaccines are known to result in an immune response involving both T- and B-cells as well as other key cell types of the immune system. Further considerations regarding the vaccines are provided in Section 5.4.

5.3.2 Justification for dose

The PK of brodalumab has been well-described in a population PK analysis including both healthy adults and adults with psoriasis, where body weight was found to be a significant predictor of brodalumab systemic exposure (18). Age was not found to be a significant predictor of brodalumab exposure, but due to the correlation between body weight and age in the paediatric population, a change in dose is warranted for the adolescent population.

The planned dose levels of brodalumab in this trial are:

- Subjects with a body weight of less than 70 kg will receive 140 mg at Weeks 0, 1, 2, and every 2 weeks thereafter.
- Subjects with a body weight 70 kg or more will receive 210 mg at Weeks 0, 1, 2, and every 2 weeks thereafter.

Due to the impact of body weight on systemic exposure, a dose level of 140 mg in subjects with a body weight below 70 kg will result in systemic exposures below the target exposure of an 80 kg adult subject. However, the efficacy data show no difference in efficacy between 140 and 210 mg dose levels for adult subjects below 70 kg. Given that the PK of brodalumab in adolescent subjects has not yet been established, a conservative dosing strategy has been chosen, justifying a reduction in dose compared to what is recommend in the adult population.

The brodalumab dose will be based on the subject's body weight at baseline (Week 0, Day 1) and will not be changed during the trial.

5.4 Ethical considerations

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

Participation in this trial is voluntary and subjects can withdraw at any time. The subject's legally authorised representative(s) will give informed consent, and subjects must give their informed consent (assent) as appropriate and according to national laws and regulations. No vulnerable subjects incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, female subjects who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled. Female subjects must agree to use highly effective methods of contraception, e.g., preferred in adolescents hormonal contraception associated with inhibition

of ovulation (oral, intravaginal, transdermal) or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), to prevent pregnancy during the clinical trial and until 12 weeks after discontinuation of treatment with brodalumab or until 15 weeks after discontinuation of treatment with ustekinumab. In addition, all female subjects will have pregnancy tests performed before, during, and at end of trial to ensure that the administration of the investigational medicinal product (IMP) will be discontinued upon confirmation of pregnancy to minimise the exposure of the foetus to the IMP.

To ensure safety of the trial subjects, investigators are informed only to enrol subjects they expect can complete wash out of previous psoriasis medications during the screening period without experiencing intolerable worsening of psoriasis symptoms. The subjects and/or their legally authorised representatives will be informed to contact the investigator if the subject's psoriasis worsens.

Paediatric plaque psoriasis is a chronic, relapsing disease that can cause significant morbidity, multiple somatic and psychiatric comorbidities (13, 20) and psychosocial stress for children and adolescents.

Treatment with topical corticosteroids is the most commonly utilised treatment in children with psoriasis, and is typically sufficient to control mild skin disease, which is the majority of cases. For patients with moderate disease, combination therapy or phototherapy can be effective (21, 22). However, for some paediatric patients with moderate-to-severe plaque psoriasis who have widespread disease, or disease refractory to topical combination or phototherapy, there continues to be an unmet medical need.

For many systemic agents, including some biologic therapies, efficacy and safety have not been established in paediatric patients and the treatments are not licensed for paediatric use. Biologic therapies, which are available or in development, offer the potential to address this deficit in the care of paediatric patients with plaque psoriasis. Currently, the approved therapies for paediatric psoriasis include: etanercept from age ≥6 years, ustekinumab from age ≥12 years, and adalimumab from age ≥4 years (EMA) (15). In adults, brodalumab is more effective in achieving clearance than ustekinumab, etanercept, and adalimumab (23, 24, 25); based on a direct comparison for ustekinumab and a systemic review and network meta-analysis study for etanercept and adalimumab. Given that, brodalumab has the potential to improve the care of paediatric patients with psoriasis and provide a solid therapeutic benefit.

The efficacy of brodalumab will be evaluated in this placebo-controlled trial in adolescents with moderate-to-severe plaque psoriasis who are otherwise healthy. Recognising that

prolonged placebo treatment is not optimal in this population, a 2:2:1:1 (brodalumab: ustekinumab:placebo followed by brodalumab:placebo followed by ustekinumab) randomisation is planned to increase the opportunity for subjects to receive active treatment. Subjects randomised to placebo will, after 12 weeks of treatment, receive active treatment with either brodalumab or ustekinumab. The placebo control is considered to provide the best design for an efficient assessment of both benefit and risk in adolescents. The placebo treatment from Week 0 until Week 12 will enable a formal test of superiority, comparing brodalumab with placebo in a double-blind manner. Demonstrating superiority to placebo will require fewer paediatric subjects than would be required to demonstrate superiority to an active comparator. This will enable to minimise the number of paediatric subjects required for the trial while maintaining a high statistical power. Minimising the number of subjects is an important ethical aspect, especially in the paediatric population, and this trial design is consistent with this requirement. In addition, all subjects in this trial may receive rescue treatment if the severity of their disease increases by more than 25% 4 weeks after baseline.

The WHO guidelines recommend that a booster dose of TT-containing vaccine is given at age 4 to 7 years (first booster) and another booster dose (second booster) is given in adolescence (i.e., at age 12 to 15 years). Immunisation guidelines for children and adolescents across European countries, USA, and Australia, developed by country-specific paediatric authorities, have implemented a second booster dose of an adult formulation of Tdap, which is routinely given between 9 and 17 years of age almost worldwide (26, 27). Tdap replaced the adolescent dose of Td to prevent increasing reports of pertussis among adolescents. The subjects to be enrolled in the current trial are between 12 and 17 years of age. To date, only few data on vaccination coverage of TT-containing vaccine in adolescents in Europe are available. A French study reports that 85% of school children aged 14 to 15 years are up-to-date for diphteria, tetanus, and pertussis (28). According to data from the Danish State Serum Institute, 84% of children born in 2006 are covered with TT-containing vaccine (29). In the USA, up to 52.1% of adolescents have received the Tdap vaccine (30). Thus, the subjects who have not yet received the scheduled adolescent dose of Td/Tdap will be vaccinated with a booster based on the subject's previous history of vaccination with TT-containing vaccines and current local guidelines.

The ethical considerations for including the subjects covered by Tdap have been thoroughly evaluated and are supported by available scientific data. It has been reported that 23% of healthy adolescents from 13 to 15 years of age who have received at least 6 doses of diphteria toxoid as a part of their scheduled vaccination programme were missing the protective level of diphteria antibodies. 68% had basic protection between 0.1-1.0 IU/mL and only 11% had high protection levels above 1.0 IU/mL, corresponding to a long-term protection (31).

Another study reports a diphteria antitoxin geometric mean level of 0.71 IU/mL in 88% of adolescents who had received 6 doses and the percentage of subjects with the protective levels of antibodies against diphteria decreases further after 20 years of age (32). An immediate booster vaccination is recommended when IgG levels of anti-diphteria toxoid antibodies are 0.1-1.0 IU/mL (33). Moreover, children with autoimmune disorders receiving immunosuppressive medication show decreased in vitro lymphocyte proliferation in response to tetanus antigen (34) and a lower geometric mean concentration of antibodies against diphteria and tetanus is found in children suffering from juvenile idiopathic arthritis compared with healthy controls (35). Based on the above evidence, a booster dose of Td vaccine during the trial will ensure long-term protective levels of anti-diphteria and -tetanus antibodies, resulting in better protection against these diseases.

The vaccination and withdrawal of blood samples planned in the trial expect to give no greater harm or discomfort than if done during routine diagnostic venipuncture procedure or scheduled vaccination. The amount of blood to be collected in the trial is calculated according to the current guidelines (36) and will not exceed 3% of total blood volume during a period of 4 weeks and 1% at any single time for all trial subjects. Qualified trial personnel with experience in paediatric venipuncture will conduct the invasive procedures required in the trial. Furthermore, local anesthesia and/or “virtual reality” tools can be applied to reduce discomfort and/or pain that might be caused by venipuncture, unless the trial subjects do not want to use any.

Suicidal ideation and behaviour (SIB) events, including completed suicide, have been reported in subjects treated with brodalumab. However, the majority of subjects with suicidal behaviour had a history of depression and/or SIB, and a causal association between treatment with brodalumab and increased risk of SIB is not indicated. Trial subjects will be monitored for depression and SIB by the Patient Health Questionnaire-9 modified for adolsecents without question number 9 (PHQ-A) and the Columbia-Suicide Severity Rating Scale questionnaires (C-SSRS). The investigator must discontinue subjects from trial treatment in case of C-SSRS suicidal ideation level 4 or 5, any suicidal behaviour, or a PHQ-A score ≥15, corresponding to moderate to severe depression (37). Furthermore, adolescents with a recent history of depression (within 2 years), C-SSRS suicidal ideation level 4 or 5 (that is, ‘some intent to act, no plan’ or ‘specific plan and intent’), or any suicidal behaviour (that is, ‘actual suicide attempt’, ‘interrupted attempt’, ‘aborted attempt’, or ‘preparatory actions’) are not allowed to participate in the trial since a history of prior depression and/or SIB are known risk factors for new SIB events.

In accordance with the current version of the ICH Good Clinical Practice (GCP) guidelines, qualified medical personnel employed by LEO Pharma A/S (hereafter referred to as LEO Pharma) will be readily available to advise on trial-related medical questions. Medical monitoring will be performed throughout the trial. In addition, an independent data monitoring committee (DMC, see Appendix 3H) is set up to review the clinical data ensuring safety of the trial subjects.

5.5 Benefit/risk assessment

There is an unmet medical need for highly effective new therapies for use in adolescents with moderate-to-severe psoriasis as currently approved immunosuppressive medications either have long-term toxicities or a less efficacious profile.

Brodalumab is currently approved for adults in the EU, UK, UAE, Japan, Taiwan, Thailand, Hongkong, China, Canada, and the USA. Comprehensive efficacy, safety, and PK data related to the administration of brodalumab in adults with moderate-to-severe psoriasis are available. These data provide sufficient support to initiate this clinical phase 3 trial in adolescents with moderate-to-severe psoriasis with a body weight of 30 kg or above at baseline. For this trial, adolescents with a body weight below 30 kg are not allowed to participate. Based on the weight references for boys and girls between 12 and 17 years of age in Europe, it can be expected that 95% of the subjects will be in the weight range from 30 to 95 kg (38, 39).

In the clinical phase 3 programme for brodalumab in adults, the only adverse events (AEs) that showed dose dependency were infections and neutropenia. These may occur with increased frequency in subjects receiving a higher dose of brodalumab. A PK modelling and simulation approach based on a population PK model for brodalumab in adults (18), combined with the efficacy results from the phase 3 trials in adults (see Panel 6), has been used to support the choice of the optimal brodalumab doses in adolescents. A lower dose of brodalumab has been chosen for adolescents with a body weight less than 70 kg to ensure the sufficient safety and optimal efficacy profile in this paediatric population (see Section 5.3.2).

The active comparator (i.e., ustekinumab) is part of the standard treatment of moderate-to-severe plaque psoriasis in adolescents from the age of 12 years who are inadequately controlled by, or intolerant to, other systemic therapies or phototherapies in Europe. All subjects, participating in the trial will receive effective biologic therapy (brodalumab or ustekinumab) during the maintenance period and it is expected that many will experience a significant reduction of psoriasis symptoms. The frequent clinical monitoring and contacts with trial site personnel will increase the quality of subject's psoriasis care as well as the understanding of the disease. The subjects will also become familiar with self-injections. This

will enable a safe and effective home-based administration of any other biologic therapies in the future.

The risk to subjects in this trial will be minimised by fulfilment of all eligibility criteria and by close clinical monitoring. Measures are in place in this trial as follows:

- Exclusion of subjects with untreated systemic infections or low complete blood count (see Section 8.3).
- Exclusion of subjects with active or latent tuberculosis (see Section 8.3).
- Close safety monitoring of subjects throughout the treatment phase (see the schedule of trial procedures in Section 4).
- Safety monitoring of the subjects after completed treatment phase (further details are given in Section 7.1.4).

It is expected that many of the eligible subjects will have been immunised with Tdap within the past 5 years and thus should not be immunised with a Tdap booster during the trial. However, these subjects can safely receive a Td booster dose during the trial. The safety of Tdap and Td/TD administration at different intervals has been studied in 7156 children and adolescents. The study reports that Tdap can be safely administered at intervals as short as 18 months after a previous Td/TD vaccine. Among the study subjects with most recent prior Td/TD vaccine, injection site erythema was slightly increased and swelling was significantly increased, however, no Arthus-like reactions or serious AEs were reported (40). The safety of Tdap vaccination less than 2 years following prior tetanus vaccination has also been evaluated among healthcare personnel and pregnant women. None of the studies found an increase rate of moderate-to-severe vaccine-related AEs in those vaccinated less than 2 years after the previous Td vaccine compared with those vaccinated 2 years or more after the previous Td vaccine (41, 42). The above-mentioned studies provide evidence that it is safe to include adolescents with a history of prior TT-containing vaccine, administered no later than 18 months prior to the first dose of trial treatment. Tdap booster can be administered at intervals as short as 5 years since the initial Tdap booster and is well-tolerated and immunogenic in adolescents (43). The vaccination history of every single subject will be carefully evaluated by the investigator, and the appropriate TT-containing vaccine will be administered during the trial.

Live vaccines will not be allowed during the trial. Inactivated or non-live vaccines, including COVID-19 vaccines, will be allowed from Week 12.

Altogether, the risks associated with participating in this clinical trial are considered low and outweighed by the benefit of a potentially improved future treatment option for adolescents,

with a body weight of 30 kg or more, suffering from psoriasis. There is an opportunity for a positive treatment effect for the subjects participating in this clinical trial based on currently available clinical data.

6 Trial objectives and endpoints

Panel 7: Primary objective and endpoints supporting the primary objective

Primary objective	Endpoints supporting the primary objective
To determine the efficacy of subcutaneous administration of brodalumab compared with placebo in treating adolescents with moderate-to-severe plaque psoriasis.	*Primary endpoint:* • Having at least 75% improvement in Psoriasis Area and Severity Index (PASI) score from baseline (PASI 75 response), assessed at Week 12. *Key secondary endpoints:* • Static Physician's Global Assessment (sPGA) score of 0 or 1, assessed at Week 12. • sPGA score of 0, assessed at Week 12. • PASI 90 response, assessed at Week 12. • PASI 100 response, assessed at Week 12. • Children's Dermatology Life Quality Index (CDLQI) total score of 0 or 1, assessed at Week 12. *Secondary endpoint:* • Family Dermatology Life Quality Index (FDLQI) total score of 0 or 1, assessed at Week 12. *Other endpoints:* • Change from baseline in Adolescent Pruritus numeric rating scale (NRS) (weekly average), assessed at Week 12. • Improvement of at least 4 units in Adolescent Pruritus NRS (weekly average), assessed at Week 12. • Change from baseline in Itch-related Sleep NRS (weekly average), assessed at Week 12.

Abbreviations: CDLQI, Children's Dermatology Life Quality Index; FDLQI, Family Dermatology Life Quality Index; NRS, numeric rating scale; PASI, Psoriasis Area Severity Index; sPGA, static Physician's Global Assessment.

Panel 8: Secondary objectives and endpoints supporting the secondary objectives

Secondary objectives	Endpoints supporting the secondary objectives
To evaluate the efficacy of brodalumab compared with ustekinumab in treating adolescents with moderate-to-severe plaque psoriasis.	*Other endpoints:* • PASI 75 response, assessed separately at Week 12 and Week 52. • PASI 90 response, assessed separately at Week 12 and Week 52. • PASI 100 response, assessed separately at Week 12 and Week 52. • sPGA score of 0 or 1, assessed separately at Week 12 and Week 52. • sPGA score of 0, assessed separately at Week 12 and Week 52. • CDLQI total score of 0 or 1, assessed separately at Week 12 and Week 52. • FDLQI total score of 0 or 1, assessed separately at Week 12 and Week 52. • Change from baseline in Adolescent Pruritus NRS (weekly average), assessed at Week 12 and Week 52. • Improvement of at least 4 units in Adolescent Pruritus NRS (weekly average), assessed separately at Week 12 and Week 52. • Change from baseline in Itch-related Sleep NRS (weekly average), assessed at Week 12 and Week 52.
To evaluate the safety of brodalumab compared with placebo (until Week 12) and ustekinumab (throughout the trial) in adolescents with moderate-to-severe plaque psoriasis.	*Secondary endpoints:* • Occurrence of adverse events (AEs) up to Week 60. • Presence of anti-drug antibodies (ADA), assessed at Weeks 4, 16, and 52. • Serum concentration of interleukin-17 (IL-17) and blood levels of T-cell subsets ($CD4^+$ and $CD8^+$), assessed at Weeks 8, 12, and 52. *Other endpoints:* • Laboratory toxicity, assessed at Weeks 4, 16, and 52. • Vital signs, assessed at Weeks 4, 16, and 52. • Blood levels of T-helper cells (Th1, Th17, and Th22), assessed at Weeks 8, 12, and 52. • Concentration of blood biomarkers, assessed at Weeks 8, 12, and 52. • Columbia-Suicide Severity Rating Scale (C-SSRS) score up to Week 60. • Patient Health Questionnaire-9 modified for adolescents without question number 9 (PHQ-A) score up to Week 60.

Panel 8: Secondary objectives and endpoints supporting the secondary objectives (continued)

Secondary objectives	Endpoints supporting the secondary objectives
To evaluate the pharmacokinetics of brodalumab in adolescents with moderate-to-severe plaque psoriasis.	*Secondary endpoint:* • Serum concentrations of brodalumab, assessed at Weeks 4, 8, 10, 12, 16, 22, and 52. *Other endpoint:* • Area under the serum concentration-time curve at Weeks 10-12, derived using all available concentrations in Weeks 0-52.
To evaluate the immunogenicity of a tetanus toxoid (TT)-containing vaccine in adolescents with moderate-to-severe plaque psoriasis who are treated with brodalumab or placebo.	*Secondary endpoint:* • Anti-tetanus toxoid antibodies (aTTA) ≥0.1 IU/mL, assessed at Week 12 (post-vaccination). *Other endpoints:* • Change from baseline in lymphocyte subsets ($CD4^+$, $CD8^+$, and $CD19^+$), assessed at Week 12 (post-vaccination). • Change from baseline in aTTA, assessed at Week 12 (post-vaccination). • Booster response to TT-containing vaccine, defined as: o 3-fold increase of aTTA, assessed at Week 12, if subject has an aTTA ≤1.0 IU/mL at Week 0. o ≥2.5 IU/mL increase of aTTA, assessed at Week 12, if subject has an aTTA>1.0 IU/mL at Week 0. • Change from baseline in aTTA, assessed at Week 8 (pre-vaccination).

