Cover Page

Study title: Efficacy and safety comparison of brodalumab versus guselkumab in adult subjects with moderate -to -severe plaque psoriasis and inadequate response to ustekinumab; COBRA
LEO Pharma number: LP0160-1510
NCT number: NCT04533737
Date: 02-Feb-2023

Statistical analysis plan

LP0160-1510

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

Design of trial:

Phase 4 – efficacy trial

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

LEO Pharma A/S	**Trial ID:**	**LP0160-1510**
	Date:	**02-Feb-2023**
	Version:	**1.0**

Statistical analysis plan statement

Approval statement, LEO Pharma A/S

Electronic signatures made within LEO Pharma Clinical Vault are legally binding equivalent of traditional handwritten signatures. The following persons have approved this statistical analysis plan by using electronic signatures as presented on the last page of this document:

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Guidance documents

This statistical analysis plan is designed to comply with the standards issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 Structure and Content of Clinical Study Reports, E6 Good Clinical Practice, E9 Statistical Principles for Clinical Trials, and E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials.

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List of panels

List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ADRG	analysis data reviewer's guide
ANCOVA	analysis of covariance
ASDD	analysis set definition document
ATC	Anatomic Therapeutic Chemical Classification
CI	confidence interval
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	clinical trial protocol
CTR	clinical trial report
Define.xml	data definition document
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
eDiary	electronic diary
FAS	full analysis set
FWER	family-wise error rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IE	intercurrent event
IGA	Investigator's Global Assessment
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intention-to-treat
LS	least squares
MAR	missing at random
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index

PASI 90	at least 90% improvement from baseline in PASI score
PASI 100	100% improvement from baseline in PASI score
PCS	physical component summary
PHQ-8	Patient Health Questionnaire-8
PP-IGA	palmoplantar IGA
PP-PASI	palmoplantar PASI
PRO	patient-reported outcome
PT	preferred term
Q2W	every 2 weeks
Q8W	every 8 weeks
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36v2	36-item Short Form Health Survey version 2, acute recall
SIB	suicidal ideation and behaviour
SOC	system organ class
sPGA	static Physician's Global Assessment
sPGA-G	sPGA of genitalia
TFL	Tables, Figures and Listings
TNF-α	tumour necrosis factor-α
TTE	time-to-event

Version history

The statistical analysis plan (SAP) for trial LP0160-1510 is based on the clinical trial protocol (CTP) dated 10-Mar-2022.

SAP version	Date	Change	Rationale
1.0	02-Feb-2023	Not applicable	Original version

1 Introduction

The statistical analysis will be performed as outlined in the CTP version 5.0. This SAP, prepared before the unblinding of the trial, but after the blind review of the data, supplements the CTP and contains a more technical and detailed elaboration of topics related to the specification and implementation of the statistical analysis described in the CTP. The level of detail should enable the reader to reproduce all statistical analyses described in the SAP and the CTP.

Changes to the protocol-planned analyses are described in Section 6.

Data handling decisions and derivation rules used in the analysis datasets are specified in the analysis data reviewer's guide (ADRG) and Data Definition document (define.xml).

1.1 Trial objectives, estimands, and endpoints

Trial objectives and endpoints are presented in Panel 1.

Panel 1. Objectives and endpoints

Objectives	Endpoints
Primary objective	
To compare the efficacy of brodalumab with guselkumab in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Primary endpoint* • Having PASI 100 response at Week 16.
Secondary objectives	
To evaluate the efficacy of brodalumab compared with guselkumab while on treatment for up to 28 weeks in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Key secondary endpoint* • Time to PASI 100 response. *Secondary endpoint* • Time to PASI 90 response.
To evaluate the efficacy of brodalumab compared with guselkumab through Week 28 in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Secondary endpoints* • Having PASI 100 response, assessed separately at Weeks 4, 8, and 28. • Having PASI 90 response, assessed separately at Weeks 4, 8, 16, and 28. • Having IGA of 0, assessed separately at Week 16 and Week 28.

Objectives	Endpoints
	• Having IGA of 0 or 1, assessed separately at Week 16 and Week 28. • Having DLQI total score of 0 or 1, assessed separately at Weeks 4, 8, 12, 16, 20, 24, and 28. • Change in SF-36v2 from baseline, assessed separately at Weeks 4, 8, 16, and 28. *Exploratory endpoints* • Having PASI 100 response, assessed separately at Weeks 1, 2, 6, 10, 12, and 14. • Having IGA of 0, assessed separately at Week 4 and Week 8. • Having IGA of 0 or 1, assessed separately at Week 4 and Week 8. • Having IGA of 0 or 1 and at least a 2-grade improvement from baseline, assessed separately at Week 4, 8, 16, and 28. • Change from baseline in pruritus NRS 11 points (weekly average), assessed separately at Weeks 4, 8, 16, and 28. • Improvement of at least 4 units in pruritus NRS 11 points (weekly average), assessed separately at Weeks 4, 8, 16, and 28. • Change from baseline in pain NRS 11 points (weekly average), separately assessed at Weeks 4, 8, 16, and 28. • Having absolute PASI ≤1, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≤2, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≤3, assessed separately at Weeks 4, 8, 16, and 28. • Having absolute PASI ≤5, assessed separately at Weeks 4, 8, 16, and 28. • Absolute PASI at Weeks 4, 8, 16, and 28. • Having PP-PASI 100 response, assessed separately at Weeks 4, 8, 16, and 28. • Having PP-IGA 0/1 response, assessed separately at Weeks 4, 8, 16, and 28. • Having sPGA-G 0/1 response, assessed separately at Weeks 4, 8, 16, and 28.

Objectives	Endpoints
To evaluate the safety of brodalumab compared with guselkumab throughout the trial (28 weeks) in adult subjects with moderate-to-severe plaque psoriasis and prior inadequate response to ustekinumab.	*Secondary endpoints* • Occurrence of treatment-emergent AEs from baseline to Week 28.

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

Estimands for each type of endpoint in the trial are presented in Panel 2.

Panel 2. Estimands

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

Endpoint type	Primary/ Supplementary[1]	Estimand definition				
		Population	Treatment condition	Variable	Intercurrent events strategy[2]	Population level summary[3]
Time-to-event	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Time to response prior to permanent discontinuation of IMP independent of pandemic restrictions	'While on treatment', 'Hypothetical', 'Treatment-policy'	Aalen-Johansen estimate of the cumulative incidence function
Continuous based on investigator assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Endpoint	'Treatment-policy', 'Hypothetical', 'Treatment-policy'	Difference in LS-means estimated by ANCOVA
Continuous based on subject assessments	Primary	Subjects with an inadequate response to ustekinumab[4]	Brodalumab vs. guselkumab	Endpoint	'Treatment-policy', 'Hypothetical', 'Hypothetical'	Difference in LS-means estimated by ANCOVA

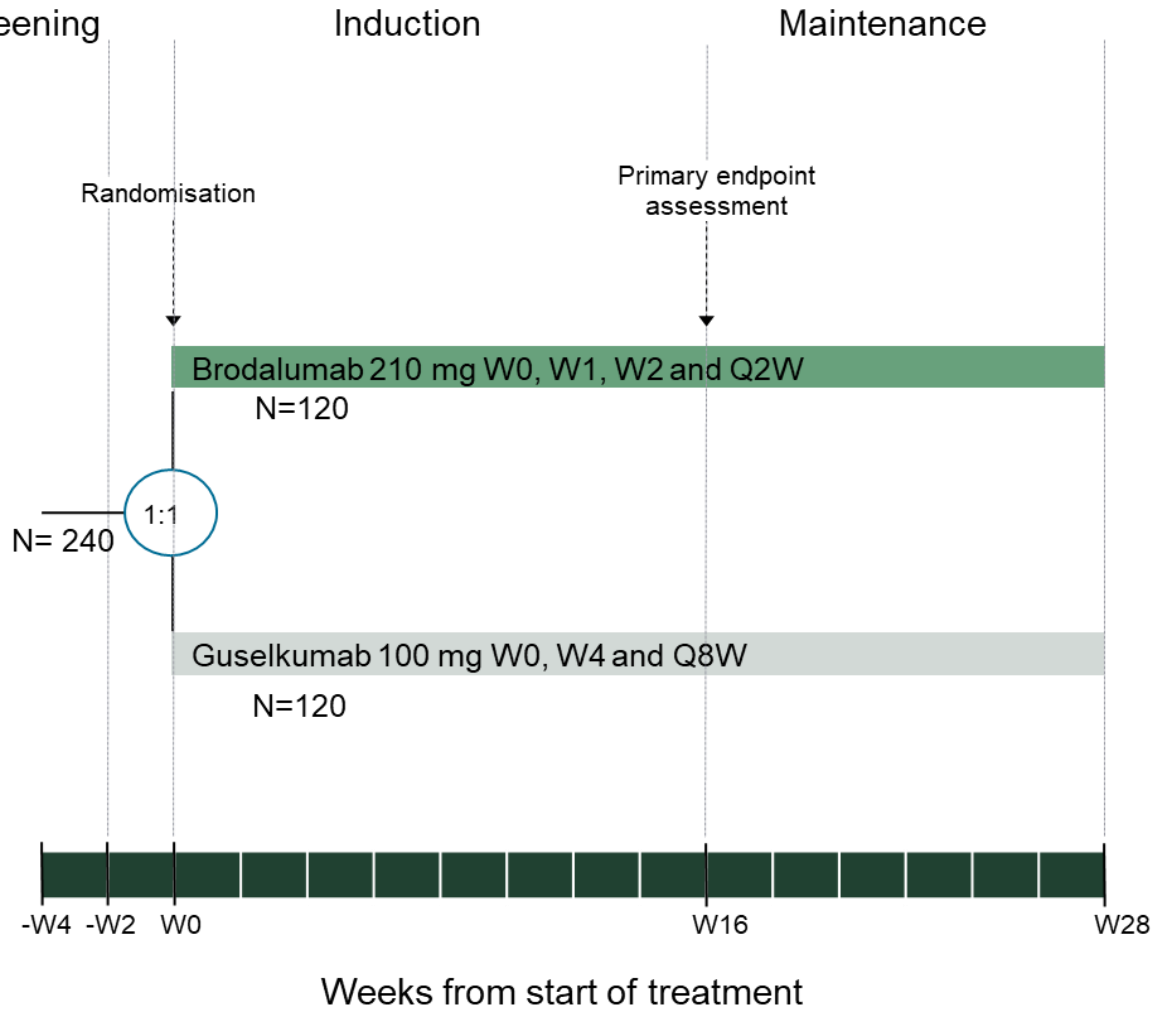
Abbreviations: ANCOVA = analysis of covariance; IMP = investigational medicinal product; LS = least squares.

1) For primary and key secondary endpoints, the main analysis associated with the primary estimand is used to assess significance based on the proposed multiplicity control procedure (see Section 2.1).
2) Refers to the strategies for handling occurrences of the intercurrent events permanent discontinuation of IMP independent of pandemic restrictions, permanent discontinuation of IMP due to pandemic restrictions, and unblinding of subjects, respectively, in the analysis.
3) Refers to the population level summary, which forms the basis for making treatment comparisons.
4) As defined in CTP Sections 8.2 and 8.3. For endpoints based on PP-PASI or PP-IGA, the population is restricted to those subjects with an inadequate response to ustekinumab who have palmoplantar psoriasis. For endpoints based on sPGA-G, the population is restricted to those subjects with an inadequate response to ustekinumab who have genital psoriasis.

1.2 Trial design

This trial is a phase 4, randomised, blinded (subject and assessor), parallel-group, multi-site, clinical trial. The trial is designed to evaluate the efficacy and safety of standard administration of brodalumab compared with standard administration of guselkumab for the treatment of moderate-to-severe plaque psoriasis in adult subjects with inadequate response to ustekinumab. A schematic of the trial design is provided in Panel 3.

Panel 3: Trial design



Abbreviations: Q2W = every 2 weeks; Q8W = every 8 weeks; W = week, N = number of subjects.

Eligible subjects will be randomised to either brodalumab or guselkumab treatment regimen as described below. Randomisation will be stratified by body weight (≤100 kg, >100 kg).

Arm 1 (brodalumab + dummy 1):

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

Arm 2 (guselkumab + dummy 2):

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

Discontinuation and withdrawal

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

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

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

- Permanent discontinuation of IMP occurs when all **further trial treatment** is stopped.
- Withdrawal from trial occurs when all **further trial activities** are stopped before the final visit at Week 28. This can happen either at the same time as permanent discontinuation of IMP or later.

Protocol amendments

As described in Panel 4, the CTP has been amended three times. Please refer to the CTP, dated 10-Mar-2022, for more in-depth descriptions of the changes in each section for each amendment.

Panel 4. Protocol amendments

Document	Date	Short description of changes with potential impact on data interpretation or analysis
Original protocol	18-Jun-2020	Not applicable
Amendment 1 (substantial)	19-Aug-2020	The main reasons for this amendment, based on input provided during the Voluntary Harmonisation Procedure in EU, are: • to add the discontinuation criterion for subjects who show no response after 16 weeks of treatment. • to add an evaluation by a specialist in case of a positive QuantiFERON® test. • to add an additional sensitivity analysis to assess the robustness of the results of the primary analysis with respect to the use of prohibited medication and procedures among subjects not discontinuing IMP. Furthermore, capturing of 'lack of efficacy' in case of aggravation/exacerbation/worsening of the trial disease has been clarified, and albumin-to-creatinine test at screening was changed to only be performed in case of abnormal urine dipstick test.
Amendment 2 (substantial)	22-Jan-2021	The main reason for this amendment was to provide a possibility to perform minimum safety and efficacy assessments via the use of electronic communications followed by delivery of IMP to subjects for self-injections in case of emergency COVID-19 pandemic restrictions. Such a delivery of IMP to a subject for self-injection would lead to unblinding of the subject, since the two active IMPs are packaged open-label and are visually distinct from each other, containing different volumes of solution. Estimands were updated with strategies to handle occurrences of permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects. The eCRF and statistical analyses were updated accordingly.

Amendment 3 (substantial)	10-Mar-2022	The main reason for this amendment was to reduce the sample size and amend the eligibility criteria to ease recruitment. To address the amended eligibility criteria, prior TNF-α inhibitor use at baseline (≤1, >1) was included as a factor in all analysis models.

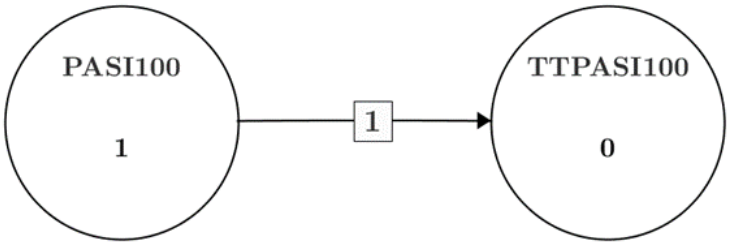
Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; IMP = investigational medicinal product; TNF-α = tumour necrosis factor-α.

2 Testing strategy

2.1 Testing hierarchy

To control the FWER of the analysis of the pre-specified primary and key secondary endpoints at the 5% significance level, the hierarchical testing procedure illustrated in Panel 5 has been defined. The test of the null hypotheses will be based on the pre-specified main analysis of the primary estimands. The initial weight allocated to each hypothesis test is specified in Panel 5. Initially, 100% of the weight is allocated to the hypothesis test of the primary endpoint. If the null hypothesis associated with the primary endpoint is rejected, the key secondary endpoint will be assessed.

Panel 5. Hierarchical testing procedure to control the FWER for the pre-specified primary and key secondary endpoints



Abbreviations: FWER = familywise error rate; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in PASI score; TTPASI100 = time to PASI 100.

2.2 Statistical hypotheses

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

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

will be tested versus the 1-sided alternative,

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

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

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

will be tested versus the alternative,

$$H_1: \lambda_{broda}(t) \neq \lambda_{gus}(t), \text{ for some } t \in (0,28).$$

3 Sample size

Sample size documentation is provided in the CTP Section 14.1.