Abbreviations: ADA, anti-drug antibodies; AEs, adverse events; aTTA, anti-tetanus toxoid antibodies; 2 (2)
C-SSRS, Columbia-Suicide Severity Rating Scale; CDLQI, Children's Dermatology Life Quality Index; FDLQI, Family Dermatology Life Quality Index; IL-17, interleukin-17; NRS, numeric rating scale; PASI, Psoriasis Area Severity Index; PHQ-A, Patient Health Questionnaire-9 modified for adolescents, without question number 9; sPGA, static Physician's Global Assessment; Th, T-helper; TT, tetanus toxoid.

Estimands

The applied estimands, addressing different aspects of the trial objectives, are defined and discussed in Section 14.3.6.

7 Trial design

7.1 Overall trial design

7.1.1 Overview of the trial design

This is a clinical phase 3, randomised, placebo-controlled and comparator-controlled trial designed to evaluate the efficacy, safety, tolerability, and PK of brodalumab treatment in adolescents (from 12 to 17 years of age) with moderate-to-severe plaque psoriasis.

A schematic of the trial design is provided in Panel 1. The trial design includes 4 periods:

- A screening period of up to 4 weeks (Week -4/-2 to Week 0).
- An induction period of 12 weeks (Week 0 to Week 12 - treatment phase).
- A maintenance period of 40 weeks (Week 12 to Week 52 - treatment phase).
- A safety follow-up period of 8 weeks (Week 52 to Week 60 - off-treatment phase).

The trial periods are further described in Sections 7.1.2, 7.1.3.3, and 7.1.4. Eligible trial participants will be randomised at Week 0 (Day 1) to 1 of the following 4 treatment arms in a 2:2:1:1 ratio:

- Brodalumab (brodalumab for 52 weeks of treatment).
- Ustekinumab (ustekinumab for 52 weeks of treatment).
- Placebo followed by brodalumab (brodalumab placebo for the first 12 weeks of treatment and brodalumab for the last 40 weeks).
- Placebo followed by ustekinumab (brodalumab placebo for the first 12 weeks of treatment and ustekinumab for the last 40 weeks).

The brodalumab arm and the placebo arms will be double-blinded until Week 12 (Week 0 to Week 12). The ustekinumab treatment will be open-label throughout the treatment phase (Week 0 to Week 52). The blinding is further described in Section 9.3.1.

A schedule of all trial-specific assessments are provided in Panel 2 (screening and induction period) and Panel 3 (maintenance and safety follow-up periods), and all assessments are further described in Section 11.

It will be recorded in the eCRF if a visit was performed. If not, a reason will be provided, including whether the reason for the missed visit was due to pandemic restrictions.

7.1.2 Screening period (Week -4 to Week 0)

A screening visit will occur within 28 days prior to initiation of the treatment phase in this trial. At the screening visit, the subjects' eligibility to enter the trial will be checked. This could entail wash out of medications that are not allowed; all prohibited medications are listed in Panel 12. The eligibility criteria are listed in Section 8.

7.1.3 Treatment phase (Week 0 to Week 52)

7.1.3.1 Induction period (Week 0 to Week 12)

The treatment phase begins with a 12-week induction period.

Subjects randomised to the brodalumab arm or any of the placebo arms will receive subcutaneous injections of brodalumab or brodalumab placebo at Weeks 0, 1, 2, 4, 6, 8, and 10. The dose will be determined by the subject's body weight at Week 0 (Day 1):

- Subjects weighing 30 to <70 kg will receive 140 mg brodalumab in 1.0 mL solution or brodalumab placebo in 1.0 mL solution.
- Subjects weighing ≥70 kg will receive 210 mg brodalumab in 1.5 mL solution or brodalumab placebo in 1.5 mL solution.

Subjects randomised to ustekinumab will receive subcutaneous injections of ustekinumab at Weeks 0 and 4. The ustekinumab dose will be determined by the subject's body weight at each dosing visit:

- Subjects weighing 30 to <60 kg will receive 0.75 mg ustekinumab per kg body weight.
- Subjects weighing ≥60 and ≤100 kg will receive 45 mg ustekinumab.
- Subjects weighing >100 kg will receive 90 mg ustekinumab.

7.1.3.2 Vaccination (Week 8)

Subjects randomised to the brodalumab arm or any of the placebo arms will receive an intramuscular injection of 0.5 mL non-live T-cell-dependent TT-containing vaccine at Week 8 to evaluate the vaccine response during treatment with brodalumab:

- Subjects who have received either a combined tetanus and diphtheria (Td) vaccine for more than 18 months prior to the first dose of brodalumab or placebo or a combined tetanus, diphtheria, and pertussis (Tdap) vaccine for more than 5 years prior to the first dose of brodalumab or placebo will receive Tdap vaccine at Week 8 in this trial.
- Subjects who have received Tdap vaccine more than 18 months but less than 5 years prior to the first dose of brodalumab or placebo will receive Td vaccine at Week 8 in this trial.

- Subjects who have not received the scheduled adolescent dose of Td/Tdap for the last 5 years will be vaccinated with a booster based on the subject's previous history of vaccination with TT-containing vaccines and current local guidelines.

Subjects randomised to ustekinumab only will not receive the vaccination.

7.1.3.3 Maintenance period (Week 12 to Week 52)

As psoriasis is a chronic disease requiring long-term treatment, it is also relevant to evaluate the efficacy and safety of brodalumab as a maintenance treatment. To assess the duration of response, the 12-week induction period will be followed by continued treatment until Week 52.

Subjects randomised at Week 0 to either brodalumab or ustekinumab will continue on the allocated treatment throughout the maintenance period:

- Subjects on brodalumab treatment will receive subcutaneous injections of brodalumab at Week 12 and every 2 weeks thereafter, with the last brodalumab dose administered at Week 50.
- Subjects on ustekinumab treatment will receive subcutaneous injections of ustekinumab at Weeks 16, 28, and 40.

Subjects randomised at Week 0 to the placebo arm followed by brodalumab will switch to brodalumab treatment in the maintenance period and receive subcutaneous injections of brodalumab at Weeks 12, 13, 14, and every 2 weeks thereafter, with the last brodalumab dose administered at Week 50. The brodalumab dose will be determined by the subject's body weight at Week 0 (Day 1) in accordance with the rules described for the induction period (Section 7.1.3.1) and will not be changed even if the subject's body weight crosses 70 kg.

Subjects randomised at Week 0 to the placebo arm followed by ustekinumab will switch to ustekinumab treatment in the maintenance period and receive subcutaneous injections of ustekinumab at Weeks 12, 16, 28, and 40. The ustekinumab dose will be determined by the subject's body weight at each dosing visit in accordance with the rules described for the induction period (Section 7.1.3.1).

7.1.4 Safety follow-up period (Week 52 to Week 60)

All subjects will be followed in an off-IMP treatment period during a safety follow-up. The safety follow-up visit is scheduled at Week 60. However, in case of early termination (see Section 10), the safety follow-up visit will occur sooner. This 8-week safety follow-up period will allow for adequate wash out of brodalumab (covers 5 half-lives of brodalumab) and is appropriate for short-term safety evaluation after the treatment is completed.

7.2 Number of subjects needed

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

Assuming a screening failure rate of 25%, approximately 160 subjects will be screened and 120 subjects will be randomly assigned to a treatment arm in the trial:

- 40 subjects randomised to brodalumab.
- 40 subjects randomised to ustekinumab.
- 20 subjects randomised to placebo followed by brodalumab.
- 20 subjects randomised to placebo followed by ustekinumab.

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

7.3 End of trial definition

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

A subject is considered to have finalised the trial if having concluded all periods of the trial including the safety follow-up visit, regardless of early IMP discontinuation or not.

Final collection of data for the primary endpoint occurs at Week 12. However, the primary analysis and the safety evaluation will be done after the last subject has completed the trial at Week 60.

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 Panel 2. 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, and if not, it will be specified which criteria are violated.

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. Signed and dated informed consent must be provided by the subject's legal representative(s) and by the subject (as applicable according to national laws or regulations).
2. Subject was diagnosed with chronic plaque psoriasis at least 6 months before randomisation as determined by the investigator.
3. Subject has a diagnosis of moderate-to-severe plaque psoriasis as defined by PASI score ≥12, sPGA score ≥3, and body surface area (BSA) ≥10% at screening and at baseline.
4. Subject's age is ≥12 to <18 years at baseline.
5. Subject's body weight is ≥30 kg at screening and at baseline.
6. Subject, in whom topical therapy is not adequate, and who is candidate for systemic therapy.
7. Subject has positive varicella zoster antibodies at screening.
8. Subject has no evidence of active or latent tuberculosis according to local standard of care for patients requiring initiation of a biologic treatment.
    - A tuberculosis test can be performed at the central laboratory.
    - If a local laboratory test is performed to confirm this criterium, the local laboratory must be assessed before the local testing is performed.
9. Female subjects must have a negative pregnancy test at screening and at baseline.

10. Female subject must agree to use a highly effective* form of birth control throughout the trial and during 15 weeks after last administration of ustekinumab (45) and 12 weeks after last administration of brodalumab.

    *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 (estrogen 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), vasectomised partner (given that the subject is monogamous).

11. Subject and/or subject's legally authorised representatives are capable of learning to administer subcutaneous injections.
12. Subject is able and willing to follow protocol-required trial visits and trial procedures.

8.3 Exclusion criteria

Subjects must not enter the trial if any of the following exclusion criteria are fulfilled:

Skin disease-related

1. Subject is 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 subjects with plaque psoriasis.

Tetanus vaccination-related

2. Subject has been vaccinated with a TT-containing vaccine ≤18 months prior to the first dose of IMP.
   Subject has been vaccinated with a TT-containing vaccine within 5 years prior to the first dose of IMP - applicable for countries in EU + UK.
3. Subject has developed Guillian-Barre syndrome within 6 weeks after a previous vaccination with TT-containing vaccine.
4. Subject has a planned vaccination with other vaccines than the scheduled Tdap or Td vaccine during the trial. Inactivated and non-live vaccines, e.g. COVID-19 and human papillomavirus [HPV] vaccines, are allowed after completion of Visit 10 (Week 12).
5. Subject has developed encephalopathy within 7 days of administration of a previous pertussis antigen-containing vaccine.
6. Subject has experienced an Arthus-type hypersensitivity reaction following a previous dose of TT-containing vaccine.

7. Subject has developed transient thrombocytopenia or neurological complications following previous vaccinations against diphtheria or tetanus.
8. Subject has a history of severe allergic reactions to either vaccine or vaccine components including, but not limited to, aluminium, formaldehyde, and latex.
9. Subject has received vaccination with any vaccine within 1 month prior to first dose IMP, documented or subject reported.
10. Subject has been treated with blood products within 3 months prior to screening.
11. Subject has been treated with interferon within 3 months prior to screening.

Other medical conditions

12. Subject has a planned surgery, which, in the opinion of the investigator, will interfere with the planned IMP treatment (any planned surgery must be recorded).
13. Subject has an active infection or history of infections, defined as:
    - Subject has had any active infection for which systemic anti-infectives were used within 4 weeks prior to first dose of IMP.
    - Subject has had a serious infection, defined as requiring hospitalisation or intravenous anti-infectives within 8 weeks prior to the first dose of IMP.
    - Subjects has recurrent or chronic infections or other active infections that, in the opinion of the investigator, might cause this trial to be detrimental to the subject.
    - Subject has a serious skin infection requiring parenteral (intravenous or intramuscular) antibiotics, antiviral, or antifungal medication.
14. Subject has any systemic disease considered by the investigator to be uncontrolled and immunocompromising the subject and/or placing the subject at undue risk of intercurrent diseases*.

    *Such diseases include, but are not limited to, renal failure, heart failure, liver disease, diabetes, and anaemia.
15. Subject has a known history of Crohn's disease.
16. Subject has positive hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C virus antibody, or human immunodeficiency virus serology at screening. Subjects with positive hepatitis B surface antibody are eligible provided they have negative hepatitis B surface antigen and negative hepatitis B core antibody (blood pattern in hepatitis B vaccinated subjects).
17. Subject has any active malignancy.
18. 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.
19. Subject has a history of suicidal behaviour (i.e., actual suicide attempt, interrupted attempt, aborted attempt or preparatory actions) based on the C-SSRS at screening or at baseline.

20. Subject has suicidal ideation of level 4 or 5 (some intent to act, no plan, or specific plan and intent) based on the C-SSRS at screening or at baseline.
21. Subject has a PHQ-A (PHQ-9 modified for adolescents, without question number 9) score of ≥10, corresponding to moderate-to-severe depression at screening or at baseline.
22. Subject has a history of depressive disorder with severe episode(s) within the last 2 years.

Wash out and non-permitted medications/treatments

23. Subject has used topical corticosteroids or topical anthralin/dithranol within 7 days prior to first dose of IMP (exceptions are specified*).

    *Topical corticosteroids class V-VII (WHO classification) are allowed on the face, axillae, and groin (see Section 9.6); bland emollients (without urea or alpha or beta hydroxy acids) and shampoo without steroids are permitted.

24. Subject has received any of the following specified treatments[#] within 28 days prior to first dose 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; or oral or parenteral corticosteroids including intramuscular or intraarticular administration; or any other immune modulating therapy for psoriasis or any other indication (with the exception that: otic, nasal, ophthalmic, and inhaled corticosteroids within recommended doses are permitted).

25. Subject has received any of the following biologic immune modulating therapies prior to first dose of IMP:

    Approved agents:

    - Within 2 weeks for etanercept.
    - Within 4 weeks for adalimumab.

    Other commercially available biologics:

    - Within 8 weeks for infliximab.

    Other experimental biologics:

    - Within 12 weeks or 5 half-lives whichever is longer.

26. Subject has received anti-IL-12/23p40 within 12 months prior to the first dose of IMP.
27. Subject has previously had an inadequate response to anti-IL-12/23p40 therapy.
28. Subject has previously received anti-IL-17 therapy.
29. 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 5 half-lives of the active substance.
30. Subject is undergoing other non-approved investigational procedures.

Laboratory abnormalities

31. Subject has laboratory abnormalities at screening, including any of the following:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x the upper limit of normal (ULN).
    - Serum direct bilirubin equal to or higher than 1.5 mg/dL (≥25.7 µmol/L).
    - White blood cell (WBC) count <3.00 x 10^9/L.
    - Absolute neutrophil count (ANC) <2.00 x 10^9/L.
    - Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2.

General

32. Subject has a known or suspected hypersensitivity to any component(s) of the IMPs (see Sections 9.1.1, 9.1.2, and 9.1.3).
33. Female subject who is pregnant or lactating.
34. Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give informed consent and/or to comply with all required trial procedures.
35. Subject has any disorder[*] which, in the opinion of the investigator, is not stable and could:
    - Affect the safety of the subject throughout the trial.
    - Influence the findings of the trial.
    - Impede the subject's ability to complete the trial.

    [*]Examples include, but are not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders and major physical impairment.

36. Subject has any abnormal finding[#] which, in the opinion of the investigator, may:
    - Put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    [#]The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis.

37. Subject or subject's legally authorised representative(s) has a language barrier, mental incapacity, unwillingness, or lacking ability to understand the trial-related procedures
38. 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.

39. Subject is employed at the trial site or directly involved with the planning or conduct of the trial, or immediate family member of such individuals.
40. Subject has previously been randomised and dosed in this clinical trial.
41. Subject is currently participating in any other interventional clinical trial.
42. 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. 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 identification number (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.

After informed consent is obtained, the screening may begin. The date of first screening activity could be on the same day or a later date than the informed consent was signed. At screening, a subject ID number will be assigned by a central interactive response technology (IRT) system. The subject ID will be used to identify the subject during the screening process and throughout trial participation. Subjects for whom the subject's legally authorised representative(s) have given written informed consent for their participation in the trial (including subjects who have given written assent to participate in the trial, as appropriate and according to national laws and regulation) and who have been assigned a subject ID are considered 'screened' subjects. The investigator will maintain a log of all screened subjects (screening log). This log will be anonymous and will include the allocated subject ID and the reason(s) for not entering the trial, if applicable.

8.4.2 Screening failures

Screening failures are defined as subjects who consent to participate in the trial, but are not subsequently assigned to trial treatment. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects to meet the consolidated standards of reporting trials (CONSORT) publishing requirements (46) and to respond to queries from regulatory authorities.

The following data will be collected in the eCRF for screening failures:

- Date of informed consent(s).
- Demographics (age, sex, ethnicity, race).
- Reason for screen failure:
    - Failure to meet eligibility criteria (specify which).
    - Lost to follow-up.
    - Withdrawal by subject.
    - Withdrawal by parent/guardian.
    - Other (specification is required).
- Date of screening 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 exclusion criterion 19, 20, 21, or 22. In the event of re-screening, a new informed consent must be obtained and a new subject ID must be assigned. For subjects who are re-screened, the subject ID from the previous screening will be recorded in the eCRF. All screening assessments and laboratory samples must be repeated. Due to the blood volumes, re-screening is allowed no earlier than 2 months after the initial screening.

9 Treatments

9.1 Trial product description

9.1.1 Brodalumab and placebo

Brodalumab is a recombinant fully human monoclonal IgG2 antibody that binds with high affinity to the human interleukin-17 receptor A (IL-17RA) and blocks the interaction with IL-17A, IL-17E, and IL-17F.

Panel 9: Identification of brodalumab and placebo

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size of primary packaging	Manufacturer responsible for batch release
Brodalumab 140 mg brodalumab in 1 mL solution	Solution for subcutaneous injection.	Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: proline, glutamate, polysorbate 20, water for injections.	1 pre-filled syringe with **140 mg brodalumab** in 1 mL solution.	LEO Pharma A/S.
Placebo	Solution for subcutaneous injection.	Brodalumab placebo solution is similar to the active brodalumab solution except that it does not contain any active substance.	1 pre-filled syringe with 1 mL solution.	LEO Pharma A/S.
Brodalumab 210 mg brodalumab in 1.5 mL solution	Solution for subcutaneous injection.	Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: proline, glutamate, polysorbate 20, water for injections.	1 pre-filled syringe with **210 mg brodalumab** in 1.5 mL solution.	LEO Pharma A/S.
Placebo	Solution for subcutaneous injection.	Brodalumab placebo solution is similar to the active brodalumab solution except that it does not contain any active substance.	1 pre-filled syringe with 1.5 mL solution.	LEO Pharma A/S.