4 Trial analysis sets

All screened subjects will be accounted for in the CTR. For the purposes of analysis, the following analysis sets are defined:

Panel 6: Trial analysis sets

Trial analysis set	Description
Intention-to-treat (ITT) analysis set	All randomised subjects. Subjects will be included in the analyses according to the planned (randomised) treatment.
Full analysis set (FAS)	All randomised subjects with at least 1 post-baseline PASI assessment. Subjects will be included in the analyses according to the planned (randomised) treatment.
Safety analysis set (SAF)	All subjects who received IMP. Subjects will be included in the analyses according to the treatment they actually received.

Abbreviations: FAS = full analysis set; IMP = investigational medicinal product; ITT = intention-to-treat; PASI = Psoriasis Area and Severity Index; SAF = safety analysis set.

The ITT analysis set is used for presenting disposition of subjects, demographics and other baseline characteristics. The FAS is used to analyse endpoints and assessments related to the efficacy objectives, and the SAF is used to analyse the endpoints and assessments related to safety.

Analyses of endpoints based on PP-PASI or PP-IGA will be based on the FAS restricted to those subjects who have a positive PP-PASI score at baseline. Analyses of endpoints based on sPGA-G will be based on the FAS restricted to those subjects who have a positive sPGA-G value at baseline.

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 in the analysis set definition document (ASDD).

5 Statistical analysis

5.1 General principles

Unless otherwise specified, significance tests will be two-sided using the 5% significance level. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified. Least squares (LS)-mean estimates will be based on the observed margins.

Inference based on multiple imputation methods will consist of n=250 imputed datasets to ensure that the between-imputation variance is estimated with adequate precision. For the analysis of binary endpoints relying on multiple imputation methods to address missing data, the risk differences and log odds ratios along with the associated standard errors will be pooled directly based on Rubin's rules to quantify the potential treatment benefit. For the analysis of multiply-imputed datasets using analysis of covariance (ANCOVA), the estimated regression coefficients and associated standard errors will be pooled directly using Rubin's rules.

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

Efficacy assessments will be summarised numerically and graphically by protocol defined visit week for the two treatment groups. The summarisation will be done based on all observed data, as well as with data collected after occurrence of intercurrent events excluded. Continuous efficacy data will be graphically summarised using spaghetti plots, where individual subject trajectories and mean trajectories will be plotted by connecting subsequent non-missing values by straight lines. Categorical efficacy data will be summarised using stacked bar charts, where

missing data will be explicitly accounted for by being represented on the plot as a separate category.

For each combination of protocol defined visit week (16 and 28) and treatment group, the percent change from baseline in PASI will be presented using a waterfall plot, representing subject-specific values as bars plotted in descending order. The plot will represent subjects with missing values as dots (or equivalent) and use a colouring scheme for highlighting bars corresponding to subjects who have experienced intercurrent events prior to the time of endpoint assessment.

For analysis of non-daily assessments, the baseline assessment is defined as the latest available assessment at or prior to the baseline visit (Visit 2; Week 0). For analysis of the daily pruritus and pain NRS assessments, nominal Days are defined as relative days starting with the randomization date as Day 1. The Day value is incremented by 1 for each date following the randomization date. Dates prior to the randomization date are decremented by 1, with the date preceding the randomization date designated as Day -1 (there is no Day 0). With this designation of Days, nominal Week q is defined as starting on Day $7 \cdot q - 7$ and ending on Day $7 \cdot q - 1$ for non-positive integers q and starting on Day $7 \cdot q - 6$ and ending on Day $7 \cdot q$ for positive integers q. Panel 7 explicitly describes selected nominal weeks for the analysis of daily pruritus and pain NRS assessments.

Panel 7. Selected nominal weeks for the analysis of pruritus and pain NRS assessments

Week (nominal weeks)	Start of the week	End of the week
Week 0	Day -7	Day -1
Week 1	Day 1	Day 7
Week 4	Day 22	Day 28
Week 8	Day 50	Day 56
Week 16	Day 106	Day 112
Week 28	Day 190	Day 196

Calculation of a pruritus or pain NRS weekly average requires available data to have been recorded on at least 4 days within the given week – otherwise the weekly average will be considered missing. The baseline weekly average is defined as the latest available weekly average at or prior to Week 0.

In case of differences between the IRT and the eCRF in recorded values of the stratification factor, baseline body weight (≤100 kg, >100 kg), the value recorded in the eCRF will be used for analysis.

Handling of missing values and imputation

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

The 'delta-adjusted' pattern-mixture model provides a convenient framework for assessing the impact of departures from the missing at random (MAR) assumption in instances where the 'control-based' pattern-mixture model is not reasonable, e.g. when comparing 2 active treatments. For continuous endpoints, the 'delta-adjusted' pattern-mixture model assumes that within a given treatment arm, the mean response value among withdrawn subjects differs from the mean response among subjects remaining in the trial by a specified margin, denoted by Δ. For a given treatment arm at a specific timepoint, missing data are imputed based on the distribution of the conditional mean fitted to the observed data adjusted by the specified margin, Δ. When imputing missing ordinal data in the context of a logistic regression model, Δ is interpreted as the odds ratio of a given level on the logarithmic scale for withdrawals vs. completers.

5.2 Extent of exposure

Exposure will be summarised based on the SAF. For each treatment group, the summary will include the total patient years of exposure, the total patient weeks of exposure and the exposure time, based on the categories '< 16 weeks', '16-24 weeks', and '> 24 weeks'. For each treatment group, the summary will also include the total patient years of observation, beginning from the date of randomisation and ending at the date of last contact. Subjects will be considered exposed to IMP within 5 half-lives after the most recent date of IMP administration with half-lives assumed to be as described in Panel 8. Exposure time will be truncated at the end of observation, i.e. at the date of last contact.

Panel 8. Assumed half-lives for investigational medicinal products

IMP	Assumed half-life	Rationale for assumption
Brodalumab Trade name: Kyntheum®	10.9 days	According to (1), "(…) the estimated half-life of brodalumab was 10.9 days at steady-state after every other week subcutaneous dose of 210 mg"
Guselkumab Trade name: Tremfya®	16.5 days	According to (2), "Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies". Based on this, the average of 15 days and 18 days will be the assumed half-life.
Placebo 1.0 mL (dummy 1 to mimic guselkumab)	0.0 days	According to the CTP Panel 6, "The placebo solution (…) does not contain any active substance".
Placebo 1.5 mL (dummy 2 to mimic brodalumab)	0.0 days	According to the CTP Panel 6, "The placebo solution (…) does not contain any active substance".

Abbreviations: CTP = clinical trial protocol; IMP = investigational medicinal product. **Notes:** The described IMPs refer to those identified in CTP Panel 6.

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

5.3 Intercurrent events

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

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

  Derivation of events from data: This event will be taken to have occurred if the data recorded in the 'End of treatment' eCRF form fulfil all of the following.

  - 'Has the subject completed the treatment period?' is answered 'No'
  - 'Primary reason for permanent discontinuation from IMP?' is not answered 'Death' or 'Lost to follow-up'
  - 'Was the decision to permanently discontinue IMP related to COVID-19 pandemic restrictions?' is not answered 'Yes'.

  The timing of the event will be taken as the reported 'Date of last administration of IMP'.

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

are quarantines, travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff, and interruptions to supply chain of IMP.

Derivation of events from data: This event will be taken to have occurred if the data recorded in the 'End of treatment' eCRF form fulfil all of the following.

- 'Has the subject completed the treatment period?' is answered 'No'
- 'Primary reason for permanent discontinuation from IMP?' is not answered 'Death' or 'Lost to follow-up'
- 'Was the decision to permanently discontinue IMP related to COVID-19 pandemic restrictions?' is answered 'Yes'.

The timing of the event will be taken as the reported 'Date of last administration of IMP'.

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

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

  II) Subject becoming accidentally unblinded.

  Derivation of events from data: I) will be taken to have occurred at (scheduled or unscheduled) visits fulfilling both conditions,

  - 'Type of visit' is answered 'Remote visit due to COVID-19 pandemic restrictions' in the 'Visit' or 'Visit (Unscheduled)' form
  - 'Number IMP(s) dispensed according to IRT system' is not answered '0' in the 'IMP Compliance, Dispensation and Administration' form.

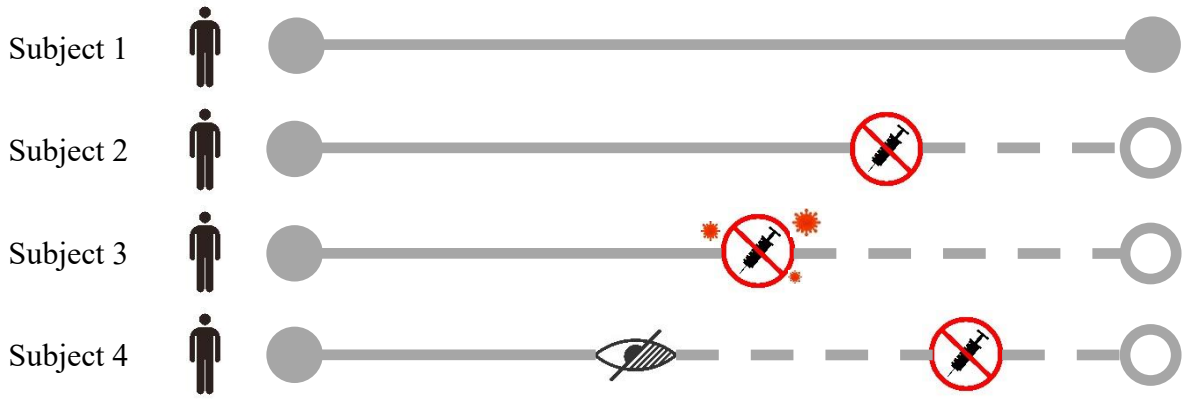
  II) will be taken to have occurred when unblinding of a subject is reported for a visit in a protocol deviation. Instances of II) will be identified by evaluating the descriptions for all the trial's protocol deviations.

The timing of the intercurrent event will be taken as the earliest 'Visit date' where either I) or II) has occurred.

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

Journeys of 4 subjects from randomisation to primary endpoint visit are illustrated in Panel 9.

Panel 9: Examples of subject journeys with respect to intercurrent events



Notes: Subject 1 completes the treatment period, subject 2 permanently discontinues IMP independent of pandemic restrictions, subject 3 permanently discontinues IMP due to pandemic restrictions, while subject 4 becomes unblinded and subsequently permanently discontinues IMP independently of pandemic restrictions.

Depending on the estimand strategy selected, the occurrence of an intercurrent event may be ignored, lead to exclusion of data observed after the occurrence of the event, become a component in the definition of the endpoint, or restrict the relevant observation window to the time prior to the occurrence of the intercurrent event. Unblinding and permanent discontinuation of IMP – either independent of pandemic restrictions or due to pandemic restrictions – may occur to the same subject. If these intercurrent events occur on the same date, permanent discontinuation of IMP will be assumed to have occurred first. If an intercurrent event occurs on

the same date as an endpoint assessment the endpoint assessment will be assumed to have occurred first.

The number and percentage of subjects experiencing intercurrent events will be summarised by visit week interval for each treatment group.

5.4 Primary estimand analysis

Panel 10 associates each efficacy endpoint with one of the primary estimands defined in Panel 2.

Panel 10. Overview of the statistical analysis of efficacy endpoints

Endpoint	Type of endpoint	Primary estimand
Primary endpoint		
PASI 100 response at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Key secondary endpoint(s)		
Time to PASI 100 response	TTE	Primary estimand for TTE endpoints
Secondary endpoints		
Time to PASI 90 response	TTE	Primary estimand for TTE endpoints
Having PASI 100 response at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 4	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 8	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 16	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 90 response at Week 28	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having IGA of 0 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 or 1 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having IGA of 0 or 1 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having DLQI total score of 0 or 1 at Week 4	Binary	Primary estimand for binary endpoints based on continuous subject assessments

Endpoint	Type of endpoint	Primary estimand
Having DLQI total score of 0 or 1 at Week 8	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 12	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 16	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 20	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 24	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Having DLQI total score of 0 or 1 at Week 28	Binary	Primary estimand for binary endpoints based on continuous subject assessments
Change in SF-36v2 PCS measure from baseline at Week 4	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 PCS measure from baseline at Week 8	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 PCS measure from baseline at Week 16	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 PCS measure from baseline at Week 28	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 MCS measure from baseline at Week 4	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 MCS measure from baseline at Week 8	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 MCS measure from baseline at Week 16	Continuous	Primary estimand for continuous endpoints based on subject assessments
Change in SF-36v2 MCS measure from baseline at Week 28	Continuous	Primary estimand for continuous endpoints based on subject assessments
Exploratory endpoints		
Having PASI 100 response at Week 1	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 2	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 6	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 10	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 12	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having PASI 100 response at Week 14	Binary	Primary estimand for binary endpoints based on continuous investigator assessments
Having IGA of 0 at Week 4	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments

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

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

Endpoint	Type of endpoint	Primary estimand
Having PP-IGA 0/1 at Week 4	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 8	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having PP-IGA 0/1 at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 4	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 8	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 16	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments
Having sPGA-G 0/1 response at Week 28	Binary	Primary estimand for binary endpoints based on ordinal investigator assessments

Abbreviations: DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; MCS = mental component summary; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PASI 90 = at least 90% improvement from baseline in PASI score; PASI 100 = 100% improvement from baseline in PASI score; PCS = physical component summary; PP-PASI = palmoplantar PASI; PP-IGA = palmoplantar IGA; SF-36v2 = 36-item Short Form Health Survey version 2, acute recall; sPGA-G = static Physician's Global Assessment of genitalia; TTE = time-to-event.

5.4.1 Primary estimand for binary endpoints

For the primary estimands associated with binary endpoints, Panel 11 provides an overview of those strategies that are specified in Panel 2 for addressing each of the intercurrent events described in section 5.3.

Panel 11. Intercurrent events strategies for primary estimands associated with binary endpoints

Type of endpoint	Estimand	Strategy for addressing IE		
		Permanent discontinuation of IMP independent of pandemic restrictions	**Permanent discontinuation of IMP due to pandemic restrictions**	**Unblinding of subject**
Binary based on investigator assessments	Primary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Treatment-policy': Occurrences of the IE will be ignored
Binary based on subject assessments	Primary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm

Abbreviations: IE = intercurrent event; IMP = investigational medicinal product.

As seen in Panel 11 the strategy for addressing unblinding of subjects will depend on whether the endpoint of interest is based on subject assessments or investigator assessments. In addition, the controlled multiple imputation algorithm, referred to by Panel 11, will depend on the scale for the endpoint of interest (continuous vs. ordinal). This will be elaborated on below.

Binary endpoints based on investigator assessments

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

- Having PASI 100 response at Week 16

The primary estimand associated with this endpoint can be seen to assess the difference in the rate of achieving PASI 100 response at Week 16 without permanently discontinuing IMP regardless of subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur. In the following, we elaborate on the estimand strategy specified in Panel 11 for this estimand, specifically the strategies for addressing the two intercurrent events related to permanent discontinuation of IMP.

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

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

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

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

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

In practice, both of these hypothetical questions will be addressed, although in reverse order, by carrying out the steps in Panel 12, each of which will be elaborated on further below. The steps are based on the envisaged hypothetical scenario where permanent discontinuation of IMP due to pandemic restrictions would not occur and subjects who have experienced this event would respond like similar subjects who have not experienced it. In addition to outlining the 'hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions, Panel 12 specifies the handling of missing data in the main analysis of the primary estimand.

Panel 12. 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the primary estimand for the primary endpoint

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

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in PASI score.

When performing Step no. 1 in Panel 12, data collected after permanent discontinuation of IMP will be excluded from the imputation models, regardless of the reason for treatment discontinuation. This is well aligned with the 'composite' strategy described above for addressing

permanent discontinuation of IMP independent of pandemic restrictions, where data collected after permanent discontinuation of IMP is irrelevant for the value of the estimand's variable.

For subjects who prior to Week 16 have permanently discontinued IMP due to pandemic restrictions, the values imputed in Step no. 1 may be thought of as PASI 100 responses at Week 16, conditional on treatment adherence, thereby addressing the hypothetical question b) stated above. Similarly, Step no. 2 in Panel 12 may be thought of as addressing the hypothetical question a) for these subjects.