9.1.2 Ustekinumab

Ustekinumab is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines.

Panel 10: Identification of ustekinumab

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size of primary packaging	Source
Ustekinumab Trade name: Stelara®	Solution for subcutaneous injection.	45 mg ustekinumab in 0.5 mL solution, including the following excipients: L-histidine and L-histidine monohydrochoride monohydrate, polysorbate 80, sucrose, and water for injection.	1 vial with **45 mg ustekinumab** in 0.5 mL solution.	Janssen Biologics B.V. Commercially available; supplied by CMO.

Abbreviations: CMO, contract manufacturing organisation.

9.1.3 Vaccines

Panel 11: Identification of the vaccines

Investigational medicinal product	Dosage form	Active ingredient and concentration	Pack size of primary packaging	Source
Tdap vaccine	Suspension for intramuscular injection	Combined tetanus, diphtheria, and acellular pertussis vaccine (absorbed, reduced antigen content). Each 0.5 mL dose is formulated to contain: tetanus toxoid ≥20 IU, diphtheria toxoid ≥2 IU and pertussis toxoid 20 µg. All antigens adsorbed on aluminium hydroxide, hydrated (0.5 mg Al). The other excipients: sodium chloride, sodium hydroxide and water for injections. May contain traces of formaldehyde, which are used during the manufacturing process.	0.5 mL single-dose pre-filled syringes.	Commercially available; supplied by CMO.
Td vaccine	Suspension for intramuscular injection	Combined tetanus and diphtheria vaccine (absorbed, reduced antigen content). Each 0.5 mL dose is formulated to contain: tetanus toxoid ≥20 IU and diphtheria toxoid ≥2 IU, absorbed to aluminium hydroxide, hydrated, corresponding to 0.5 mg aluminium. The other excipients are: sodium hydroxide, sodium chloride, and water for injections. May contain traces of formaldehyde, which are used during the manufacturing process.	0.5 mL single-dose pre-filled syringes.	Commercially available; supplied by CMO.

Abbreviations: CMO, contract manufacturing organisation; Td, tetanus and diptheria; Tdap, tetanus, diphteria, and pertussis.

9.2 Administration of IMP

9.2.1 Administration of brodalumab, placebo, and ustekinumab

The IRT will assign the required kit number(s) for each subject at each dispensing/administration visit.

Scheduled dispensing/administration (dosing) days are shown in Panel 2 and Panel 3. The first day of administration is considered Day 1 (Week 0). On administration visits, all other visit activities should be handled prior to administration of brodalumab, placebo, or ustekinumab. The last administration of brodalumab under this protocol will occur at Week 50 and the last administration of ustekinumab under this protocol will occur at Week 40.

Brodalumab, placebo, and ustekinumab must be injected subcutaneously.

Brodalumab and placebo must be injected in the upper legs (thighs) or stomach area (abdomen) by the subject, the subject's caregiver, or a qualified healthcare professional. The subject's caregiver or the healthcare professional may also give injection(s) in the upper outer arm. Subsequent injections can be given to the same or different body regions. Each pre-filled syringe is for single-use only. Brodalumab and placebo should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken or heated.

The subject will be kept under observation for 30 minutes following the first and second brodalumab injection.

The trial site staff should encourage the subjects and/or the subjects' caregiver to do the injections on their own, when properly trained. Please refer to Section 9.2.1.2 for information regarding home-based administration of brodalumab.

Ustekinumab must be administered at the trial site according to the instructions for administration provided in current summary of product characteristics (SmPC) for ustekinumab.

LEO Pharma does not recommend specific treatment for an overdose of brodalumab. The investigator will use clinical judgment to treat any overdose if necessary. See Section 13.6.1 for further details regarding overdose. An overdose of ustekinumab must be handled in accordance with current SmPC.

9.2.1.1 Conditions requiring rescheduling of administration of brodalumab, placebo, or ustekinumab

If any of the following should occur, the investigator should reschedule the IMP administration (other scheduled visit assessments should be performed):

- The subject has an intercurrent illness that, in the opinion of the investigator, may compromise the safety of the subject in the trial (e.g., viral illnesses).
- The subject is febrile (defined as ≥38°C) within 72 hours prior to IMP administration.

The rescheduled IMP administration will be reported in the eCRF as an unscheduled visit. The subseqent visit and IMP administration should be scheduled according to the schedule of the trial procedures and a minimum interval of 7 days must be kept between 2 administrations of brodalumab/placebo (except for Visit 3 and Visit 4, which are exempt from the 7-day gap requirement). If the trial visit cannot be rescheduled to maintain a minimum of 7 days to subsequent dose, the sponsor's medical expert should be contacted.

9.2.1.2 Home-based administration of brodalumab

Subjects randomised to the brodalumab arm or the placebo arm followed by brodalumab will be given the option to administer brodalumab at home at Weeks 18, 22, 24, 26, 30, 34, 38, 42, 46, and 50 (Panel 3); the injections may be performed either by the subject (under supervision by the subject's caregiver) or by the subject's caregiver. The investigator should document that instructions for use for brodalumab and placebo have been given orally and/or in writing to the subject and the subject's caregiver before any home-based administration. Subjects who refuse to do home-based administration can have the IMP administered at the trial site at these weeks.

9.2.2 Administration of vaccine

At Week 8, subjects in the brodalumab, placebo followed by brodalumab, and placebo followed by ustekinumab arms will receive a TT-containing vaccine, either Tdap or Td. The type of vaccine each subject will receive is based on the subject's previous history of vaccination with TT-containing vaccines and current local guidelines (see Section 7.1.3 for further details). The IRT will assign the required kit number for each subject.

The vaccine will be administered by the trial staff on the same day the brodalumab/placebo injections are administered; the vaccine will be given first, then brodalumab or placebo will be given afterwards (see below).

The vaccine must be given intramuscularly (e.g., in the deltoid muscle of the upper arm). The injection site must be recorded in the source documents and in the eCRF.

The subject will be kept under observation for 30 minutes following vaccination. After this observation period and when all other visit activities have been performed, the brodalumab or placebo injection will be given. Note that at Week 8, brodalumab/placebo injections must not be given in the same area as the vaccination.

Syncope can occur in association with administration of the vaccines. Procedures should be in place to prevent falling injury and to restore cerebral perfusion following syncope.

Appropriate drugs (such as epinephrine, antihistamines, corticosteroids, etc.) and medical equipment to treat acute anaphylactic reactions must be immediately available at the trial sites, and an appropriate treatment must be immediately provided according to local guidelines by site personnel.

9.2.2.1 Conditions requiring rescheduling of administration of the vaccine

If the following should occur at the visit scheduled at Week 8 (i.e., Visit 7), the investigator should reschedule the vaccine administration:

- The subject has an intercurrent moderate or severe acute illness with or without fever, that in the opinion of the investigator may compromise the safety of the subject in the trial.

If the subject has recovered between Visit 7 and Day 64, the vaccine should be administered as soon as possible and no later than on Day 64. An extra visit for vaccine administration should be scheduled and reported in the eCRF as an unscheduled visit.

9.2.3 Reporting of IMP administration in eCRF

The following data will be recorded in the eCRF for **brodalumab**, **ustekinumab**, and **placebo**:

- Date of administration.
- Time of administration, for selected visits.
- Site of subcutaneous injection (thigh, abdomen, or upper outer arm).
- Where the administration was performed, and by whom (on-site, by trial site staff; on-site, by subject's caregiver; on-site, self-injection; at home, by subject's caregiver; at home, self-injection).

The following data will be recorded in the eCRF for the **vaccine**:

- Date and time of vaccine administration.
- Site of intramuscular injection (left upper arm, right upper arm, or other site [will require a comment]).

9.3 Treatment assignment

Subjects who comply with all the inclusion criteria and who do not violate any of the exclusion criteria will be randomised centrally at Week 0 to receive treatment with brodalumab, ustekinumab, placebo followed by brodalumab, or placebo followed by ustekinumab, stratified by baseline body weight (<70 kg and ≥70 kg). The treatment assignment occurs on the basis of a computer-generated randomisation scheme in a 2:2:1:1 ratio.

The IRT will be used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking.

9.3.1 Blinding

Treatment allocation for the induction period (i.e., 'ustekinumab' or double-blind 'brodalumab/placebo') will be revealed to the investigator at randomisation at Week 0. For subject on 'brodalumab/placebo' in the induction period, the treatment allocation for the maintenance period (i.e., 'brodalumab' or 'ustekinumab') will not be revealed before the visit scheduled at Week 12.

It is not considered possible to differentiate between brodalumab and placebo visually, both solutions are colourless. For the induction period, the packaging and labelling will contain no evidence to distinguish brodalumab from placebo. For the maintenance period, treatment with brodalumab will be open-label and brodalumab will be labelled and packaged as such.

Ustekinumab and the vaccine will be administered as the commercially available product and will not be blinded.

When the IMP (brodalumab, placebo, ustekinumab, or vaccine) is administered at the trial site, it will be administered by site personnel not involved in the efficacy assessments. The efficacy assessments will be performed by an investigator (see Section 11.1) who is blinded to the treatment allocation and administration.

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, healthcare professionals 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. For a requester who is not a member of the trial staff and who does not have access to the IRT (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

Rescue treatment is allowed in all 4 treatment arms. From Week 4 and at all subsequent visits, rescue treatment is allowed in subjects with an increase of ≥25% in PASI score from baseline (Week 0, Day 1).

Before the initiation of rescue treatment, investigators should make every attempt to conduct efficacy and safety assessments (for example, disease severity scores [PASI and sPGA] and safety labs). Unscheduled visit(s) may be used for this purpose, if necessary.

Rescue treatment will consist of topical corticosteroids. Those topical corticosteroids with good therapeutic index e.g., hydrocortisone-17-butyrate, mometasone furoate, methylprednisolone aceponate should be preferred. However, it is allowed to use ultra-high potency (class I) to moderate potency (class V, IV), according to WHO classification (see Appendix 4), at the discretion of the investigator. The investigator is responsible for the

rescue treatment oversight and duration as well as switching and escalating to another therapy, when appropriate. However, it is recommended that the efficacy of the topical rescue treatment should be re-evaluated after 4 weeks of treatment and subjects who are still inadequately controlled (defined as a PASI score ≥150% of baseline PASI) might be escalated to an appropriate subsequent therapy (refer to Section 9.7 for prohibited medications and Section 10.2 for IMP discontinuation rules).

Use of any rescue treatment must be recorded in the eCRF (see Section 9.6).

9.6 Concomitant medication and concurrent procedures

Any prior and concomitant medication or vaccine (except for vaccination as part of the trial) that the subject receives from 1 year prior to screening (if relevant) through safety follow-up must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication or therapy (generic or brand name).
- Indication.
- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, 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).

Please also refer to Section 11.2.3 for specific details about history of psoriasis treatment.

The following concomitant medications related to psoriasis treatment are permitted from screening through safety follow-up (Week 60):

- Low potency topical corticosteroids (lower moderate potency [class V] to low potency [classes VI and VII] according to WHO classification [Appendix 4] may be used only on the face, axillae, and groin).
- Bland emollients (without urea or alpha- or beta hydroxy acids).
- Shampoo without steroids.

Concomitant medication for conditions other than psoriasis may be continued throughout the trial without any change in dosage whenever possible.

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.

9.7 Prohibited medications and procedures

The medications listed in Panel 12 are prohibited during the trial.

The following circumstances require permanent discontinuation of IMP:

- Use of any other biologic immunomodulating agent than brodalumab and ustekinumab.
- 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 action must be taken by the investigator to either discontinue the prohibited medication or discontinue the IMP.

Panel 12: Prohibited medications and procedures

Prohibited medication or procedure	Prohibited from	Prohibited to
Anti-IL-17 therapy other than brodalumab provided in this trial	Ever used	Week 52
Anti-IL-12/23p40 therapy other than ustekinumab provided in this trial	12 months prior to first dose of IMP	Week 52
Etanecept	2 weeks prior to first dose of IMP	Week 52
Adalimumab	4 weeks prior to first dose of IMP	Week 52
Infliximab	8 weeks prior to first dose of IMP	Week 52
Other experimental or commercially available immune modulators (e.g., IL-23 inhibitors) and any IMP other than brodalumab/placebo and ustekinumab provided in this trial	5 half-lives of active substance prior to first dose of IMP	Week 52
Ultraviolet A light therapy (with or without psoralen), ultraviolet B light therapy, eximer laser etc.	4 weeks prior to first dose of IMP	Week 52
Oral retinoids; methotrexate; cyclosporine; systemically administered calcineurin inhibitors; azathioprine; thioguanine; hydroxyurea; fumarates; apremilast; or oral or parenteral corticosteroids including intramuscular or intraarticular administration (with the exception that: otic, nasal, ophthalmic, or inhaled corticosteroids within recommended doses are permitted)	4 weeks prior to first dose of IMP	Week 52
Topical therapy for psoriasis e.g., calcineurin inhibitors, vitamin D analogues, class I-V (WHO classification) topical corticosteroids (TCS) • Use of TCS class V-VII (WHO classification) are allowed on the face, axillae, and groin through the trial (see Section 9.6) • Shampoos without steroids are permitted • Bland emollients without urea or beta or alpha hydroxy acids are permitted	1 week prior to first dose of IMP	Week 52
Use of live vaccine	4 weeks prior to first dose of IMP	Week 52
Use of any vaccine[1].	4 weeks prior to first dose of IMP	Week 52

Abbreviations: IL, interleukin; IMP, investigational medicinal product; SmPC, summary of product characteristics; TCS, topical corticosteroids; WHO, World Health Organization. 1 (2)

[1] For subjects in the placebo and brodalumab arms: inactivated or non-live vaccines, including COVID-19 vaccines, are allowed from Week 12. For subjects in the ustekinumab arm: inactive or non-live vaccines are allowed according to ustekinumab's SmPC during the trial.

Prohibited medication or procedure	Prohibited from	Prohibited to
Blood products	3 months prior to first dose of IMP	Week 52
Interferon	3 months prior to first dose of IMP	Week 52

Abbreviations: IMP, investigational medicinal product. 2 (2)

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication.

As described in Section 9.5, some prohibited medications are allowed as rescue treatment for subjects with an increase of ≥25% in PASI score from baseline (Week 0, Day 1). Such instances of use of rescue treatment for the indication being investigated do not constitute a protocol deviation. If prohibited medications are used for reasons other than rescue treatment, they must be recorded as protocol deviations

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMP will be packaged in individually numbered kits.

Primary and secondary packaging materials will be individually labelled.

The labelling of IMPs will be in accordance with Annex 13, 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 (brodalumab, placebo, ustekinumab, and vaccines) 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. The temperature during storage should be monitored by a calibrated, stationary, and continuously recording system. Minimum requirement is a calibrated min/max thermometer. A temperature log must be kept to document the storage within the right temperature interval, 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 and contact their CRA for further guidance:

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

Damaged IMP should be documented in the IRT 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 IMP at the trial site, for maintaining adequate control of the IMP, and for documenting all transactions with them.

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

An individual drug accountability form (or similar) must be kept of the IMP dispensed/administered to (and returned by, in case of home-based administration [Section 9.2.1.2]) each subject randomised in the trial. This individual drug accountability form should 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, where also inventory status of all IMP at the trial site will be maintained.

The IMP dispensed for home-based administration should be stored in accordance with the label. If the IMP is administered at home (as described in Section 9.2.1.2), the used syringes will be discarded in disposal containers at home. The subject should return unused IMP and empty trial kit cartons at the next trial site visit (as shown in Panel 3). At end of treatment (Week 52), the subject must have returned all unused IMP, empty trial kit cartons, and disposal containers containing used IMP. Returned IMP (used or unused) can be stored at trial site at room temperature and must be stored separately from non-allocated IMP.

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. No accountability is required for returned disposal containers; these can be disposed according to Section 9.8.5.

All unused IMP (including trial kit cartons) supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma will be returned to the CMO. Prior to their 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 on drug accountability forms and in the IRT.

Please refer to the trial product handling manual for further details.

9.8.4 Treatment compliance

The site staff will keep the drug accountability records up to date. Any non-compliance (subject received partial dose; subject received no dose) and the reason for the non-compliace will be recorded in the eCRF.

If a subject with home-based IMP administration (see Section 9.2.1.2) is found to be non-compliant, the investigator should remind the subject of the importance of following the instructions given, including using brodalumab as prescribed.

9.8.5 Trial product destruction

Used IMP (and returned disposal containers) 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 return the used IMP to the CMO for destruction according to the trial product handling manual.

Unused and used IMP 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

In order to ensure appropriate treatment of the subjects after they have completed the trial or if they have been withdrawn from the trial or discontinued IMP treatment prematurely, 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 immediately reported to the CRA by the site. The CRA must contact Global Safety at LEO Pharma 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 [e.g., an SAE or large particles in the syringe]) must be reported to the Quality department via Global Safety within 24 hours of knowledge.

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.

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 7226 3287.

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

10 Discontinuation and withdrawal

10.1 General principles

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

In order to obtain the most representative efficacy and safety evaluation of brodalumab in adolescents, it is key to assess the efficacy status of each trial subject at the planned primary endpoint visit (i.e., at Week 12 [Panel 2]) and at the planned secondary endpoint visits at Week 16 and Week 52 (Panel 3), irrespective of whether the subject has discontinued IMP or not. Therefore, permanent discontinuation of IMP is evaluated as a separate occurrence that does not necessitate that the subject also withdraws from the trial. This is to enable selected subsequent trial visits to be conducted after early discontinuation of IMP.

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

- Permanent discontinuation of IMP occurs when all further **trial treatment** is stopped. The subject will continue to participate in selected trial visit activities as outlined in Section 10.2.1.
- Withdrawal from trial occurs when stop of all **trial activities** takes place before the planned safety follow-up visit at Week 60. This may happen either at the time of permanent discontinuation of IMP or later.

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

Reason(s) for discontinuation from IMP and withdrawal from the trial must be recorded in the medical records and the eCRF.