Impute PASI 100 response at Week 16 under MAR assumptions

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

1. In each group, intermittent missing values will be imputed based on a Markov Chain Monte Carlo method, assuming an underlying multi-variate normal distribution, to obtain 250 copies of the dataset with a monotone missing data pattern (seed=645659). Negative imputed (non-baseline) 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. With reference to inclusion criterion 4, imputed baseline values below 3 will be replaced by 3.
2. In case of any missing baseline PASI scores, an ANCOVA model will be fitted to the baseline PASI score. This is to be done in the context of a proper imputation model as implemented in PROC MI using the monotone regression method. The model will include the effect of baseline body weight (≤100 kg, >100 kg). The estimated parameters, and their variances, will be used to impute missing baseline PASI scores in each of the 250 copies of the dataset generated above (seed=246673). With reference to inclusion criterion 4, imputed baseline values below 3 will be replaced by 3, and imputed values larger than 72 will be replaced by 72, thereby ensuring that imputed baseline PASI scores are within the range from 3 to 72.

3. An ANCOVA model will be fitted to the PASI score at Week 1. This is to be done in the context of a proper imputation model as implemented in PROC MI using the monotone regression method. The model will include effects of baseline body weight (≤100 kg, >100 kg), and baseline PASI score. The estimated parameters, and their variances, will be used to impute missing PASI scores at Week 1 in each of the 250 copies of the dataset generated above (seed=246673). 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.
4. For each of the 250 copies of the dataset, missing PASI scores at Week 2 will be imputed in the same way as for Week 1. The imputations will be based on an ANCOVA model with the effects of baseline body weight (≤100 kg, >100 kg) together with the PASI scores at baseline and Week 1. The estimated parameters, and their variances, will be used to impute missing values at Week 2 (the same seed=246673 will be used as in the previous step). Again, negative imputed values will be replaced by 0, and imputed values larger than 72 will be replaced by 72.
5. This stepwise procedure will then be repeated sequentially for Weeks 4, 6, 8, 10, 12, 14 and 16 with the modification that only the PASI scores from the 2 preceding visits will be included as covariates, in addition to the effect of baseline body weight (≤100 kg, >100 kg).

The missing binary PASI 100 response at Week 16 will be derived from the corresponding underlying imputed PASI score. If the model does not converge, the baseline body weight variable will be dropped.

Impute treatment adherence status at Week 16

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

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

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

For each subject having permanently discontinued IMP prior to Week 16 due to pandemic restrictions and each of the 250 copies of the dataset, a Bernoulli trial with the subject-specific success probability

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

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

The imputed value of the estimand's variable will be derived from the PASI 100 response at Week 16, conditional on treatment adherence, from Step no. 1 in Panel 12 and the result of the Bernoulli trial described above, in accordance with the 'composite' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions.

The elaborations above are based on the primary endpoint, but the same principles will be applied for the primary estimand associated with other binary endpoints based on investigator assessments. Note here, that the PASI scale is considered as continuous when carrying out Step no. 1 in Panel 12. For e.g. the binary endpoint,

- having IGA of 0 at Week 16

the underlying IGA score will be considered as ordinal rather than continuous, so Step no. 1 in Panel 12 will instead be carried out as outlined below for such an endpoint.

Impute 'having IGA of 0' response at Week 16 under MAR assumptions

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

In each group, missing values will be imputed based on fully conditional specification logistic regression to obtain 250 copies of the dataset (seed=151308). The following imputation methods are to be used in the filled-in and imputation phases:

1. In case of any missing baseline IGA values, an ordinal logistic regression model assuming proportional odds will be fitted to the baseline IGA value. This is to be done in the context of a proper imputation model as implemented in PROC MI using fully conditional specification logistic regression with the cumulative logit link function. The model will include the effect of baseline body weight (≤100 kg, >100 kg). The estimated parameters, and their variances, will be used to impute missing baseline IGA values in each of the 250 copies of the dataset.
2. An ordinal logistic regression model assuming proportional odds will be fitted to the IGA value at Week 1. This is to be done in the context of a proper imputation model as implemented in PROC MI using fully conditional specification logistic regression with the cumulative logit link function. The model will include effects of baseline body weight (≤100 kg, >100 kg), and baseline IGA. The estimated parameters, and their variances, will be used to impute missing IGA values at Week 1 in each of the 250 copies of the dataset. The imputations will be done based on the predicted probabilities associated with each of the values on the IGA scale at Week 1.
3. For each of the 250 copies of the dataset, missing values at Week 2 will be imputed in the same way as for Week 1. The imputations will be based on a proportional odds logistic regression model with the effect of baseline body weight (≤100 kg, >100 kg) together with the IGA values at baseline and Week 1. The estimated parameters, and their variances, will be used to impute missing values at Week 2.
4. This stepwise procedure will then be repeated sequentially for Weeks 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28 with the modification that only the IGA values from the 2 preceding visits will be included as covariates, in addition to the effect of baseline body weight (≤100 kg, >100 kg).

The missing binary 'having IGA of 0' response at Week 16 will be derived from the corresponding underlying imputed IGA value.

Binary endpoints based on subject assessments

The primary estimand for binary endpoints based on subject assessments can be seen to assess the difference in rate of achieving response without permanently discontinuing IMP, if permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects would not occur. In accordance with Panel 11, this estimand will address unblinding of subjects by the same 'hypothetical' strategy as used for addressing permanent discontinuation of IMP due to pandemic restrictions. This means that the above elaboration on estimand strategy also applies to the primary estimand for binary endpoints based on subject assessments with the exception that unblinding of subjects will be handled just as permanent discontinuation of IMP due to pandemic restrictions. Note that when imputing missing response values for binary endpoints based on DLQI, say 'Having DLQI total score of 0 or 1 at Week 16', the underlying DLQI total scores will be considered as continuous, cf. Panel 10. At each step of the procedure for imputing underlying DLQI total scores, imputed scores will be rounded to the nearest integer within the range from 0 to 30.

5.4.1.1 Main analysis

For each of the 250 complete datasets, the treatment effect will be estimated, along with the associated standard error, from a logistic regression model, adjusted for baseline body weight (≤100 kg, >100 kg) and the baseline value of the underlying response variable. Based on Rubin's rules, a combined estimate and standard error for the treatment effect will be calculated and the associated t statistic will be used for testing the null hypothesis that the response rate for the brodalumab arm is less than or equal to the rate for the guselkumab arm, against the alternative that brodalumab is superior to guselkumab. The statistical test will be based on the odds ratio or, equivalently, on the log-odds ratio as expressed through the treatment coefficient in the logistic regression model. In practice, the t test will be carried out as a two-sided test at the 5% significance level, where the null hypothesis will only be rejected in favour of the stated alternative if the treatment effect estimate is in favour of brodalumab. This corresponds to a one-sided test at the 2.5% significance level.

To quantify the magnitude of the potential treatment effect, estimates of the LS-mean risk difference and odds ratio will be presented along with the associated 95% confidence intervals

(CIs), based on combining estimates and associated standard errors from the 250 analyses using Rubin's rules.

5.4.1.2 Sensitivity analyses

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

5.4.1.2.1 Robustness with respect to MAR assumption

These sensitivity analyses will assess the robustness of the results of the main analysis with respect to the MAR assumption. For subjects experiencing intercurrent events to be addressed by 'composite' or 'hypothetical' strategies, cf. Panel 11, the data observed after the occurrence of such events will be excluded from the imputation models for the following sensitivity analyses. Missing data will be imputed in separate sensitivity analyses based on each of the following imputation algorithms:

- Non-responder imputation.
- 'Delta-adjusted' pattern-mixture model.

The sensitivity analysis based on non-responder imputation will be done from the same multiply-imputed datasets as were used for the main analysis with the following modification. All binary response values that were originally imputed for missing data that did not arise after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies, will instead be imputed as non-responses.

For sensitivity analyses based on 'delta-adjusted' pattern-mixture models, multiply-imputed datasets will be generated just as for the main analysis (including the use of the same seeds) with the following modification. After having obtained 250 copies of the dataset with a monotone missing data pattern, imputed scores will be adjusted by a specified margin Δ for those remaining missing scores, which did not arise after the occurrence of intercurrent events specified to be addressed by 'composite' or 'hypothetical' strategies. The adjustment by Δ will be applied subsequently at each visit up to the end of the trial, in addition to using previously Δ-adjusted values as predictors. The same margin Δ will be used for both treatment groups. Panel 13 specifies the margins to be used.