Subjects who withdraw from the trial and subjects who permanently 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 if IMP is discontinued prematurely, the subject should be treated at the discretion of the investigator (Section 9.9).

Throughout the protocol, last date of IMP administration is defined as date of the subject's last dose of IMP.

Subjects will permanently discontinue IMP in the event of:

- An anaphylactic reaction or other severe systemic reaction to IMP.
  If the IMP is the vaccine, and the subject has received the last IMP (which is brodalumab or placebo) for more than 72 hours prior to the vaccine administration without any concerns or reactions, then the subject should continue in the trial.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing (e.g., Crohn's disease).
- A diagnosis of malignancy during the trial, excluding carcinoma in situ of the cervix, or localised squamous or basal cell carcinoma of the skin.
- Evidence of pregnancy.
- Any infection that is opportunistic, such as active tuberculosis or 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-A score of ≥15 corresponding to moderately severe to severe depression. The subject must be referred to a mental health professional.
- A need of concomitant therapies or treatments, which are prohibited throughout trial participation (see Section 9.7).
- Any single measurement of ANC <0.50x10^3/µL.
- Severe laboratory abnormalities:
  - ALT and/or AST values >3xULN with total bilirubin >2xULN (unless elevated bilirubin is related to Gilbert-Meulengracht Syndrome).
  - Confirmed AST and/or ALT >5xULN (for more than 2 weeks).

Refer to Section 10.3 for details on the handling of subject discontinuation and to Panel 2 and Panel 3 for assessments to be performed in case of early discontinuation of IMP.

Data to be recorded in the eCRF
The primary reason for early 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.
- Withdrawal by parent/guardian.
- Lost to follow-up.
- Death.
- Pregnancy.
- Other.

If 'other' is selected, a specification must be provided in the eCRF. If the discontinuation is related to an AE, the details of this must also be reported (Section 13).

10.2.2 Reasons for temporary discontinuation of IMP

Administration of IMP may 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. If the dosing window is missed (see Panel 2 and Panel 3) because of persistent infection, that dose should not be administered. Please refer to Sections 9.2.1 and 9.2.2 for rescheduling of IMP administration.
- Other intercurrent illnesses or major surgery. The administration of the IMP should be withheld until the event has resolved in the opinion of the investigator.

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

- ANC $\geq 0.50 \times 10^3/\mu L$ – $\leq 1.5 \times 10^3/\mu L$ and fever (appropriate treatment must be initiated and blood samples/cultures and other appropriate specific cultures must be obtained according to the local paediatric guidelines). The administration of the IMP must be withheld until the infection has resolved in the opinion of the investigator and the ANC $> 1.5 \times 10^3/\mu L$.
- Positive urine pregnancy test. The administration of the IMP must be withheld until a negative serum pregnancy test is available.

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.

10.3 Early termination assessments

Early permanent discontinuation of IMP

All subjects who permanently discontinue IMP for any reason will be encouraged to continue in the trial for collection of scheduled efficacy and safety assessments or at least attend a visit at Week 12, Week 16, and Week 52 for collection of assessments related to primary and secondary endpoints.

Subjects who permanently discontinue IMP **before Week 12** will be asked to attend at least:

- An early termination visit, as soon as possible and within 2 weeks of the last IMP administration, according to Panel 2. If discontinued at Week 10, the early termination visit should be aligned with the primary endpoint visit (12 weeks after randomisation).
- A primary endpoint visit (12 weeks after randomisation).
    - A safety follow-up visit (8 weeks after the last IMP administration).
    - A secondary endpoint visit (16 weeks after randomisation).
    - A secondary endpoint visit (52 weeks after randomisation).

Blood samples will only be collected at the early termination visit. At other visits, described above, the efficacy and safety will be evaluated, but no otherwise scheduled blood samples will be collected.

Subjects who has received the last IMP **at Week 12 and after** will be asked to attend at least:

- An early termination visit, as soon as possible and within 2 weeks of the last IMP administration, according to Panel 3. If discontinued at Week 50, the early termination visit should be aligned with the secondary endpoint visit (52 weeks after randomisation).
- A safety follow-up visit (8 weeks after last administration of IMP).
- A secondary endpoint visit (16 weeks after randomisation, if applicable).
- A secondary endpoint visit (52 weeks after randomisation).

Blood samples will only be collected at the early termination visit. At other visits, described above, the efficacy and safety will be evaluated, but no otherwise scheduled blood samples will be collected.

Female subjects who permanently discontinue IMP will need to stay on contraceptives for 12 weeks (for brodalumab) or 15 weeks (for ustekinumab) after last IMP administration. A urine pregnancy test (human chorionic gonadotropin) should be performed at the early termination visit, safety follow-up visit, and at 12 weeks (for brodalumab) or 15 weeks (for ustekinumab) after last IMP administration. This can be assessed at unscheduled visits, or at any of the above scheduled visits.

The investigator will review any AEs which will be followed-up according to Section 13.7, if the subject agrees.

Early discontinuation from trial
Randomised 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 and a safety follow-up visit 8 weeks after last IMP administration. 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, after at least 3 attempts.

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/or subject's legally representatives 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. 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:

- Panel 2 includes all assessments during the screening period and the induction period of the treatment phase (including assessments to be performed in case of early termination, if applicable).
- Panel 3 includes all assessments during the maintenance period of the treatment phase and the safety follow-up period (including assessments to be performed in case of early termination, if applicable).

Refer to Section 7.1 for further details on the trial design.

Assessments and procedures scheduled at each trial visit should be performed in the sequence shown in Panel 13, while laboratory assessments can be performed at any time prior to 'Patient-reported outcomes for safety assessments'.

Panel 13: Sequence of assessments

* Rater-administered C-SSRS and self-administered PHQ-A questionnaires.

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

paediatric plaque psoriasis and have documented experience and/or training in use of the assessments required by the protocol and must be a physician.

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

The blinded investigator performing the efficacy assessments should be qualified dermatologists preferably with experience in paediatric psoriasis.

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

AEs must be assessed by a physician (Section 13.2).

Review of the C-SSRS, PHQ-A, and other safety assessments must be performed by qualified physicians.

Site staff administering the C-SSRS must be trained in the administration of the scale. The training certificate must be archived in the investigator trial file before any C-SSRS assessments.

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 (requires a specification to be provided).
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino.

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

The duration of psoriasis (to the nearest whole year) will be recorded in the eCRF. For subjects with current or previous psoriatic arthritis, psoriatic arthropathy, or other

immunoinflammatory diseases, the duration (to the nearest whole year) will be recorded in the eCRF.

11.2.3 Trial disease treatment history

It will be recorded in the eCRF if the subject has ever taken any psoriasis- and psoriatic arthritis-specific medication or medication for other immunoinflammatory diseases (including biologic and non-biologic systemic therapy and/or topical therapy) or had had any phototherapy or photochemotherapy at any time in the subject's history. For these medications and therapies, 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, acitretin, ultraviolet A light therapy with psoralen, or ultraviolet B light therapy. Please also refer to Section 9.6 for recording of prior and concomitant medications.

11.2.4 Medical history

Other relevant past and concurrent medical illnesses, based on subject interview, will be recorded in the eCRF; the start date and stop date will be recorded; it will also be recorded if the condition, diagnosis, or treatment is ongoing. Please also 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 and alcohol consumption will be recorded in the eCRF. It will be recorded:

- If the subject has ever consumed tobacco. If applicable, type, amount, and frequency of tobacco consumed and duration of the consumption 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

The PASI is the most widely used tool in clinical practice and clinical trials to assess the severity and extent of psoriasis (47). The PASI score will be assessed according to the schedule of trial procedures (Panel 2 and Panel 3). 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 PASI assessment will be recorded in the eCRF.

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 14. It should be noted that 'upper extremities' includes arms and hands, 'trunk' includes the axilla and groin, and 'lower extremities' includes legs, buttocks, and feet.

The investigator will also assess the extent of psoriasis within each of the 4 body regions according to the area score scale shown in Panel 15. The assessment of extent is the percentage of that body region that is affected and not the percentage BSA affected. For example, if one arm and hand was totally affected, and the other arm and hand was totally unaffected, the extent assessment for the upper extremities would be 50% (half of that body region being affected).

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 16).

The investigator must evaluate subject eligibility in relation to inclusion criterion 3 for the PASI score at screening (Visit 1) and at baseline (Visit 2; Week 0).

Panel 14: 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)

Abbreviations: PASI, Psoriasis Area and Severity Index.

Source: Modified from 47.

Panel 15: 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

Abbreviations: PASI, Psoriasis Area and Severity Index.

Source: Modified from 47.

Panel 16: 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 (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.

Source: Modified from 47.

11.3.2 Static Physician's Global Assessment

The sPGA is an instrument used in clinical trials to rate the severity of the subject's global psoriasis and is based on a 6-point scale ranging from 0 (clear) to 5 (very severe) (Panel 17).

The sPGA score will be assessed according to the schedule of trial procedures (Panel 2 and Panel 3). 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 sPGA score will be recorded in the eCRF.

The investigator must evaluate subject eligibility in relation to inclusion criterion 3 for the sPGA score at screening (Visit 1) and at baseline (Visit 2; Week 0).

Panel 17: sPGA severity score scale

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

11.3.3 Body surface area involvement

The investigator will assess the total psoriatic involvement on the arms, trunk, and legs (excluding any involvement on skin folds and genitals) as a percentage of the total BSA. As a guidance for this estimate, the surface of a full, flat palm (including the 5 fingers) of an adolescent subject corresponds to approximately 1% of the total BSA.

As an additional guidance for assessment of the full BSA with psoriatic involvement, the complete BSA (100%) can be divided into regions that approximates percentages of BSA as follows: head and neck (10%), upper extremities (20%), the trunk including the axillae and groin (30%), and finally the lower extremities, including the buttocks (40%).

The BSA will be assessed and recorded in the eCRF in accordance with the schedule of trial procedures in Panel 2 and Panel 3.

The investigator must evaluate subject's eligibility in relation to inclusion criterion 3 for the BSA at screening (Visit 1) and at baseline (Visit 2; Week 0).

11.3.4 Patient-reported outcomes for efficacy and health-related quality of life

The subjects will receive an electronic diary (eDiary) device and eDiary training at screening (Visit 1). The eDiary should be returned at the last visit at the latest.

Each subject and subject's parent/legally authorised representative 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 his or her efficacy assessments. The investigator should not question the subject's answers for any of the patient-reported outcomes. The investigator must review the data for timeliness and completeness.

Symptoms reported in the patient-reported outcomes 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 Patient Health Questionnaire-A (see Section 11.7.1).

11.3.4.1 Children's Dermatology Life Quality Index

The Children's Dermatology Life Quality Index (CDLQI) questionnaire is designed and validated in subjects with dermatological conditions from 5 to 16 years (48).

The CDLQI is available in text and cartoon versions. The text version (48) will be used in this trial. It consists of 10 items addressing the subject's perception of the impact of their skin disease on various aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and the treatment (48). Each item is scored on a 4-point Likert scale (0 = 'not at all'; 1 = 'only a little; 2 = 'quite a lot'; 3 = 'very much'). The item on school time (item 7) has an additional response category 'prevented school', which is also scored '3'. 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 CDLQI will be completed by the subjects at the trial site according to the schedule of trial procedures in Panel 2 and Panel 3.

11.3.4.2 Family Dermatology Life Quality Index

The Family Dermatology Life Quality Index (FDLQI) questionnaire is designed and validated to evaluate the impact of the subject's skin disease on the quality of life of the subject's relative (49, 50).

The FDLQI is available as a text version. It consists of 10 items addressing the subject's relative perception of the impact of the subject's skin disease on various aspects of his/her quality of life over the last month such as: emotional distress, social life, job and leisure activities, physical well-being, time spent on helping the subject with e.g., treatment procedures, extra housework, and routine household expenditure (49, 50). Each item is scored on a 4-point Likert scale (0 = 'not at all'; 1 = 'only a little; 2 = 'quite 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 FDLQI must be completed by the same relative of the subject throughout the trial. The FDLQI will be completed at the trial visits, or 1 day before the trial visits, according to the schedule of trial procedures in Panel 2 and Panel 3.

11.3.4.3 Adolescent Pruritus NRS

Subjects will assess their worst itch over the past 24 hours using an 11-point numeric rating scale (NRS) (Adolescent Pruritus NRS) with 0 indicating 'no itch' and 10 indicating 'worst itch possible'. Subjects will complete the Adolescent Pruritus NRS as part of the eDiary (Section 11.3.4) from at least 7 days before the baseline visit at Week 0 until Week 52. The eDiary should be completed each day, preferably in the evening.

11.3.4.4 Itch-related Sleep NRS

Subjects will rate how much their psoriasis interfered with their sleep the last night using an 11-point NRS (Itch-related Sleep NRS) with 0 indicating that it 'did not interfere' and 10 indicating that it 'completely interfered'. Subjects will complete the Itch-related Sleep NRS as part of the eDiary (see Section 11.3.4) from at least 7 days before the baseline visit at Week 0 until Week 52. The eDiary should be completed each day, preferably in the evening.

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). Vital signs will be measured in a supine position following at least 5 minutes of rest.

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 if the subject should be randomised into the trial (respecting exclusion criterion 36).

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine position 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.

The 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 will be reported as an AE in accordance with Section 13.3.

11.4.2 Physical examination

A thorough physical examination of the subject including whole body inspection of the skin, auscultation of heart, lungs, and abdomen, palpation of the abdominal organs, inspection of regional lymph nodes, and neurological status must be performed according to the schedule of trial procedures (Section 4).

If an unacceptable abnormal finding is identified during the physical examination at the screening visit, the subject must not be randomised into the clinical trial (respecting exclusion criterion 36).

If an abnormal finding at any other visit than the screening visit is considered by the investigator to be clinically significant, it will be reported as an AE in accordance with the principles for data entry in Section 13.3.

At least 1 physical examination should be done if the subject terminates the trial before Week 52 for any reason and if the subject accepts this procedure.

It will be recorded in the eCRF if a physical examination was performed and 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 will be reported as an AE in accordance with Section 13.3.

11.4.3 Electrocardiogram

A single 12-lead resting digital ECG will be recorded after the subject has been supine for at least 5 minutes at the visits indicated in the schedule of trial procedures (Section 4).

A pre-evaluation of the ECG will be performed by the investigators to evaluate immediate subject safety. At a minimum, the date of ECG collection will be recorded in the source documents.

The ECG data will be transferred to a central ECG service company for central evaluation. A cardiologist at the ECG service company will analyse and interpret the ECG data. The ECG service company will provide ECG evaluation reports to the trial sites. The collection and transmission of ECG data will be described in a separate ECG manual.

The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date when the evaluation is performed. The investigator has the final decision on the clinical significance of ECG abnormalities.

Subjects should not be randomised before the evaluation report from the ECG service company of the ECG performed at Visit 1 is received at site. If the Visit 1 ECG is evaluated as abnormal and considered by the investigator to be clinically significant, it will be at the investigator's discretion if the subject should be randomised into the trial (respecting exclusion criterion 36); if such a subject is randomised, the investigator should provide a justification in the medical record.

It will be recorded in the eCRF if an ECG was performed and the investigator's assessment of ECG results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'); if an ECG 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 will be reported as an AE in accordance with Section 13.3.

11.4.4 Body measurements: height and weight

The subject's height (without shoes) will be measured; the subject's weight (in indoor clothing and without shoes) will be measured. The subject's height and weight will be recorded in the eCRF according to the schedule of trial procedures (Section 4).

11.4.5 Laboratory testing

11.4.5.1 Overview of all laboratory tests

Blood and urine samples will be collected according to the schedule of trial procedures (Section 4).

See Panel 18 for an overview of all laboratory tests to be conducted in this trial.

Panel 18: Laboratory tests

Chemistry	Haematology
Sodium Potassium Creatinine Urea nitrogen Calcium Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Uric acid Bilirubin[1] Lactate dehydrogenase Cholesterol Low density lipoprotein cholesterol High density lipoprotein cholesterol Triglycerides Glucose Albumin Protein C-reactive protein Estimated glomerular filtration rate (eGFR)[2]	Erythrocytes Hematocrit Hemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes White blood cell (WBC) differentials: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils Absolute neutrophil count (ANC) Thrombocytes T-lymphocyte subsets B-lymphocytes
Serology[2]	**Urinalysis[3]**
Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody Human immunodeficiency virus-1 antibody Human immunodeficiency virus-1 antibody confirmation Human immunodeficiency virus-2 antibody Human immunodeficiency virus-2 antibody confirmation Varicella zoster antibody	Protein Glucose Ketones Occult blood Leukocytes Nitrite
Serum pregnancy test[4]	**Other tests**
Choriogonadotropin beta	Tuberculosis (only if applicable) Serum concentrations of brodalumab for pharmacokinetics (PK) Anti-drug antibodies (ADA) Anti-tetanus toxoid antibodies (aTTA) Blood biomarkers (including interleukin (IL)-17, IL-10, IL-6, CXCL9, CCL20, S100-A12, Caspase-8)

1) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
2) Measured at screening only. The eGFR will be calculated using the Schwartz formula (51).
3) 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 laborartory.
4) Urine pregnancy tests will be performed at the trial site throughout the trial. If a urine pregnancy test is positive, a serum pregnancy test has to be done to confirm the result. At screening, a serum pregnancy test is always performed regardless of the urine pregnancy test result.

11.4.5.2 Investigator evaluation of laboratory tests

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 to confirm the abnormality.

The site staff will record in the eCRF if a blood sample was taken as well as the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant').

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 take an additional sample in order to reject or confirm the initial finding within 28 days, and if normalised, be randomised into the trial.

Urine samples will be tested at the trial site with a dipstick and it will be recorded in the eCRF if the result was normal or abnormal. If dipstick sampling was not performed, a reason will be given. If a urine 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 local assessment of significance. The investigator's assessment of the central laboratory analysis result ('normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant') must also be recorded in the eCRF.

Female subjects will have a serum pregnancy test performed at screening and a urine pregnancy test performed both at screening and baseline prior to randomisation. The test will be repeated at the visits stated in the schedule of trial procedures in Section 4. The date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative'). If a urine pregnancy test is positive, the result must be confirmed by a serum pregnancy test.

Any 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 as well as any new clinically significant sign, symptom or illness will be reported as an AE in accordance with Section 13.3.

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.