Panel 13. Margins to be used for adjustment in 'delta-adjusted' pattern mixture models

Type of score	Score	Interpretation of Δ	Margin Δ					
Continuous	PASI	Shift in score	-4.5	-3.0	-1.5	+1.5	+3.0	+4.5
Continuous	PP-PASI	Shift in score	-18	-12	-6	+6	+12	+18
Continuous	DLQI total score	Shift in score	-4.5	-3.0	-1.5	+1.5	+3.0	+4.5
Continuous	SF-36v2 PCS	Shift in score	-18	-12	-6	+6	+12	+18
Continuous	SF-36v2 MCS	Shift in score	-18	-12	-6	+6	+12	+18
Continuous	Pruritus NRS (weekly average)	Shift in score	-0.36	-0.24	-0.12	+0.12	+0.24	+0.36
Continuous	Pain NRS (weekly average)	Shift in score	-0.36	-0.24	-0.12	+0.12	+0.24	+0.36
Ordinal	IGA	Shift in log-odds for IGA = 0	-0.09	-0.07	-0.05	+0.05	+0.07	+0.09
Ordinal	PP-IGA	Shift in log-odds for PP-IGA = 0	-0.35	-0.27	-0.17	+0.17	+0.27	+0.35
Ordinal	sPGA-G	Shift in log-odds for sPGA-G = 0	-0.35	-0.27	-0.17	+0.17	+0.27	+0.35

Abbreviations: DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; MCS = mental component summary; NRS = numeric rating scale; PASI = Psoriasis Area and Severity Index; PCS = physical component summary; sPGA = static Physician's Global Assessment; PP-IGA = palmoplantar IGA; PP-PASI = palmoplantar PASI; SF-36v2 = 36-item Short Form Health Survey version 2, acute recall; sPGA-G = sPGA of genitalia.

With m denoting the number of post-baseline assessments scheduled to be performed per subject for a given score, the margins Δ in Panel 13 generally approximate multiples

$$-1/m,\ -2/(3m),\ -1/(3m),\ 1/(3m),\ 2/(3m),\ \text{and}\ 1/m$$

of the scoring range for continuous scores, and log(odds ratios) corresponding to the odds ratios

$$\sqrt[m]{1/4},\ \sqrt[m]{1/3},\ \sqrt[m]{1/2},\ \sqrt[m]{2},\ \sqrt[m]{3},\ \sqrt[m]{4}$$

for ordinal scores. The reason for considering *m* in the above specifications is that the potential difference emerging between subsequent assessments for withdrawals vs. completers may be expected to be larger when the subsequent assessments are further distanced in time.

5.4.1.2.2 Robustness with respect to assumption that treatment effect does not depend on baseline body weight stratum

This sensitivity analysis will assess the robustness of the results of the main analysis with respect to the assumption that the effect of treatment does not depend on baseline body weight. To carry out this sensitivity analysis, an interaction term between baseline body weight (≤100 kg, >100 kg) and treatment arm will be included in the logistic regression model described in the main analysis.

5.4.1.2.3 Robustness with respect to use of prohibited medication and procedures

These sensitivity analyses will assess the robustness of the results of the main analysis with respect to the assumption that use of prohibited medication and procedures, cf. CTP Panel 7, has no influence on the endpoint of interest among subjects not discontinuing IMP. This will be done by excluding data collected after use of prohibited medication and procedures. Missing data resulting from such exclusions will be imputed in separate sensitivity analyses based on each of the following imputation algorithms:

- Non-responder imputation.
- 'Delta-adjusted' pattern-mixture model.

For subjects using prohibited medication and procedures or experiencing intercurrent events to be addressed by 'composite' or 'hypothetical' strategies cf. Panel 11, the data observed after the occurrence of such events will be excluded from the imputation models.

Following these exclusions, multiple imputation of missing scores will be done just as in the main analysis (including the use of the same seeds) for missing data, which

- did not arise after use of prohibited medication and procedures, or
- did arise after use of prohibited medication and procedures that happened after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies (i.e. the value of the estimand's variable will in such a case be determined by the strategy for addressing the intercurrent event).

For the sensitivity analysis based on non-responder imputation, all binary response values corresponding to missing data arising after use of prohibited medication and procedures that did not happen after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies, will be imputed as non-responses.

For the sensitivity analysis based on 'delta-adjusted' pattern-mixture models, imputed scores will, as described in section 5.4.1.2.1, be adjusted by a specified margin Δ (Panel 13) for missing scores arising after use of prohibited medication and procedures that did not happen after the occurrence of intercurrent events to be addressed by 'composite' or 'hypothetical' strategies.

If use of prohibited medication and procedures occurs on the same date as an intercurrent event or an endpoint assessment, the use of prohibited medication and procedures will be assumed to have occurred last.

5.4.2 Primary estimand for time-to-event endpoints

For the primary estimands associated with time-to-event endpoints, Panel 14 provides an overview of those strategies that are specified in Panel 2 for addressing each of the intercurrent events described in section 5.3.

Panel 14. Intercurrent event strategies for primary estimands associated with time-to-event endpoints

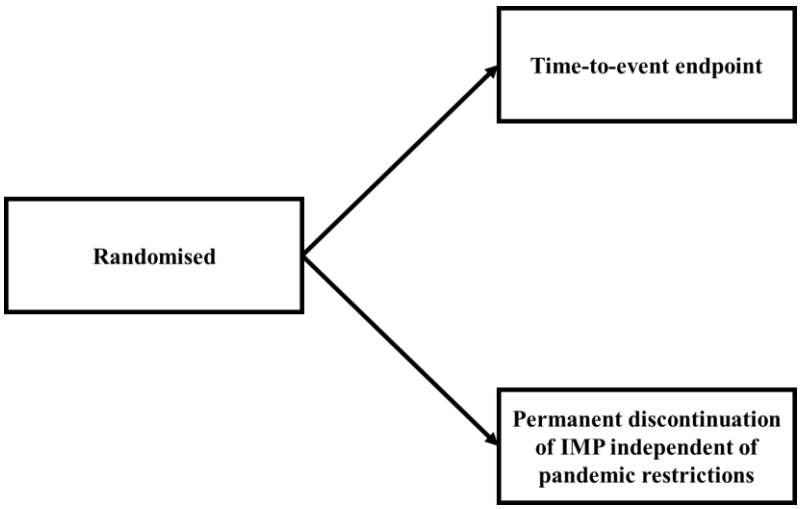
Type of endpoint	Estimand	Strategy for addressing IE		
		Permanent discontinuation of IMP independent of pandemic restrictions	**Permanent discontinuation of IMP due to pandemic restrictions**	**Unblinding of subject**
Time-to-event	Primary	'While on treatment': The IE is accounted for as a competing risk in a competing risks model	'Hypothetical': Occurrences of the IE will lead to right censoring, assumed to be non-informative, in a competing risks model	'Treatment-policy': Occurrences of the IE will be ignored

Abbreviations: IE = intercurrent event; IMP = investigational medicinal product.

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

Panel 15 describes the competing risks model mentioned in Panel 14 as part of the strategy for addressing the two intercurrent events related to permanent discontinuation of IMP. For subjects permanently discontinuing IMP due to pandemic restrictions, the time to event will be right censored at the time of discontinuation. This is thought of as a 'hypothetical' strategy, the envisaged scenario being that permanent discontinuation of IMP due to pandemic restrictions would not occur and that among those at risk of an event at time *t*, the event hazards of those who experienced permanent discontinuation of IMP due to pandemic restrictions at time *t* are similar to the hazards of those who did not experience it.

Panel 15. Competing risks model describing the primary estimand for time-to-event endpoints



Abbreviations: IMP = investigational medicinal product.

5.4.2.1 Main analysis

The null hypothesis,

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

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

$$H_1: \lambda_{broda}(t) \neq \lambda_{gus}(t), \text{ for some } t \in (0,28),$$

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

To quantify the magnitude of the potential treatment effect, the estimated cumulative incidence functions for the competing risks model displayed in Panel 15 will be presented for the groups defined by treatment arm and baseline body weight (≤100 kg, >100 kg), based on the Aalen-Johansen estimator, along with pointwise 95% confidence bands. Differences between treatment groups in the estimated cumulative incidence functions for the model will also be presented for each baseline body weight stratum (≤100 kg, >100 kg), along with corresponding 95% CIs. Additionally, the estimated sub-distributional hazard ratios comparing treatment arms and corresponding 95% CIs for the 2 competing risks based on fitting Fine and Gray models, stratified by baseline body weight (≤100 kg, >100 kg) and adjusted for the baseline PASI score will be presented.

In addition to permanent discontinuation of IMP due to pandemic restrictions – which will be considered a potential right-censoring event as part of the estimand strategy – the main analysis will consider the following as potential right-censoring events.

- **Completion of trial (administrative censoring)**. This potential right-censoring event will be taken to have occurred if 'Did the subject complete the trial?' is answered 'Yes' on the 'End of trial' eCRF form. The timing of the event will be taken as the reported 'Date of last contact'.

- **Withdrawal from trial**. This potential right-censoring event will be taken to have occurred if 'Did the subject complete the trial?' is answered 'No' on the 'End of trial' eCRF form. The timing of the event will be taken as the reported 'Date of last contact'.

We refer to these as 'potential' right-censoring events since they will only lead to right-censoring if, by the time of their occurrence, the subject is still at risk for the two events shown in Panel 15. If a potential right-censoring event happens on the same date as one of the events illustrated on Panel 15, the latter will be assumed to have happened first.

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

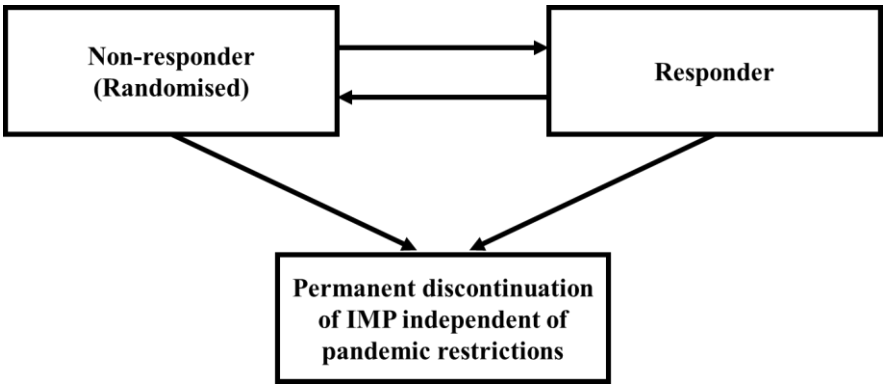
response is first observed. Also, unless subjects who achieve the time-to-event endpoint maintain it until the time of their next visit, they will not be observed to have experienced the event.

5.4.2.2 Sensitivity analyses

5.4.2.2.1 Robustness with respect to intermittent follow-up

For a given subject in the main analysis, the time to response while remaining on treatment is imputed using the scheduled timing of the visit where the desired response is first observed. In order to assess the robustness of the results of the main analysis with respect to this imputation strategy, the probability of achieving a response prior to discontinuation of IMP independent of pandemic restrictions will be estimated based on the multi-state model illustrated in Panel 16.

Panel 16. Multi-state model for the sensitivity analysis accounting for the intermittent nature of the observation process



Abbreviations: IMP = investigational medicinal product.

For this analysis, we formulate the likelihood function for an intermittently observed continuous-time Markovian 3-state process $\{Z(t) \mid 0 \leq t\}$ in terms of its transition probabilities, as in (3). Given a subject-specific vector of time-fixed covariates $\boldsymbol{x}$ and states j, k of the 3-state process, the transition probability

$$p_{jk}(s,t \mid \boldsymbol{x}) = \text{Prob}\{Z(t) = k \mid Z(s) = j, \boldsymbol{x}\}$$

is the probability that a subject in state j at time s will be in state k at time t for $0 \leq s \leq t$.

Letting n denote one of the N randomised subjects in the trial we let

$$0 = v_{n,0} < v_{n,1} < \cdots < v_{n,M_n} \leq 28$$

denote the (potentially subject-specific) inspection times, measured in weeks after randomization, and we let

$$z_{n,0},\ z_{n,1},\ \ldots\ , z_{n,M_n}$$

denote the states observed for the subject at these times. A subject could be observed to be a non-responder (or responder) and permanently discontinue IMP independently of pandemic restrictions at one and the same visit, say at the Week 20 visit. Such a situation will be interpreted as observing the subject to be in the 'Non-responder (Randomised)' (or 'Responder') state at the inspection time 20 weeks and observing the subject to be in the 'Permanent discontinuation of IMP independent of pandemic restrictions' state at the inspection time 20.1 weeks.

Conditional on the initial distribution of subjects amongst states and the distribution of covariates, the likelihood function can then be written as the product of independent contributions L_n from each of the N randomized subjects of the trial:

$$L = \prod_{n=1}^{N} L_n = \prod_{n=1}^{N} \prod_{m=1}^{M_n} p_{z_{n,m-1} z_{n,m}}(v_{n,m-1}, v_{n,m} \mid \boldsymbol{x_n}) .$$

Under certain regularity conditions, we can consider the transition intensities

$$q_{jk}(t \mid \boldsymbol{x}) = \lim_{\Delta t \to 0} \frac{p_{jk}(t, t+\Delta t \mid \boldsymbol{x})}{\Delta t} \text{ for } 0 \leq t \text{ and states } j, k \text{ with } j \neq k$$

and

$$q_{jj}(t \mid \boldsymbol{x}) = -\sum_{k \neq j} q_{jk}(t \mid \boldsymbol{x}) \text{ for } 0 \leq t \text{ and states } j.$$

Conversely, the transition probability matrix (p_{jk}) can, again under certain regularity conditions, be retrieved from a given transition intensity matrix (q_{jk}) using the Kolmogorov differential equations.

The sensitivity analysis will estimate state occupation probabilities for the model displayed in Panel 16 for the groups defined by treatment arm and randomisation strata. This will be done using the **msm** package in R, based on the above-described likelihood with transition intensities that are constant in time within each group. The state occupation probabilities that are to be estimated in this sensitivity analysis can only be expected to be in agreement with the cumulative incidences that are to be estimated in the main analysis, if responders remain in the Responder state (without permanently discontinuing IMP independently of pandemic restrictions).

Proportional transition intensity regression models will also be fit, assuming the baseline transition intensities are piecewise constant in time. In other words, for a given partition of the time interval [0,28], $0 = \tau_0 < \tau_1 < \cdots < \tau_P = 28$, the transition intensities will be assumed to have the form,

$$q_{jk}(t \mid \boldsymbol{x}) = q_{jkp} \exp(\boldsymbol{\beta_{jk}} \cdot \boldsymbol{x}) \text{ for } p \in \{1, \ldots, P\},\ \tau_{p-1} \leq t < \tau_p \text{ and states } j, k,$$

where $\boldsymbol{\beta_{jk}}$ is a vector of transition $j \rightarrow k$ specific regression parameters describing the treatment group, baseline body weight (≤100 kg, >100 kg), and baseline PASI score. Models based on the following partitions of the time interval [0,28] will be fit:

- Constant baseline transition intensities
- Piecewise constant baseline transition intensities based on the partition of the time interval [0,28] with cut-point $\tau_1 = 14$.

For the latter partition and a given transition denoted by $j \rightarrow k$, if there are no observed transitions within a given time interval defined by the partition, the cut-points for modeling that specific transition will be reduced to ensure that at least one transition is observed within each defined time interval.

5.4.2.3 Supplementary analysis

Proportional hazard regression models will be fit for the cause-specific hazard rates of achieving PASI 100 response and permanent discontinuation of IMP independent of pandemic restrictions. The models will be stratified by body weight (≤100 kg, >100 kg) and will include baseline PASI score as a continuous covariate. The estimated cause-specific hazard ratios comparing treatment arms will be presented along with 95% CIs.