11.4.6 Blood sampling for analysis of vaccine antibodies

Blood samples will be collected to determine levels of anti-tetanus toxoid antibodies (aTTA) at pre-determined time points according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the sample was taken; if not, a reason will be provided.

Blood sampling times must be recorded on the laboratory requisition forms ('date and hours'). Collection, handling, and shipment instructions for blood samples for analysis of aTTA levels are provided in a laboratory manual.

11.4.7 Blood sampling for analysis of ADA

Blood samples will be collected to determine anti-drug antibody (ADA) levels at pre-determined time points according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the sample was taken; if not, a reason will be provided.

Blood sampling times must be recorded on the laboratory requisition forms ('date and hours'). Collection, handling, and shipment instructions for blood samples for analysis of ADA levels are provided in a laboratory manual.

Serum samples for determination of presence or absence ADA will be analysed by a laboratory using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will be analysed for the presence of neutralising antibodies. Details of the analytical method used will be described in an ADA bioanalytical report.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of brodalumab concentration for PK assessments

A blood sample for analysis of brodalumab concentration for PK assessments will be collected at the time points specified in the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the blood samples for PK assessments were taken; if not, a reason will be provided.

Blood sampling times must be recorded on the laboratory requisition forms ('date and hours'). Collection, handling, and shipment instructions for the blood samples for PK assessments will be provided in a laboratory manual.

Serum samples for determination of brodalumab concentrations will be analysed by a laboratory using a validated bioanalytical method. Details of the analytical method used will be described in the bioanalytical report.

11.6 Pharmacodynamics

11.6.1 Overview

Treatment with brodalumab is known to increase the serum levels of IL-17 as a result of IL-17R blockade. Consequently, as part of the assessment of the pharmacodynamic effects of brodalumab treatment, the level of IL-17 and lymphocyte subsets will be measured. Blood biomarkers and lymphocyte subsets will be measured to assess the effect of brodalumab as well as the vaccination on the immune system in adolescents with psoriasis treated with brodalumab.

11.6.2 Blood sampling for analysis of IL-17 and other blood biomarkers

Blood samples for analysis of IL-17 and other immunological and inflammatory biomarkers that reflect the effect of the vaccination and the psoriasis severity will be collected at the time points specified in the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the blood samples were taken; if not, a reason will be provided.

Blood sampling times must be recorded on the laboratory requisition forms ('date and hours'). Collection, handling, and shipment instructions for the blood biomarker samples will be provided in a separate laboratory manual.

Biomarkers to be analysed include IL-17, IL-10, IL-6, CXCL9, CCL20, S100-A12, and Caspase-8; additional biomarkers of relevance to psoriasis may be analysed from these samples to serve as pharmacodynamic markers of drug effect, if deemed relevant.

11.6.3 Blood sampling for analysis of T- and B-lymphocyte subsets

Blood samples for analysis of T- and B-lymphocyte subsets (including $CD4^+$, $CD8^+$, T-helper (Th)1, Th17, Th22, and $CD19^+$ cells) will be collected at the time points specified in the schedule of trial procedures (Section 4). It will be recorded in the eCRF if the blood samples were taken; if not, a reason will be provided.

Blood sampling times must be recorded on the laboratory requisition forms (‘date and hours’). Collection, handling, and shipment instructions for the blood samples for measurement of T- and B-lymphocyte subsets will be provided in a separate laboratory manual.

11.7 Other assessments

11.7.1 Patient-reported outcomes for safety assessments

The C-SSRS and PHQ-A 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.

11.7.1.1 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 (52). The C-SSRS defines 5 subtypes of SIB in addition to self-injurious behaviour with no suicidal intent.

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 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 19 and 20 for the C-SSRS components 'history of suicidal behaviour' and 'suicidal ideation' at screening (Visit 1) and at 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 other visits. The C-SSRS assessments will be transcribed into the eCRF.

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

11.7.1.2 Patient Health Questionnaire, adjusted for adolescents

PHQ-A is a severity measure for depression in children 11 to 17 years of age. PHQ-A is adapted from PHQ-9 and modified for adolescents (53). The PHQ-A is a validated and widely used 9-item version of the Patient Health Questionnaire depression scale designed to clinically assess subjects for symptoms and signs of depression (53).

Eight questions of the questionnaire will be applied in this trial. Question number 9: "Thoughts that you would be better off dead, or of hurting yourself in some way?" will be removed. The PHQ-9 and PHQ-8 have a similar sensitivity and specificity to detect major depression (54). Furthermore, the removed question number 9 will be adequately covered by the C-SSRS, described above. Each question is rated on a 4-point scale (0=Not at all; 1=Several days; 2=More than half the days; and 3=Nearly every day). The total score of 8 questions can range from 0-24. The subject must complete all 8 questions.

The PHQ-A (i.e., PHQ-9 adopted for adolescents, without question number 9) takes approximately 3 minutes to complete.

PHQ-A scores ≥10 must be reported as an AE and the subject referred to a mental health professional (score ≥10 is cut-point for defining current depression) (53). Subjects scoring ≥15 must in addition be discontinued from IMP.

11.7.2 Photography (selected trial sites)

Subjects at selected trial sites will be asked to participate in a voluntary photography component of the trial which involves digital photography assessments to show disease progression over time. Participation in this photography component requires that the subject and the legal authorised representative provide additional informed consent with the possibility to choose for which purpose (scientific and/or commercial) the photographs can be used. It is estimated that photos will be taken of approximately 40 subjects.

Digital colour photographs will be taken of the legs including feet (dorsal and ventral image), torso including arms (dorsal and ventral image), and head (anterior image) according to the schedule of trial procedures (Section 4). The photographs must always be taken with underwear (modesty garments, provided by the central photography vendor) and female subjects should have their breasts hidden. All faces (eyes and mouth) will be anonymised upon receipt of the images by the central photography vendor. It will be recorded in the eCRF if the photograph(s) was taken; if not, a reason should be provided. If deemed necessary (e.g. in case of poor quality), photographs can be retaken at the next visit.

Photography equipment, standards, and procedures are provided to the trial sites by the central photography vendor. Instructions for photography will be provided to the sites in a photography manual.

The photographs will have no other subject identifier than the subject ID, year of birth, visit number, and date, and will be transmitted electronically to the photography vendor using a secure file transfer protocol.

The photographs must be included as part of the individual subject source documentation.

Depending on the subject's consent, LEO Pharma may use the photographs in publications, posters, and similar types of information material or media targeting patients and healthcare professionals. The photographs may also be part of training material used for training and educational purposes. Steps will be taken to ensure that the identity of the subject is protected by blinding or covering any potential identifying features in the photographs.

11.8 Estimate of total blood volume collected

Blood samples will be drawn in this trial as indicated in Panel 2 and Panel 3. The blood volume to be collected will not exceed 72 mL during a period of 4 weeks, or 24 mL at any single time throughout the trial. This is in compliance with the current ethical guidelines on trial-related blood loss in children (36). The above volumes are acceptable for the subject with the body weight of 30 kg and total blood volume of 2400 mL (36). The total volume of blood to be drawn in the trial corresponds to approximately 33% of blood volume drawn during a single blood donation (approximately 500 mL).

11.9 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.

11.9.1 End of treatment form

An end of treatment form will be completed in the eCRF for all subjects when they have had their last administration of IMP. This form will also be completed for subjects who discontinue IMP prematurely 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 period and, if not, whether the reason for not completing the treatment period was related to pandemic restrictions (e.g. 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 the supply chain of IMP). If the subject did not complete the treatment, the date of last administration of IMP and the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

11.9.2 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:

- Last scheduled visit number for which data is recorded.
- If the subject completed the trial. If not, the primary reason for early termination and whether the reason for not completing the trial was related to pandemic restrictions (e.g. 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 the supply chain of IMP) must be recorded.

- Date of last contact.
- Primary reason for withdrawal from trial (lack of efficacy, adverse event, withdrawal by subject, withdrawal by parent/guardian, lost to follow-up, death, pregnancy, other).
    - 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 their last visit, that is, the safety follow-up visit at Week 60, or earlier in case of early trial termination (see Section 10).

11.10 Storage of biological samples

Blood samples collected for PK, aTTA, and biomarkers will be retained for as long as the quality of the material permits evaluation, but will be discarded after completion of the clinical trial report (CTR).

Blood samples collected for analysis of ADA and nAb will be stored in the biobank established by LEO Pharma for no longer than 10 years after completion of the CTR.

12 Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

This trial is the first clinical trial in the LEO Pharma paediatric investigational plan for brodalumab, which has been agreed with PDCO and EMA.

The trial population will comprise both male and female subjects to explore differences in effects between genders and across the adolescent age range. Psoriasis prevalence in children correlates in a linear manner with age with a low prevalence in the age range from 0 to 6 years and a higher prevalence in the age range from 11 to 18 years (2). The paediatric investigational plan for brodalumab is designed to follow the safety principle, i.e., the adolescent trial must be conducted before the trial in children, aged 6 to 11 years. Thus, children will not be exposed to brodalumab before efficacy, safety, and PK data from the adolescent trial have been analysed and indicated that it is appropriate to initiate the trial in children. Furthermore, the adolescent population is more comparable with adults with fewer differences in pharmacokinetic and safety profiles (55). This enables extrapolation of brodalumab PK, pharmacodynamics, and safety data from the completed development programme in adults to this adolescent trial.

The most important inclusion criterion for entry into the trial is a diagnosis of chronic plaque psoriasis for at least 6 months before randomisation to ensure correct diagnosis and rule out differential diagnosis. Furthermore, the subject must be a suitable candidate for systemic treatment. Subjects diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions are not allowed to participate in the trial to ensure a homogenous disease population and interpretability of efficacy results.

The number of paediatric patients available for clinical trials is often limited, which poses a challenge for including a sufficient number of subjects in the trial. Moreover, administration of IMP by injection, the mandatory trial-specific blood sampling, and the additional vaccination may further impact the recruitment of adolescents for this trial.

Minimising the number of trial subjects is an important ethical aspect, especially in paediatric trials. Inclusion of a double-blind placebo arm from Week 0 to Week 12 will enable a formal test of superiority of brodalumab compared to placebo, and demonstrating superiority of brodalumab to placebo will require fewer paediatric subjects than would be required to demonstrate superiority of brodalumab to an active comparator. Thus, inclusion of a placebo arm in this trial will minimise the number of paediatric subjects required for the trial while maintaining a high statistical power.

The open-label ustekinumab arm will enable a safety evaluation and a descriptive efficacy comparison of brodalumab to ustekinumab. No formal hypotheses regarding brodalumab vs ustekinumab or placebo vs ustekinumab will be tested. Ustekinumab is part of the standard treatment of moderate-to-severe plaque psoriasis in adolescents (from the age of 12 years), who are inadequately controlled by, or intolerant to, other systemic therapies or phototherapies. The administration of ustekinumab in an open-label manner will significantly reduce the number of injections. According to the SmPC of Stelara® (45), ustekinumab must be administered at Weeks 0, 4, and then every 12 weeks. The blinding of ustekinumab until Week 12 would require a double dummy design, leading to a significant increase in the number of subcutaneous injections. Furthermore, to adequately power a formal statistical test of superiority comparing brodalumab to ustekinumab would require a significantly larger sample size. In light of the previously described potential challenges of recruitment of adolescent subjects, this would impact the feasibility of the trial design.

The double-blind induction period (Week 0 to Week 12) is considered appropriate for evaluating the primary objective of the trial as double-blinding of the subject's treatment (brodalumab or placebo) is maintained and the possible observer bias regarding treatment effects is minimised. All efficacy assessments will be performed by an investigator, who is blinded to the treatment allocation (brodalumab/placebo, ustekinumab, and vaccine) throughout the trial, which will minimise observer bias also in the open-label ustekinumab arm.

Psoriasis is a chronic condition, requirering a long-term therapy. Therefore, it is important to evaluate the efficacy and safety of brodalumab as maintenance treatment. To allow for assessment of the duration of treatment response, the 12-week induction period will be followed by continued 40 weeks treatment until Week 52. Subjects, who are initially treated with placebo will switch to either brodalumab or ustekinumab, and will thus receive 40 weeks of active treatment in the maintenance period. The duration of the treatment phase (induction and maintenance periods) is the same as those in the pivotal clinical phase 3 trials in adults, and is also considered sufficient for evaluation of the duration of treatment response in adolescents.

12.2 Appropriateness of assessments

The clinical efficacy of brodalumab treatment will be assessed by PASI and sPGA:

- PASI is the most thoroughly validated and the most extensively studied psoriasis clinical severity score, which assesses the extent of psoriasis at 4 anatomic sites with the signs of erythema, scale, and elevation (56).

- sPGA is a validated and standardised global score of the patient's overall disease severity, and can be used in conjunction with PASI for assessment of clinical efficacy (57).

The efficacy endpoints sPGA score of 1 or 0 and PASI 75 are recommended by both EMA and the United States Food and Drug Administration (FDA) for assessment of clinical efficacy (57, 58) and recognised as important endpoints in clinical trials in psoriasis by regulatory authorities in the EU.

Validated patient-reported questionnaires (CDLQI, FDLQI) have also been included to assess the efficacy of brodalumab on patient-reported outcomes and health-related quality of life.

Blood concentrations of brodalumab will be analysed using validated bioanalytical methods. To minimise the number of blood samples, a population PK approach will be used to quantify the systemic brodalumab exposure in adolescents.

The trial will evaluate the percentage of subjects with seroprotective aTTA at Week 12, defined as aTTA ≥0.1 IU/mL at Week 12 (43, 59) and whether the subjects achieve a booster response at Week 12, defined as a 3-fold increase in IgG at Week 12 if IgG ≤1.0 IU/mL at baseline, or IgG ≥2.5 IU/mL if IgG >1.0 IU/mL at baseline. These response criteria were developed based on the criteria for positive vaccine response in the assays used for determining aTTA. The aTTA booster response definition takes into account that some subjects may have high pre-vaccination anti-tetanus IgG levels and may therefore not be able to elicit the same increase in anti-tetanus IgG levels as those with low pre-vaccination IgG levels. It has also been reported, that antigen-specific B- and T-cells and IL-17 are increased after vaccination and remain above the baseline for more than 4 weeks after the vaccination (60). The vaccine-induced changes in B- and T-cells and IL-17 levels will therefore be evaluated at Week 12 in this trial.

Subjects who do not achieve clinical response and subjects who loose clinical response will not be excluded from further participation in the trial. This approach has been chosen to increase the likelihood that subjects from the placebo arm will stay in the trial until administration of the vaccine at Week 8 and evaluation of the vaccine responses at Week 12.

It has been reported that IL-17-producing Th17 cells are increased and positively correlated with disease severity in children with psoriasis (19). Brodalumab treatment in adult patients, who received a constant 140 mg or 210 mg dose of brodalumab every 2 weeks through the treatment period increased the median serum IL-17A levels by 3- to 4-fold relative to baseline (61). IL-17 cytokines play a role in several homeostatic and pathogenic processes. Scientific literature suggests that IgG antibodies can cross the blood-brain barrier, albeit in low amounts,

and that the Th17/IL-17 axis may potentially play a role in depression (62, 63, 64, 65). However, the observed brodalumab plasma concentrations in patients with SIB events were similar to the overall subject population in the individual trials (61, 66, 67) and there is no clear evidence of a relationship between brodalumab (systemic exposure) and SIB events (68). The current trial will evaluate the serum IL-17 levels in adolescents treated with brodalumab by use of an established assay.

Data on antibodies against brodalumab (ADAs) will be collected and the potential for immunogenicity will be evaluated throughout the trial.

Furthermore, safety will be assessed using standard clinical methods of subject evaluations, such as AE monitoring, ECG, vital signs, and clinical laboratory measurements.

13 Adverse events

13.1 Definition and classification of adverse events

Adverse events (AEs) and serious adverse events (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, placebo, ustekinumab, and vaccine).

13.2 Collection of adverse event reports

AEs must be collected from time of first trial-related activity after the subject has signed the informed consent form until subject´s completion of the clinical trial (defined in Section 7.3).

AEs must be assessed by a physician.

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 11.4.5 for principles for data entry in the eCRF.

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, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first administration of the 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, e.g., dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, 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 immediately, without undue delay and no later than 24 hours of obtaining knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to IMPs, device, or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

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 7226 3287.

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 in order 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 IEC(s) of SAEs, as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial including any protocol required post-treatment follow-up period, should not be routinely sought or recorded. However, such events should be reported immediately without undue delay and no later than 24 hours of obtaining knowledge 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 the IMP (brodalumab/placebo), the current edition of the Investigator's Brochure, edition 13 and subsequent updates.
- For the comparator (ustekinumab), the current SmPC in the EU.
- For Td and Tdap vaccines, the current SmPC in the EU.

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.

The following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma (78), 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 (AESI) have been defined: suicidal ideation and behaviour (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 immune modulating biologics used for psoriasis. AESIs must be reported to LEO Pharma as described in Panel 19.

Panel 19: 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. Broadly, medication errors fall into 3 categories: wrong medication, wrong dose (including overdose, form, concentration, amount), and 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 the 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.

Plaque psoriasis is a fluctuating disease with possible periods of remission. In case of relapses/recurrences, only aggravations/exacerbations exceeding normal disease fluctuation or lesions appearing in a body area normally not affected by plaque psoriasis should be reported as an AE.

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). Once a subject leaves the clinical trial, the investigator should follow-up on the outcome of all non-serious AEs classified as of possibly/probably related to the IMP for 2 weeks or until the final outcome is determined, whichever comes first.

All 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 from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome should be reported as 'recovering/resolving' or 'not recovered/not resolved' at the investigator´s discretion. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. 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.*" (69).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO 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 the clinical trial procedure or of the temporary halt providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO 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 endpoint for this trial is the PASI 75 response status at Week 12. Denoting the Week 12 PASI 75 responder rates for the adolescent brodalumab dosing regimen and pooled placebo arms by π_{broda} and $\pi_{placebo}$ respectively, the following null hypothesis,

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

will be tested versus the 1-sided alternative,

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

by assessing if the lower limit of the 95% confidence interval (CI) for the difference in responder rates is >0 and by comparing the 2-sided p-value with the 5% significance level.

For the purposes of this trial, the PASI 75 composite endpoint is defined as achieving a PASI 75 response without prior discontinuation of IMP treatment or previously satisfying the requirements for rescue treatment. Under the assumption that the Week 12 response rates for the PASI 75 composite endpoint in the adolescent brodalumab dosing regimen and pooled placebo arms are 80% and 15% respectively, a sample size of 40 subjects per arm, will provide >99% power to detect a significant treatment difference.

In addition to the primary endpoint, the precision of the estimate of the difference in vaccine response rates between the adolescent brodalumab dosing regimen and pooled placebo arms, was taken into consideration when arriving upon a final sample size.

For the purposes of the sample size calculation, the precision was taken to be half the width of the associated 95% CI for the estimated difference in the Week 12 vaccine response rates between the adolescent brodalumab dosing regimen and pooled placebo arms. Panel 20 provides the 95th percentile for the precision of the estimated difference in vaccine response rates, from 100 000 simulations assuming the rate of vaccine response is equal in the 2 arms. The 95% CIs were calculated based on

$$\left(p_{broda} - p_{placebo}\right) \pm 1.96 \times \sqrt{\left(\frac{p_{broda}\left(1 - p_{broda}\right)}{n_{broda}} + \frac{p_{placebo}\left(1 - p_{placebo}\right)}{n_{placebo}}\right)}$$

where p_{broda} and $p_{placebo}$ are the estimated Week 12 vaccine response rates for the adolescent brodalumab dosing regimen and pooled placebo arms respectively, and n_{broda} and $n_{placebo}$ are the number of subjects randomised to the respective arms. Therefore, for a given set of assumptions regarding the sample size and response rates provided in Panel 20, we

would expect that the probability of obtaining a 95% CI for the difference in response rates less precise than the corresponding value in Panel 20 to be ≤5%.

Panel 20: Estimated one-sided 95% upper confidence limit for the precision of the estimated difference in vaccine response between the brodalumab dosing regimen and placebo arms assuming the probability of vaccine response is equal in the 2 arms

	Probability of vaccine response	
Sample size/arm	**70%**	**80%**
30	24.6%	22.8%
35	22.8%	20.8%
40	21.2%	19.5%

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All randomised subjects will be included in the full analysis set (FAS) and will be analysed for efficacy up to Week 12. Analyses based on the FAS, will be analysed according to the randomised treatment allocation. Exclusions from the FAS can be considered in special cases as described in ICH E9, Section 5.2.1., Full Analysis Set. If it is decided to exclude a randomised subject from the FAS, a justification addressing ICH E9 will be given.

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

A PK analysis set will be defined as all subjects who received brodalumab, who have at least 1 PK sample.

A population PK analysis set will be defined as all subjects in the PK analysis set, who have at least 1 sample with a quantifiable concentration.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the analysis set definition document before breaking the randomisation code.

14.3 Statistical analysis

14.3.1 General principles

Unless otherwise stated, significance tests will be two-sided with a significance level of 5%. CIs will be presented with 95% degree of confidence. Efficacy analyses will be based on the FAS. Safety analyses will be based on the safety analysis set.

The presentation of sensitivity analyses and the secondary estimand will be reserved for primary and key secondary endpoints only.

For induction period-related endpoints, i.e., endpoints assessed at or over the initial 12-week treatment phase, separate treatment contrasts comparing the adolescent brodalumab dosing regimen to the pooled placebo (consisting of subjects randomised to either of the treatment arms scheduled to receive placebo for the first 12 weeks) and the ustekinumab arm will be presented.

For maintenance period-related endpoints, i.e., endpoints assessed at or over the entire 52-week treatment phase, 2 separate analyses comparing the adolescent brodalumab dosing regimen versus ustekinumab will be presented:

- Brodalumab (consisting of subjects randomised to the brodalumab arm [a constant brodalumab arm]) versus ustekinumab (consisting of subjects randomised to the ustekinumab arm [a constant ustekinumab arm]).
- Pooled brodalumab (consisting of all subjects randomised to receive brodalumab during the maintenance period [a mixed brodalumab arm]) versus pooled ustekinumab (consisting of all subjects randomised to receive ustekinumab during the maintenance period [a mixed ustekinumab arm]).

For the purposes of stratified analyses, the strata defined by baseline body weight (<70 kg and ≥70 kg) may be pooled in order to ensure there is a sufficient number of subjects in every stratum. In the event that all strata are pooled into a single stratum, inference based on the general association test statistics for the Cochran-Mantel-Haenszel (CMH) test, simplifies to $Q_P \frac{n-1}{n}$, where Q_P is the test statistic for the Pearson chi-square test, and n is the sample size.

Imputation algorithms specified in Section 14.3.2.1 will be implemented using PROC MI.

Inference based on multiple imputation methods will consist of n=250 imputed data sets to ensure that the between-imputation variance is estimated with adequate precision. For the analysis of binary endpoints using the CMH test and relying on multiple imputation methods to address missing data, the test-statistics will be pooled based on the procedure proposed by

Li et al (70) and outlined by Ratitich, Lipkovich, and O'Kelly (71) in order to derive the final p-value. Additionally, the common risk differences and associated standard errors will be pooled directly, based on Rubin's rules, in order to quantify the potential treatment benefit. In the event of a potential disagreement between the pooled p-value and 95% CI for the estimated common risk difference, inference will be based on the pooled p-value. For the analysis of multiply imputed data sets using generalised estimating equation (GEE) or analysis of covariance (ANCOVA), the estimated regression coefficients and associated standard errors will be pooled directly using Rubin's rules.

LSMeans will be estimated based on the observed margins. For analyses that rely on the missing at random assumption, the observed margins dataset should contain data entries corresponding to missed visits.

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, 1st quartile, 3rd quartile, standard deviation (SD), minimum, and maximum values.

The analyses specified in the protocol will be reviewed in relation to the blinded data. If a statistical analysis plan is required, it will be finalised before breaking the blind.

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

14.3.2 Handling of missing values

Likelihood methods, as well as single and multiple imputation methods will be implemented in order to account for the presence of missing data in the statistical analysis of the primary and secondary endpoints. The missing data methods specified in Sections 14.3.6.1 and 14.3.6.2 are designed to assess the robustness of the results of the primary analysis, with respect to the assumptions made regarding missing data. For imputation-based methods, non-monotone missing data will be imputed based on a Markov Chain Monte Carlo (MCMC) method, assuming an underlying multi-variate normal distribution for continous endpoints and the fully-conditional specification method for binary or ordinal endpoints.

Multiple impupation methods that will be implemented as a part of the sensitivity analyses of the primary and key secondary endpoints include the 'control-based' pattern mixture model

outlined by Ratitich and O'Kelly (72), as well as imputation models assuming that missing data is missing at random (MAR) within the randomised treatment arms.

The 'control-based' pattern mixture model assumes that the mean response value among subjects no longer receving active treatment is given by the mean response among the reference/placebo arm. Missing data in subjects receiving either active or reference treatment at a given time point is imputed based on the distribution of the conditional mean fitted to the observed data amongst the appropriate reference arm.

14.3.2.1 Endpoint-specific considerations for multiple imputation algorithms

PASI

Imputation of missing binary PASI 75/90/100 data between Week 2 and Week 52 will be based on imputating the underlying PASI scores (range 0-72). The relevant assumptions and groups are dependent on the specified multiple imputation algorithm. Intermittent missing values will be imputed in each relevant group based on a MCMC method to obtain n=250 copies of the data set with a monotone missing data pattern (seed=992051).

Imputation of monotone missing data for each relevant patient population defined by the specified multiple imputation procedure will be based on the following 4 steps:

1. Fitting an ANCOVA model to the Week 2 PASI score including the effects of baseline PASI as a covariate, and baseline body weight (<70 kg and ≥70 kg) as a factor. The estimated parameters, and their variances, will be used to impute missing PASI scores at Week 2 in each of the n=250 copies of the dataset generated above (seed=485741). 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.
2. For each of the 250 copies of the dataset, missing PASI scores at Week 4 will be imputed in the same manner as for missing Week 2 values in step 1. The imputations will be based on the same ANCOVA model with the effects of baseline and Week 2 PASI scores as a covariate, and baseline body weight (<70 kg and ≥70 kg) as a factor. Again, negative imputed values will be replaced by 0, and imputed values larger than 72 will be replaced by 72.
3. This stepwise procedure will then be repeated sequentially through Week 52, with the modification that only the PASI scores from the preceding 2 visits be included as covariates in the ANCOVA model.
4. The missing binary PASI 75/90/100 response values over the 52-week treatment phase, will be derived from the underlying imputed PASI scores.

Ordinal variables (sPGA, CDLQI, FDLQI)

The analysis of sPGA, CDLQI, and FDLQI are based on perceived subject relevant dichotomisations, e.g., the proportion of subjects with sPGA score ≤1 at Week 12. The imputation of missing binary values for these dichotomisations, will be based on imputing the values on the underlying scales, e.g., 5-point scale for sPGA.

Imputation of missing data for each relevant trial population, defined by the specified multiple imputation procedure, will be based on the following steps:

1. In each group, missing ordinal data from Week 2 to Week 52 will be imputed based on the FCS logistic regression model. The logit link option should be specified in order to impute missing values based on an ordinal logistic regression model assuming proportional odds. Separate conditional specifications will be specified for visits with missing values. The imputation model at a given visit should depend on the values from the preceding and subsequent 2 visits (exceptions being baseline and Weeks 2, 48, and 52) as well as the stratifying factor, baseline body weight (<70 kg and ≥70 kg). n=250 complete data sets will be generated (seed=657337).
2. The missing binary response variables will be derived from the corresponding underlying imputed ordinal values.

aTTA and lymphocyte subset

Intermittent missing values will be imputed in each relevant group based on a MCMC method in order to obtain n=250 copies of the data set with a monotone missing data pattern (seed=875806).

Imputation of monotone missing data for each relevant patient population defined by the specified multiple imputation procedure will be based on the following 2-step process:

1. Fitting an ANCOVA model to the Week 8 lab value including the effects of baseline lab value as a covariate, and baseline body weight (<70 kg and ≥70 kg) as a factor. The estimated parameters, and their variances, will be used to impute missing lab values at Week 8 in each of the n=250 copies of the dataset generated above (seed=604006).
2. For each of the 250 copies of the dataset, missing lab values at Week 12 will be imputed in the same manner as for missing Week 8 values in step 1. The imputations will be based on the same ANCOVA model with the effects of baseline and Week 8 lab values as a covariate, and baseline body weight (<70 kg and ≥70 kg) as a factor.

For the booster response endpoint, missing binary response values at Week 8 and Week 12 will be derived from the imputed aTTA values.

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, satisfying the

inadequate responder criteria during the induction period, completing IMP, discontinuing IMP, and withdrawal from trial by treatment arm and overall. Within the overall summary, the number of exposed, completing IMP, discontinuing IMP, and withdrawal from trial will be presented for the 12-week induction period as well as the entire 52-week treatment phase. The reasons for permanent discontinuation of IMP and withdrawal from trial will be presented for all randomised subjects by last visit attended, treatment arm, and reason for discontinuation of IMP and/or withdrawal from trial.

In addition to the above, the number of subjects included in the FAS, the safety analysis set, and the PK analysis set will be summarised by treatment arm and in total.

Cumulative incidence plots of the time to early termination, stacked by reason for early termination and time to initiation of rescue treatment will be presented by treatment arm over the duration of the treatment phase.

14.3.4 Demographics and other baseline characteristics

Descriptive statistics of demographics and baseline characteristics will be presented for all randomised subjects 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, aTTA, and lymphocyte subsets. In addition to the above specified baseline characteristics, the following baseline measures of disease severity will be presented: PASI, sPGA, CDLQI, FDLQI, and the baseline weekly average itch severity and itch-related sleep 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

14.3.5.1 Exposure

The exposure to treatment will be tabulated by treatment arm and visit for the FAS. Separate tabulations will be presented for the 12-week induction period and the entire 52-week treatment phase.

14.3.5.2 Treatment compliance

Treatment compliance will be presented from data listings. Subjects not receiving the scheduled dose will be listed by trial site, sorted by treatment arm and subject number.

14.3.6 Estimand strategy

For each endpoint associated with a trial objective, a primary estimand will be pre-specified, and the secondary estimand will be used to further aid in the interpretation of the results. The estimands are described in a general manner to allow for the use of the same estimand for different endpoints.

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 underpinning the associated models/estimators.

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

I. **Initiation of rescue treatment:** Defined as satisfying the requirements for the initiation of rescue treatment specified in Section 9.5. This intercurrent event is handled without assessing relatedness to pandemic restrictions.

II. **Permanent discontinuation of IMP not due to pandemic restrictions:** This event occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to 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 defined in the SAP.

III. **Permanent discontinuation of IMP due to pandemic restrictions:**
This event occurs when a subject permanently discontinues IMP for reasons related to 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 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 the supply chain of IMP. The timing of the event will be defined in the SAP.

Note, there is a distinction between permanent discontinuation of IMP (an intercurrent event) and withdrawal from trial and/or lost to follow-up. Withdrawal from trial and lost to follow-

up, which are not intercurrent events, will be addressed when specifying methods and/or assumptions for handling missing data. If the withdrawal from trial is related to the pandemic restrictions, missing data will be handled as missing data related to the pandemic restrictions.

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.

The '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.

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: Overview of estimands and handling of missing data

		Estimands for binary endpoints		Estimand for continuous endpoints	Estimands for vaccine related endpoints	
Intercurrent event	**Data observed or missing**	**Primary**	**Secondary**	**Primary**	**Binary**	**Continuous**
Initiation of rescue treatment	Observed	**Composite:** N/A, value of the endpoint is determined by the intercurrent event	**Treatment policy**: Used as observed	**Treatment policy**: Used as observed	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)
	Missing	N/A, value of the endpoint is determined by the intercurrent event	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
Permannent discontinuation of IMP **not due to pandemic** restrictions	Observed	**Composite:** N/A, value of the endpoint is determined by the intercurrent event	**Treatment policy**: Used as observed	**Treatment policy**: Used as observed	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)
	Missing	N/A, value of the endpoint is determined by the intercurrent event	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
Permanent discontinuation of IMP **due to pandemic** restrictions	Observed	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)	**Hypothetical**: Treated as missing, MI (MAR within treatment arms)
	Missing	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
No intercurrent event	Observed	Used as observed	Used as observed	Used as observed	Used as observed	Used as observed
	Missing **not due to pandemic** restrictions	NRI	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
	Missing **due to pandemic** restrictions	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)

Abbreviations:MAR, missing at random; MI, multiple imputation, N/A, not applicable; NRI, non-responder imputation.

14.3.6.1 Estimand strategy for binary endpoints

14.3.6.1.1 Primary estimand for binary endpoints

The primary estimand will assess the expected difference in response rate achieved without initiation of rescue treatment or permanent discontinuation of IMP not due to pandemic restriction, as if the conduct of the trial was not impacted by pandemic related restrictions.

This implies an underlying composite strategy, assuming that the need for rescue treatment or permanent discontinuation of IMP not due to pandemic restrictions is indicative of treatment failure. But, also implied is a hypothetical strategi for mitigating any untoward influences the pandemic might have on the trial.

With the composite strategy subjects who have either permanently discontinued treatment not due to pandemic restrictions or have initiated rescue treatment prior to the endpoint visit will be defined as non-responders, reflecting an assumption that initiation of rescue treatment and permanent treatment discontinuation not due to pandemic restrictions indicates failure of the randomised treatment to achieve response.

A hypothetical strategy, in the form of a multiple imputation method, will be used to address permanent discontinuation of IMP due to pandemic restrictions. For subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit, data collected after treatment discontinuation will be excluded (including the occurrence of subsequent intercurrent events) and will be 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, assuming a similar course of events as experienced by subjects from the same treatment arm who have not discontinued IMP due to pandemic restrictions. With this purpose in mind two questions naturally arise because of the composite strategy used to address permanent discontinuation of IMP not due to pandemic restrictions:

a) Would the subject still have been on treatment at the endpoint visit without rescue treatment as opposed to having permanently discontinued IMP not due to pandemic restrictions or initiated rescue treatment beforehand?

b) If yes, would the subject have been a responder at the endpoint visit?

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. 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 primary 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 primary analysis of the primary estimand for binary endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute responder status at the endpoint visit under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit	Hypothetical strategy
		Subjects who have not experienced an intercurrent event prior to the endpoint visit and whose score at the endpoint visit is missing due to pandemic restrictions	Handling of missing data
2	Impute responder status at the endpoint visit based on NRI	Subjects who have not experienced an intercurrent event prior to the endpoint visit and whose score at the endpoint visit is missing for reasons other than pandemic restrictions	Handling of missing data
3	Impute treatment adherence status at the endpoint visit	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit	Hypothetical strategy

Abbreviations: IMP, investigational medicinal product; MAR, missing at random; NRI, non-responder imputation.

When performing Step no. 1 in Panel 22, data collected after initiation of rescue treatment or permanent discontinuation of IMP will not be applied, regardless of the reason for treatment discontinuation. This is well aligned with the composite strategy described above for addressing permanent discontinuation of IMP not due to pandemic restrictions and initiation of rescue treatment, where data collected after treatment discontinuation or initiation of rescue treatment is irrelevant for the value of the estimand's variable.

For subjects who prior to the endpoint visit have permanently discontinued IMP due to pandemic restrictions the values imputed in Step no. 1 may be thought of as the responder status at the endpoint visit, conditional on treatment adherence, thereby addressing the hypothetical question b) stated above. Similarly, Step no. 3 in Panel 22 may be thought of as addressing the hypothetical question a) for these subjects.

Impute responder status at the endpoint visit under MAR assumptions
The imputation of responder status at the endpoint visit under MAR assumptions will be carried out as outlined in Section 14.3.2.1.

Impute responder status at the endpoint visit based on NRI
For each of the 250 copies of the dataset generated in the previous step, NRI will be carried out by imputing subjects in scope as non-responders.

Impute treatment adherence status at the endpoint visit
For each treatment arm, a Cox proportional hazards regression model will be fit for the hazard rate of permanent discontinuation of IMP not due to pandemic restrictions. The models will be stratified by baseline body weight (<70 kg and ≥70 kg), and will include baseline PASI score as a continuous covariate. The time to permanent discontinuation of IMP not due to pandemic restrictions or initiation of rescue treatment 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 the endpoint visit, say at time t, the model will provide an estimated probability

$$\hat{p}(t, \text{treatment arm, baseline body weight, baseline PASI score})$$

of being on treatment at the endpoint visit conditional on being on treatment at the earlier time t in the hypothetical 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 the endpoint visit divided by the same function evaluated at time t.

For each subject having discontinued treatment prior to the endpoint visit due to pandemic restrictions and each of the 250 copies of the dataset a Bernoulli trial with the subject-specific success probability $\hat{p}$ will be performed (seed=183511) 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) stated above.

The imputed value of the estimand's variable will be derived from the responder status at the endpoint visit, 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 not due to pandemic restrictions and initiation of rescue treatment.

Primary analysis

The null hypothesis, that the response rate associated with the adolescent brodalumab dosing regimen is less than or equal to the rate in the placebo arm, will be tested againist the alternative that brodalumab is superior to placebo. For each of the 250 complete data sets, the difference in response rates between treatment arms will be analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline body weight (<70 kg and ≥70 kg) for the composite endpoint. The estimated common risk difference, across the strata defined by baseline body weight (<70 kg and ≥70 kg), between treatment arms and the corresponding standard errors from the 250 analyses will be pooled to one estimated treatment difference and associated standard error using Rubin's rule to draw inference. From these pooled estimates, the 95% CI for the treatment difference will be calculated.

The test-statistics will be pooled based on the procedure proposed by Li et al (70) and outlined by Ratitich, Lipkovich, and O'Kelly (71) in order to derive the final p-value.

In the event of a potential disagreement between the pooled p-value and 95% CI for estimated treatment difference, inference will be based on the pooled p-value.

Sensitivity analysis

The sensitivity analysis will be conducted based on the stratified CMH test, specified for the primary analysis. The sensitivity analysis will assess the robustness of the results of the primary analysis with respect to the NRI.

Subjects for whom no data for the primary endpoint has been collected at the endpoint visit for reasons other than pandemic restrictions will be imputed as in Step no. 1 rather than Step no. 2 of Panel 22, corresponding to imputation of all missing responder status data at the endpoint visit under MAR assumptions.

14.3.6.1.2 Secondary estimand for binary endpoints

The secondary estimand will assess the expected difference in response rates irrespective of initiation of rescue treatment or permanent discontinuation of IMP not due to pandemic restrictions, as if the conduct of the trial was not impacted by pandemic related restrictions.

With the "treatment-policy" strategy, the initiation of rescue treatment or permanent discontinuation of IMP not due to pandemic restrictions will be ignored, i.e., observations occurring after these intercurrent events will be incorporated into the analysis.

Missing data at the endpoint visit will be imputed assuming missing at random.

Permanent discontinuation of IMP due to pandemic restrictions will be addressed by the same hypothetical strategy as for the primary estimand, with the exceptions that:

- Data collected from subjects who have permanently discontinued IMP not due to pandemic restrictions or initiated rescue treatment prior to the endpoint visit will be included when performing Step no. 1 of the multiple imputation method, and
- Step no. 2 and 3 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 not due to 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 primary analysis of the secondary estimand for binary endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute responder status at the endpoint visit under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit	Hypothetical strategy
		Subjects whose score at the endpoint visit is missing	Handling of missing data

Abbreviations: IMP, investigational medicinal product; MAR, missing at random.

The analysis will be done as specified for the primary analysis of the primary estimand for binary endpoints.

Sensitivity analyses

Additional analyses of this estimand will assess the robustness of the imputation method for subjects with missing data at the endpoint visit for reasons other than pandemic restrictions. Imputation methods to be used for these analyses include:

- 'Control-based' pattern mixture model.
- NRI.

The hypothetical strategy and the handling of missing data for the sensitivity analyses are outlined in Panel 24.

Panel 24: Hypothetical strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the sensitivity analyses of the secondary estimand for binary endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute responder status at the endpoint visit under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit	Hypothetical strategy
		Subjects who have not experienced an intercurrent event and whose score at the endpoint visit is missing due to pandemic restrictions	Handling of missing data
2	Impute responder status at the endpoint visit based on 'control-based' pattern mixture model or NRI	Subjects who have not experienced an intercurrent event and whose score at the endpoint visit is missing for reasons other than pandemic restrictions	Handling of missing data

Abbreviations: IMP, investigational medicinal product; MAR, missing at random; NRI, non-responder imputation.

14.3.6.1.3 Supplemental analyses

For binary endpoints assessed over the duration of the trial, from Week 0 to Week 52, a supplementary analysis based on a GEE model will be carried out to illustrate the trajectory of the treatment response over the duration of the trial. The GEE model for longitudinal binary data will be based on specifying the logit link function and visit, visit by treatment interaction, baseline value, and baseline body weight (<70 kg and ≥70 kg) as fixed effects. The working correlation matrix will be specified as having an unstructured form. In the event that this model fails to converge, the model should be fit using a compound symmetry working correlation matrix.

The results of the GEE model will be presented as a figure, displaying the estimated response rates over the duration of the trial for the 4 treatment arms, along with tables providing the least squares (LS)-mean estimated response rates, difference in LS-mean response rates and associated approximate 95% CI based on the Delta-method, odds ratio and associated 95% CI and p-value. The analysis will be performed for the FAS. Subjects who initiate rescue treatement or permanently discontinue IMP not due to pandemic restrictions will be defined as non-responders. Monotone missing data for reasons other than pandemic restrictions will be imputed using NRI. Subjects who permanently discontinue IMP due to pandemic

restrictions, intermittent missing data, and monotone missing data due to pandemic restrictions will be assumed missing completely at random.

For the Week 12 PASI, sPGA, CDLQI, and FDLQI responder endpoints, the estimated cumulative incidence functions for the time from randomisation to first satisfying the responder criteria for the brodalumab, ustekinumab, and pooled placebo arms will be presented based on the Aalen-Johansen estimator. The analysis will account for the competing risks, IMP discontinuation and initiation of rescue treatment. p-values based on Gray's test for the cumulative incidence of satisfying the responder thresholds will be presented for the pairwise comparisons, brodalumab vs pooled placebo and brodalumab vs ustekinumab.

14.3.6.2 Estimand strategy for continuous endpoints

14.3.6.2.1 Primary estimand for continuous endpoints

The estimand is defined as the treatment difference in the LS-mean change from baseline at the endpoint visit irrespective of initiation of rescue treatment or permanent discontinuation of IMP not due to pandemic restrictions, as if the conduct of the trial was not impacted by pandemic related restrictions.

With the treatment policy strategy, subjects who have permanently discontinued IMP not due to pandemic restrictions or initiated rescue treatment prior to the endpoint visit will be included in the analysis with the observed score at this visit.

Permanent discontinuation of IMP due to pandemic restrictions will be addressed by a hypothetical strategy. Data collected after such an event will not be applied in the analysis. The hypothetical scenario envisaged is that permanent discontinuation of IMP due to pandemic restrictions would not occur, assuming that subjects who have experienced this event would respond like subjects from the same treatment arm who have not experienced it. The hypothetical strategy and the handling of missing data in the primary analysis are outlined in Panel 25.

Panel 25: Hypothetical strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the primary analysis of the primary estimand for continuous endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute score at the endpoint visit under MAR assumptions	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit	Hypothetical strategy
		Subjects whose score at the endpoint visit is missing	Handling of missing data

Abbreviations: IMP, investigational medicinal product; MAR, missing at random.

The imputation of scores will be carried out like the imputation of PASI scores for the secondary estimand for binary endpoints. Data collected from subjects who have permanently discontinued IMP not due to pandemic restrictions or initiated rescue treatment will be included when applying this multiple imputation method, in alignment with the treatment policy strategy used for addressing occurrences of that intercurrent event.

Primary analysis

For each of the 250 datasets, analysis will be based upon an ANCOVA model including treatment arm and baseline body weight as factors and adjusting for baseline score as covariate.

The pooled estimated difference in the LS-mean change from baseline at the endpoint visit, and the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rule to the estimates and standard errors from the aforementioned ANCOVA analyses of the imputed datasets.

14.3.6.3 Estimand strategy for vaccine-related endpoints

14.3.6.3.1 Estimand for binary vaccine-related endpoints

The hypothetical estimand is defined as the treatment difference in the response rates if all subjects adhered to the treatment regimen, in the sense that they did not discontinue IMP treatment (regardless of relation to pandemic restrictions) and rescue treatment was not made available prior to endpoint visit.

For this approach, data collected following discontinuation of IMP or the initiation of rescue treatment, is excluded from the analysis. Instead, missing data is imputed based on a multiple imputation algorithm outlined in Section 14.3.2.1, assuming that missing data is MAR within each treatment arm.

In order to account for the use of different vaccines, depending on the adolescents' vaccine history, the analysis will be performed by fitting a logistic regression model, including fixed effects for baseline, treatment, baseline body weight (<70 kg and ≥70 kg), and vaccine type. In the event that issues arise fitting the model(s) due to the fixed effects for baseline and vaccine type, the model(s) will be re-fit excluding the relevant term(s). The logistic regression model will be used to estimate the risk difference and associated 95% confidence interval based on the standardised estimator presented in Ge et al (76).

14.3.6.3.2 Estimand for continuous vaccine-related endpoints

The estimand is defined as the treatment difference in the LS-mean change from baseline at the endpoint visit if all subjects adhered to the treatment regimen, in the sense that they did not permanently discontinue IMP and rescue treatment was not given prior to the endpoint visit.

Permanent discontinuation of IMP or initiation of rescue treatment will be addressed by a hypothetical strategy that depends on the reason for treatment discontinuation. Data collected after permanent discontinuation of IMP or initiation of rescue treatment will not be applied in the analysis. The hypothetical scenario envisaged is that permanent discontinuation of IMP or rescue treatment would not occur, assuming that subjects who have permanently discontinued IMP (regardless of relation to the pandemic) or initiated rescue medication would respond like subjects having remained on treatment from the same treatment arm without initiation of rescue treatment.

The hypothetical strategy is outlined in Panel 26, together with the handling of missing data in the analysis.

Panel 26: Hypothetical strategy for addressing permanent discontinuation of IMP and rescue treatment and handling of missing data in the analysis of the secondary estimand for continuous secondary endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute score at the endpoint visit under MAR assumptions	Subjects who have permanently discontinued IMP (regardless of relation to the pandemic) or who have initiated rescue treatment prior to the endpoint visit	Hypothetical strategy
		Subjects whose score at the endpoint visit is missing	Handling of missing data

Abbreviations: IMP, investigational medicinal product; MAR, missing at random.

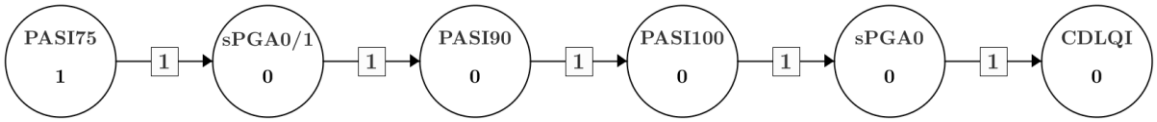
For each of the 250 datasets, analysis will be based upon an ANCOVA model including treatment arm and baseline body weight as factors and adjusting for baseline score as covariate.

The pooled estimated difference in the LS-mean change from baseline at the endpoint visit, and the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rule to the estimates and standard errors from the aforementioned ANCOVA analyses of the imputed datasets.

14.3.7 Testing Strategy

To control the familywise error rate of the analysis of the pre-specified primary and key secondary endpoints, the following hierarchical testing procedure, illustrated in Panel 27, has been defined. The hierarchial testing procedure, will assess the difference in the response rates between the adolescent brodalumab dosing regimen and pooled placebo arms at Week 12, with respect to the specified endpoints. For the purposes of controlling the familywise error rate, the test of the null hypothesis will be based on the primary analysis of the primary estimand for binary endpoints. As stated in Section 14.3.1, the hypotheses in Panel 27 will be tested at a 5% significance level. The initial weight allocated to each hypothesis test is specified in Panel 27. Initially, 100% of the weight is allocated to the hypothesis test of the primary endpoint. If a given hypothesis is rejected, the arrows in Panel 27 specify how the allocated alpha for the rejected hypothesis is redistributed among the remaining hypothesis tests.

Panel 27: Hierarchical testing procedure to control the familywise error rate for the pre-specified primary and key secondary endpoints



Abbreviations: CDLQ, Children's Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.

14.3.8 Analysis of efficacy endpoints

An overview of the analyses for efficacy endpoints can be found in Panel 28.

Panel 28: Overview of statistical analyses

Endpoint	Type of endpoint	Primary estimand	Comparison
Primary endpoint			
PASI 75 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
Key secondary endpoints			
sPGA score of 0 or 1 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
sPGA score of 0 at Week 12.	Binary.	Primaryestimand for binary endpoints.	Brodalumab vs placebo.
PASI 90 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
PASI 100 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
CDLQI score of 0 or 1 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
Secondary and other endpoints			
FDLQI score of 0 or 1 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs placebo.
PASI 75 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
PASI 75 response at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
PASI 90 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
PASI 90 response at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
PASI 100 response at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
PASI 100 response at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.

Endpoint	Type of endpoint	Primary estimand	Comparison
sPGA score of 0 or 1 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
sPGA score of 0 or 1 at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
sPGA score of 0 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
sPGA score of 0 at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
CDLQI score of 0 or 1 at Week 12	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
CDLQI score of 0 or 1 at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
FDLQI score of 0 or 1 at Week 12.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
FDLQI score of 0 or 1 at Week 52.	Binary.	Primary estimand for binary endpoints.	Brodalumab vs ustekinumab.
aTTA ≥0.1 IU/mL at Week 12.	Binary.	Estimand for binary vaccine-related endpoints.	Brodalumab vs placebo.
Change from baseline in aTTA at Week 8 and Week 12.	Continuous.	Estimand for continuous vaccine-related endpoints.	Brodalumab vs placebo.
Change from baseline in lymphocyte subsets at Week 12.	Continuous.	Estimand for continuous vaccine-related endpoints.	Brodalumab vs placebo.
Booster response to TT-containing vaccine, defined as: • 3-fold increase in aTTA at Week 12, if the subject has a baseline aTTA ≤1.0 IU/mL. • ≥2.5 IU/mL increase in aTTA at Week 12, if the subject has a baseline aTTA >1.0 IU/mL.	Binary.	Estimand for binary vaccine-related endpoints.	Brodalumab vs placebo.
Change from baseline in average weekly itch severity.	Continuous.	Primary estimand for continuous endpoints.	Brodalumab vs placebo. Brodalumab vs ustekinumab.

Endpoint	Type of endpoint	Primary estimand	Comparison
Improvement of at least 4 units in average weekly itch severity.	Binary.	GEE analysis based on the average weekly itch severity scores calculated for the continuous endpoint.	Brodalumab vs placebo. Brodalumab vs ustekinumab.
Change from baseline in average weekly itch-related sleep.	Continuous.	Primary estimand for continuous endpoints.	Brodalumab vs placebo. Brodalumab vs ustekinumab.

Abbreviations: aTTA, anti-tetanus toxoid antibodies; CDLQ, Children's Dermatology Life Quality Index; FDLQI, Family Dermatology Quality Index; GEE, generalised estimating equation; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; TT, tetanus toxoid. 3 (3)

14.3.9 Analysis of other endpoints

Itch severity and itch-related sleep loss will be assessed daily, based on an 11-point NRS, with '0' indicating 'no itch' / 'itch did not interfere' up to '10' indicating 'worst itch possible' / 'completely interfered'. The analysis will be based on assessing the difference in the LS-mean change from baseline in the average weekly itch severity and itch-related sleep loss. The baseline average weekly itch assessments will be based on the assessments recorded between Day -6 and Day 0 (pre-dose). The daily itch assessments used to calculate the average weekly itch severity and itch-related sleep loss will be anchored to the date of randomisation. For example, assessments recorded on Day 1 through Day 7 will be used to calculate the average itch during Week 1, assessments recorded on Day 8 through Day 14 will be used to calculate the average itch during Week 2, etc. In order to assess the average weekly itch severity/itch-related sleep loss, a minimum of 4 out of the 7 planned assessments must be recorded. Otherwise, the average weekly itch severity/itch-related sleep loss score will be considered missing. The primary estimand for continuous endpoints will be applied for this endpoint.

Moreover, the differences in the LS-mean change from baseline at Week 12 between adolescent brodalumab dosing regimen and the pooled placebo arms, as well as from baseline to Week 12 and Week 52 between the adolescent brodalumab dosing regimen and ustekinumab arms, will be presented along with the corresponding 95% CIs and nominals p-values, based on an MMRM, with an unstructured covariance matrix, the Kenward-Roger approximation for estimating the denominator degrees of freedom and the following mean model:

- Change from baseline = treatment + week + treatment × week + baseline body weight + baseline value.

Baseline body weight will be included in the mean model as a fixed effect factor, based on the levels defined by the randomisation strata. Plots of the LS-mean change from baseline in average weekly itch severity and itch-related sleep loss will be presented over the entire 52-week treatment phase for each treatment arm, based on the above MMRM.

In addition to the above MMRM analysis of the mean change from baseline in average weekly itch severity and itch-related sleep loss, a responder analysis will also be conducted for the weekly average itch severity endpoint among the subset of subjects with a weekly average itch severity of at least 4 units at baseline. A GEE model with logit link function will be used to assess the proportion of subjects who have achieved a reduction of at least 4 units in average weekly itch severity over the 52-week assessment period. The working correlation matrix for the GEE model will have an unstructured form and the linear predictor will take the same form, as the above MMRM for the mean change from baseline in average weekly itch severity and itch-related sleep loss. Subjects who initiate rescue treatement or permanently discontinue IMP not due to pandemic restrictions will be defined as non-responders. Monotone missing data for reasons other than pandemic restrictions will be imputed using NRI. Subjects who permanently discontinue IMP due to pandemic restrictions, intermittent missing data, and monotone missing data due to pandemic restrictions will be assumed missing completely at random. The estimated proportion and difference in proportion of subjects achieving the responder status will be presented at Week 12 and Week 52, along with corresponding CIs and nominal p-values along with plots showing the responder rate over the entire treatment phase, for all treatment arms. In the event that either model fails to converge, the model will be fit assuming a compound symmetry working correlation matrix/covariance matrix.

14.3.10 Analysis of safety

The analysis of safety will be based on the safety analysis set. The reporting of safety data will be presented for the 12-week induction period and the entire 52-week treatment phase separately. For the summaries of the 52-week treatment phase, data will only be presented for the pooled brodalumab and ustekinumab arms. In other words, subjects initially on placebo, will only contribute data to the 52-week safety summaries after they initiate active treatment at Week 12.

14.3.10.1 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 terms (PTs) 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 dosing; if outcome is missing, and no date of outcome is present, the outcome is regarded as 'not recovered'.

Treatment-emergent AEs (TEAEs) 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 started after the first use of IMP or if started before the first use of IMP and worsened in severity after first dose of IMP. The tabulations described in the following, will only include treatment-emergent events reported prior to or at the Week 60 safety follow-up visit. Tabulations of TEAEs will be presented for the following 2 scenerios:

- "While exposed to IMP", defined as TEAEs occurring within 5 x half-lifes of the most recent date of IMP administration (body weight specific half-lifes for brodalumab are based on PK modelling):
    - Brodalumab and baseline weight ≥30 kg up to but not including 50 kg – 55 days.
    - Brodalumab and baseline weight ≥50 kg up to but not including 70 kg – 35 days.
    - Brodalumab and baseline weight ≥70 kg – 55 days.
    - Ustekinumab – 105 days.
- "While in trial", defined as all TEAEs observed during the duration of the trial.

In order to facilitate a comparison versus placebo for the 'while exposed to IMP' scenario, the same baseline body weight specific time-periods specified for the brodalumab arm will be used for the placebo arm. In each of the tabulations, AEs are defined by MedDRA PTs within primary SOC. 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, premature discontinuations due to AEs, treatment-related AEs, and severe AEs will be presented.

The number and percentage of subjects reporting an event along with the number of events and the event rate per 100 subject-years for each type of AE, will be tabulated and presented by treatment arm.

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.

The causal relationship to vaccine for each type of AE will be tabulated by treatment group for the induction phase. AEs related to the vaccine are defined as AEs for which the investigator has not described the causal relationship to vaccine as 'not related'. The number AEs related to the vaccine, the number of subjects with each type of AE related to the vaccine, and the event rate per 100 subject-years for each type of 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. No narratives will be given.

Other events (medication error, misuse, and abuse of IMP) will be tabulated and listed. No narratives will be given.

14.3.10.2 Adverse events of special interest

The adverse events of special interest (AESI) for the trial are classified as important identified and important potential risks. The AESI will be tabulated and listed by treatment arm for the 12-week induction period and the entire 52-week treatment phase separately according to the safety analysis set. Panel 29 provides search criteria for the AESI.

Panel 29: Search criteria for AESI

Adverse events of special interest	Search criteria
Important identified risk	
Serious infections	MedDRA SOC: Infections and infestations; only events classified as SAE.
Important potential risks	
Suicidal ideation and behaviour	MedDRA SMQ: Suicide/self-injury (narrow).
MACE	MedDRA SMQ: Ischaemic heart disease (narrow). MedDRA SMQ: Ischaemic central nervous system vascular conditions (narrow).
Malignancy	MedDRA SMQ: Malignant or unspecified tumours (narrow).

Adverse events of special interest	Search criteria

Abbreviations: MACE, major adverse cardiac events; MedDRA, medical dictionary for regulatory activities; SMQ, standardised MedDRA queries; SOC, system organ class.

14.3.10.3 Vital signs

The change in vital signs (blood pressure, pulse, body temperature) from baseline to each visit will be summarised by visit and treatment arm as mean, SD, median, 1st quartile, 3rd quartile, minimum, and maximum values for the safety analysis set.

14.3.10.4 Clinical laboratory evaluation

The change in each of the laboratory parameters from baseline to each visit will be summarised by visit and treatment arm as mean, SD, median, 1st quartile, 3rd quartile, 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.

14.3.10.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The most severe CSSRS 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. 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. Prepatory 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.

Separate tables for the 12-week induction period and the overall treatment phase will be presented. For the induction period, a pooled placebo arm will be presented along with the brodalumab and ustekinumab arms. For the overall treatment phase, only the pooled brodalumab and ustekinumab arms will be presented.

14.3.10.6 Patient Health Questionnaire-A (PHQ-A)

The most severe PHQ-A 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. 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).

Separate tables for the 12-week induction period and the overall treatment phase will be presented. For the induction period, a pooled placebo arm will be presented along with the brodalumab and ustekinumab arms. For the overall treatment period, only the pooled brodalumab and ustekinumab arms will be presented.

14.3.11 Anti-drug antibodies

ADA status (positive, negative, missing assessment) will be summarised according to the number and percentage of subjects in each category, by treatment arm for the safety analysis set at Weeks 0, 4, 16, and 52.

14.3.12 Pharmacokinetics

The following PK parameters will be derived based on the PK analysis set:

C_{trough}	Trough (pre-dose) serum concentrations at Weeks 4, 8, 12, 16, and 52 (for brodalumab arm) and Weeks 4 and 40 (for placebo followed by brodalumab arm).
C_{W10}	Serum concentration sampled during Week 10 (for brodalumab arm) and during Week 22 (for placebo followed by brodalumab arm).
C_{W22}	Serum concentration sampled during Week 22 (for brodalumab arm).

The following PK parameter will be estimated based on the population PK analysis set:

AUC_{W10-12}	Area under the serum concentration-time curve at Week 10-12.

Due to sparse blood sampling, the AUC at Week 10-12 for the individual subjects will be estimated using a population PK analysis approach (77). Overall, the population PK model developed based on adult data from healthy subjects and subjects with plaque psoriasis will be used to derive individual model parameter estimates for the adolescents who have received brodalumab. Individual AUCs at Week 10-12 will be determined based on the individual model parameters. The details of the analysis will be specified in a population PK analysis plan prior to trial unblinding.

AUC will be listed and summarised per treatment arm (brodalumab arm and placebo followed by brodalumab arm) and combined. For subjects in the PK analysis set who have no quantifiable concentration, the AUC will be set to 'not calculated' and included in the listing, but excluded from the summary statistics. C_{trough} will be listed and summarised per treatment arm and combined (Week 4 [for brodalumab arm] and Week 16 [for placebo followed by brodalumab arm]). C_{W10} and C_{W22} will be listed. In the summary statistics, values below lower limit of quantification (LLOQ) will be set to 0.5*LLOQ.

14.3.13 Interim analysis

No interim analysis is planned.

15 References

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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 (78).

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*.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.5.2).

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

*Hospitalisation for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as an AE or SAE.

*Hospitalisation for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as an AE or SAE, even if not planned before consent to trial participation.

*Hospitalisation for routine scheduled treatment or monitoring of the studied indication not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as an AE or SAE.

*Hospitalisation for administrative, trial-related, or social purpose does not constitute an AE and should therefore not be reported as an AE or SAE.

*Complications that occur during hospitalisation are (S)AEs. If a complication prolongs hospitalisation, the event is an SAE.

*When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.

AEs of special interest 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. The categories are defined below.

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. Follow-up on an event is required until final outcome is established as described in Section 13.7.

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.

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 (79) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (80).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (81).
- EU's 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 IECs may need to fulfil their responsibilities (such as the trial protocol, protocol amendments, investigator's brochure, subject information sheet and informed consent/assent form(s), or advertisements) will be submitted to the IECs. These documents must be reviewed and approved by the IECs 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 and the subject's legally authorised representative(s) 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 and the subject's legally authorised representative(s) will

be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's legally authorised representatives' signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the informed consent form. The subject's decision not to participate or to withdraw will be respected, even if consent is given by the subject's legally authorised representative(s).

The subject's legally authorised representatives' will be re-consented to the most current version of the informed consent form(s) during the trial, if applicable.

A copy of the informed consent form(s) must be provided to the subject's legally authorised representative(s).

Subjects must give their written assent or consent as appropriate according to national laws and regulation. The subject's signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations. Subject will be re-consented to the most current version of the informed consent form(s) during the trial, if applicable and in accordance with national laws and regulations. A copy of the informed consent form(s) must be provided to the subject in accordance with national laws and regulations.

Subjects who become of legal age during the trial, will be consented to the most current version of the informed consent form for the subject's legally authorised representative, if required by national laws or regulations. Subsequently, these subjects will be re-consented to the most current version of the informed consent form for the subject's legally authorised representative during the trial, if applicable.

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 and consent to 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, gender, 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. 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 (or their legally acceptable representative[s]) 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

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 a physician.

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 ustekinumab for 52 weeks or placebo for 12 weeks followed by brodalumab or ustekinumab for 40 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, e.g., medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and important 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 eCRFs. Data recorded in the eCRFs will be accessible

to the trial site and LEO Pharma personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require 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 patient-reported outcome (ePRO) solution will be used to capture some of the patient-reported data. By the use of an ePRO solution, data will be available immediately after data entry and available for monitors and site personnel, including the investigator, with read access only. The ePRO system is a separate application from the eCRF and data captured from the eCRF and the ePRO will be stored on different servers during data capture. Data from both systems will be included in the final trial database.

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

Transmission of data is documented in more detail in the trial-specific data flow plan, which is part of the trial master file.

Software
CDISC controlled terminology version 30-Mar-2018 or newer 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 1.5 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 (81). 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 leopharmatrials.com in accordance with our Position on Public Access to Clinical Trial Information no later than 6 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 investigator in accordance with the process described here.

A multi-centre 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-centre publication is made public, or if no multi-centre 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-centre 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-centre publication.

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

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 (46).

Appendix 3F: Insurance

LEO Pharma A/S has taken out relevant insurances covering the participants in this 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: Data monitoring committee structure

Safety of the subjects will be carefully assessed by an independent DMC. All members will be independent of the trial (that is, they will not be participating investigators or employees at participating sites) and of LEO Pharma (that is, they will not be LEO Pharma employees). The DMC members are experienced with clinical trials and will be responsible for assessing the safety of the subjects through assessment of the safety of the treatment regimen during the trial and through monitoring the overall conduct of the trial.

The DMC will review data on a regular basis. Additional meetings may also be called on an ad hoc basis, as requested by the DMC or LEO Pharma. All data collected at the time of the data cut-off/scheduled meetings will be included in the summaries for the DMC, including data from subjects still ongoing in the trial. The DMC will examine summaries and listings of AEs, specific laboratory parameters and subject disposition data as detailed in the DMC charter. Full details of the analyses to be presented to the DMC will be specified in a separate DMC statistical analysis plan.

The DMC will have an independent statistician and an independent administrator who will remain independent of the trial management team.

The chairman of the DMC, in conjunction with the other members, will communicate their recommendations to LEO Pharma A/S after each meeting. The chairman of the DMC will provide written reports to LEO Pharma after each formal review to indicate the committee's recommendation regarding safety concerns and trial continuation. Further details on all aspects relating to the DMC are provided in the DMC charter.

Appendix 3I: Trial and site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IECs, or the 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 the 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´s 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: WHO model prescribing information for classification of topical corticosteroids

Potency	Class	Topical corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream, 0.05%
		Diflorasone diacetate	Ointment, 0.05%
High	II	Amcinonide	Ointment, 0.1%
		Betamethasone dipropionate	Ointment, 0.05%
		Desoximetasone	Cream or ointment, 0.025%
		Fluocinonide	Cream, ointment or gel, 0.05%
		Halcinonide	Cream, 0.1%
	III	Betamethasone dipropionate	Cream, 0.05%
		Betamethasone valerate	Ointment, 0.1%
		Diflorasone diacetate	Cream, 0.05%
		Triamcinolone acetonide	Ointment, 0.1%
Moderate	IV	Desoximetasone	Cream, 0.05%
		Fluocinolone acetonide	Ointment, 0.025%
		Fludroxycortide	Ointment, 0.05%
		Hydrocortisone valerate	Ointment, 0.2%
		Triamcinolone acetonide	Cream, 0.1%
	V	Betamethasone dipropionate	Lotion, 0.02%
		Betamethasone valerate	Cream, 0.1%
		Fluocinolone acetonide	Cream, 0.025%
		Fludroxycortide	Cream, 0.05%
		Hydrocortisone butyrate	Cream, 0.1%
		Hydrocortisone valerate	Cream, 0.2%
		Triamcinolone acetonide	Lotion, 0.1%
Low	VI	Betamethasone valerate	Lotion, 0.05%
		Desonide	Cream, 0.05%
		Fluocinolone acetonide	Solution, 0.01%
	VII	Dexamethasone sodium phosphate	Cream, 0.1%
		Hydrocortisone acetate	Cream, 1%
		Methylprednisolone acetate	Cream, 0.25%

Source: Word Health Organization. WHO model prescribing information: drugs used in skin diseases. Annex: Classification of topical corticosteroids. Geneva. 1997. http://apps.who.int/medicinedocs/en/d/Jh2918e/32.html#Jh2918e.32.1

Appendix 5: Contact list

Contact details for the clinical project manager, national lead 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

Signatory investigator

[redacted]

Appendix 6: Protocol amendment history

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

Amendment 1 (10-Jun-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 comments received during the Voluntary Harmonisation Procedure, were to:

- Extend the interval of prior tetanus-toxoid containing vaccination for inclusion into the trial in countries in EU + UK.
- Include additional blood sampling at Weeks 28, 36, and 44 for analysis of haematology and chemistry parameters.
- Include a recommendation regarding rescue treatment in case of inadequate disease control.

Furthermore, exclusion criteria #16 and #31 were updated and additional changes included in the amendment are presented in the table below. The table on the following pages describes the changes in each section, summarised as plain text, and/or 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
Synopsis – Main criteria for exclusion – 2nd bullet point; Section 8.3 Exclusion criteria – Exclusion criterion number 2.	Exclusion criterion number 2 has been updated with the following change: Subject has been vaccinated with a TT-containing vaccine ≤18 months prior to first dose of investigational medicinal product (IMP). **Subject has been vaccinated with a TT-containing vaccine within 5 years prior to the first dose of IMP - applicable for countries in EU + UK**.	Updated to extend the interval of prior tetanus-toxoid containing vaccination for inclusion into the trial in countries in EU + UK.
Section 4 Schedule of trial procedures, Panel 3.	Panel 3 has been updated as additional haematology and chemistry blood samples will be collected at Visits 16, 18, and 20.	Updated to be able to monitor laboratory values between Week 22 and Week 52.

Section no. and name	Description of change	Brief rationale
Section 5.1 Plaque psoriasis.	The definition of psoriasis has been rephrased: Psoriasis is **a chronic, immune-mediated inflammatory disorder** ~~an inflammatory skin disease~~	Updated to clarify that psoriasis is not just a skin disease.
Section 5.4 Ethical considerations.	This section has been updated with the following change: Thus, the subjects who ~~have received the adolescent dose of Td or~~ have not yet received the scheduled adolescent dose of Td/Tdap will be vaccinated with a booster **based on the subject's previous history of vaccination with TT-containing vaccines and current local guidelines**~~dose of Tdap in this trial, which is in compliance with the current recommendations on prevention of pertussis infection. The subjects who have received the adolescent dose of Tdap vaccine will be vaccinated with a dose of Td in the trial.~~	Updated to reflect the change in exclusion criterion number 2.
Section 7.1.3.2 Vaccination (Week 8).	The following text has been added in this section: • **Subjects who have not received the scheduled adolescent dose of Td/Tdap for the last 5 years will be vaccinated with a booster based on the subject's previous history of vaccination with TT-containing vaccines and current local guidelines.**	Updated to reflect the change in exclusion criterion 2.
Section 8.3 Exclusion criteria, Exclusion criterion 16.	Exclusion criterion number 16 has been updated with the following: Subject has positive hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C virus antibody, or human immunodeficiency virus serology at screening. **Subjects with positive hepatitis B surface antibody are eligible provided they have negative hepatitis B surface antigen and negative hepatitis B core antibody (blood pattern in hepatitis B vaccinated subjects).**	Updated to clarify the exclusion criterion for subjects with positive hepatitis B surface antibodies.
Section 8.3 Exclusion criteria, Exclusion criterion 31.	The following bullet point has been added in exclusion criterion number 31: • **Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2.**	Updated to clarify the threshold for eGFR.
Section 9.2.2 Administration of vaccine.	This section has been updated with the following change: The type of vaccine each subject will receive is based on the subject's previous history of vaccination with TT-containing vaccines **and**	Updated to reflect the change in exclusion criterion 2.

Section no. and name	Description of change	Brief rationale
	current local guidelines (see Section 7.1.3 for further details).	
Section 9.5 Rescue treatment.	This section has been updated with the following change: The investigator is responsible for the rescue treatment **oversight and** duration as well as switch**ing and escalating** to another ~~appropriate~~ therapy, when **appropriate**~~indicated~~. **However, it is recommended that the efficacy of the topical rescue treatment should be re-evaluated after 4 weeks of treatment and subjects who are still inadequately controlled (defined as a PASI score ≥150% of baseline PASI) might be escalated to an appropriate subsequent therapy (refer to Section 9.7 for prohibited medications and Section 10.2 for IMP discontinuation rules).**	Updated to clarify that investigator is responsible for the oversight of rescue treatment and to include recommendations for the use of rescue treatment in case of inadequate disease control.
Section 11.4.5.1 Overview of all laboratory tests, Panel 18.	eGFR and a reference to the Schwartz formula have been added in Panel 18: **Estimated glomerular filtration rate (eGFR)[2]** [2] Measured at screening only. **The eGFR will be calculated using the Schwartz formula (52).**	Updated to reflect the updated exclusion criterion number 31.
Section 11.8 Estimate of total blood volume collected.	This section has been updated with the following change: The total volume of blood to be drawn in the trial corresponds to approximately ~~27~~**33**% of blood volume drawn during a single blood donation (approximately 500 mL).	Updated to be able to monitor laboratory values between Week 22 and Week 52.
Throughout	Minor editorial revisions.	Minor, and are therefore not summarised.

Signature Page for TMF-000115641 v6.0

Reason for signing: Approved	Manage rdict(s) Name: [redacted] Capacit Date of signature: 04-Oct-2021 22:04:39 GMT+0000
Reason for signing: Approved	Manage Name: [redacted] Capacit Date of signature: 05-Oct-2021 06:09:50 GMT+0000
Reason for signing: Approved	Manage r Verdict(s) Name: [redacted] Capacit Date of signature: 05-Oct-2021 07:00:34 GMT+0000
Reason for signing: Approved	Manage Name: [redacted] Capacit Date of signature: 05-Oct-2021 08:52:06 GMT+0000
Reason for signing: Approved	Manage er Verdict(s) Name: [redacted] Capacit Date of signature: 07-Oct-2021 10:06:26 GMT+0000

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