5.4.3 Primary estimand for continuous endpoints

For the primary estimands associated with continuous endpoints, Panel 17 provides an overview of those strategies that are specified in Panel 2 for addressing each of the intercurrent events described in section 5.3.

Panel 17. Intercurrent events strategies for primary estimands associated with continuous endpoints

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

Abbreviations: IE = intercurrent event; IMP = investigational medicinal product; MAR = missing at random.

Again, the strategy for addressing unblinding of subjects will depend on whether the endpoint of interest is based on subject assessments or investigator assessments. This will be elaborated on below.

Continuous endpoints based on investigator assessments

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

- Absolute PASI at Week 16

The primary estimand associated with this endpoint can be seen to assess the LS-mean difference in absolute PASI at Week 16 regardless of permanent discontinuation of IMP and subjects becoming unblinded, if permanent discontinuation of IMP due to pandemic restrictions would not occur. In the following, we elaborate on the estimand strategy described in Panel 17 for this estimand, specifically the 'hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions.

The hypothetical scenario envisaged is that permanent discontinuation of IMP due to pandemic restrictions would not occur and that subjects who have experienced this event would respond like similar subjects who have not experienced it. Data collected after permanent discontinuation of IMP due to pandemic restrictions will be excluded. The 'hypothetical' strategy and the handling of missing data in the main analysis are outlined in Panel 18.

Panel 18. 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the primary estimand for 'Absolute PASI at Week 16'

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

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

The imputation of PASI scores at Week 16 will be carried out as specified for the primary

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

Continuous endpoints based on subject assessments

The primary estimand for continuous endpoints based on subject assessments can be seen to assess the LS-mean difference in the continuous endpoint regardless of permanent discontinuation of IMP, if permanent discontinuation of IMP due to pandemic restrictions and unblinding of subjects would not occur. In accordance with Panel 17, this estimand will address unblinding of subjects by the same 'hypothetical' strategy as used for addressing permanent discontinuation of IMP due to pandemic restrictions. This means that the above elaboration on estimand strategy also applies to the primary estimand for continuous endpoints based on subject assessments with the exception that unblinding of subjects will be handled just as permanent discontinuation of IMP due to pandemic restrictions.

5.4.3.1 Main analysis

Each of the 250 imputed datasets will be analysed based on an ANCOVA model, including baseline body weight (≤100 kg and >100 kg), and treatment arm as factors and adjusting for the baseline value of the endpoint as a covariate. The pooled estimate of the difference in the LS-mean between the brodalumab and guselkumab arms, along with the associated 95% CIs and nominal p-values, will be presented based on applying Rubin's rules to the estimates and standard errors from the aforementioned ANCOVA analyses of the imputed datasets.

5.4.3.2 Sensitivity analyses

Rather than assuming missing data are MAR, the sensitivity analyses will impute missing data based on 'delta-adjusted' pattern-mixture models, as described in section 5.4.1.2.1.

5.5 Supplementary estimand analysis

The presentation of supplementary estimands, as defined in Panel 2, will be reserved for the primary endpoint only. For the supplementary estimands, Panel 19 provides an overview of the strategies for addressing each of the intercurrent events described in section 5.3.

Panel 19. Intercurrent event strategies for supplementary estimands

Estimand	Strategy for addressing IE		
	Permanent discontinuation of IMP independent of pandemic restrictions	**Permanent discontinuation of IMP due to pandemic restrictions**	**Unblinding of subject**
First supplementary	'Treatment-policy': Occurrences of the IE will be ignored	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Treatment-policy': Occurrences of the IE will be ignored
Second supplementary	'Composite': The IE is incorporated as a component in a composite variable with the endpoint of interest	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm	'Hypothetical': Data collected after occurrence of the IE will be excluded. Resulting missing data will be imputed from a controlled multiple imputation algorithm

Abbreviations: IE = intercurrent event; IMP = investigational medicinal product.

5.5.1 First supplementary estimand

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

In accordance with Panel 19, permanent discontinuation of IMP independent of pandemic restrictions will be addressed using the 'treatment-policy' strategy. Specifically, permanent discontinuation of IMP independent of pandemic restrictions will be ignored. The same strategies for addressing permanent discontinuation of IMP due to pandemic restrictions and unblinding of

subjects will be used, and missing data will be handled in the same way as for the main analysis of the primary estimand, with the exceptions that:

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

These exceptions are introduced to align with the 'treatment policy' strategy for addressing permanent discontinuation of IMP independent of pandemic restrictions, which simply ignores treatment discontinuations of that nature. Panel 20 summarises the procedure.

Panel 20. 'Hypothetical' strategy for addressing permanent discontinuation of IMP due to pandemic restrictions and handling of missing data in the main analysis of the first supplementary estimand for the primary endpoint

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

Abbreviations: IMP = investigational medicinal product; MAR = missing at random; PASI = Psoriasis Area and Severity Index, PASI 100 = 100% improvement from baseline in PASI score.

5.5.1.1 Main analysis

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

5.5.1.2 Sensitivity analysis

Sensitivity analyses of this estimand will assess the robustness of the imputation method for subjects with missing data. The following imputation methods will be used as described in section 5.4.1.2.1:

- Non-responder imputation.
- 'Delta-adjusted' pattern-mixture model.

5.5.2 Second supplementary estimand

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

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

5.5.2.1 Main analysis

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

5.6 Safety analysis

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

5.6.1 Adverse events

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

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

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

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

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

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. An overall summary of the most frequent AEs by PT (≥ 5% in any treatment group) will be presented. The most frequent AEs (≥ 5% in any treatment group) will be tabulated by SOC and PT, and will be presented by PT and severity using histograms. The most frequent non-serious AEs (≥ 5% in any treatment group) will also be tabulated by SOC and PT. The most frequent AEs (≥ 5% in any treatment group) will be presented by SOC using dot plots.

SAEs will be evaluated separately and a narrative for each will be given – an overall summary and tabulation by SOC and PT of SAEs will be presented. AEs leading to withdrawal from trial or permanent discontinuation of IMP will be tabulated and listed. Cumulative frequency plots of AEs, AEs leading to withdrawal from trial and AEs leading to permanent discontinuation of IMP will also be produced.

Other events involving IMP (medication error, misuse, and abuse of IMP) will be summarised.

5.6.2 Adverse events of special interest

The AESIs for the trial are classified as important identified and important potential risks (CTP Section 13.5.2). The AESI will be tabulated and listed by treatment arm according to the safety analysis set for the 'while exposed to IMP' and 'while on trial' scenarios. It has been recorded in the eCRF whether or not an adverse event is an adverse event of special interest.

5.6.3 Vital signs

Vital signs are tabulated as described in the CTP Section 14.3.9.3. In addition, vital signs will be summarised by protocol defined visit week and a shift table will be produced showing 'low', 'normal' and 'high' categories at baseline against those at the end of the treatment period. The normal ranges to use for this classification are provided in Panel 21.

Panel 21. Normal ranges to be used for shift tables involving vital signs parameters

Parameter	Normal range
Body temperature	36°C – 38°C
Diastolic Blood Pressure	50 mmHg – 105 mmHg
Systolic Blood Pressure	90 mmHg – 180 mmHg
Pulse	50 beats/min – 120 beats/min

Abbreviations: °C = degree Celsius; min = minute; mmHg = millimeter of mercury.

5.6.4 Physical examination

Physical examinations will be listed by subject.

5.6.5 Clinical laboratory evaluation

Clinical laboratory evaluations are tabulated as described in the CTP Section 14.3.9.4. In addition, laboratory reference ranges will be tabulated. Maximum post-baseline values (including unscheduled visits) and end of treatment values of selected chemistry and hematology parameters will be summarised by thresholds. Means and mean changes from baseline will be presented graphically for selected chemistry and hematology parameters.

5.6.6 Columbia-Suicide Severity Rating Scale

C-SSRS evaluations are tabulated as described in the CTP Section 14.3.9.5. To clarify, occurrences of the composite event 'Any suicidal ideation or behaviour during the trial' will be derived from categories 1 to 9, and occurrences of the composite event 'Suicidal behaviour' will be derived from categories 6 to 9, in accordance with CTP Section 11.5.2.

5.6.7 Patient Health Questionnaire-8

PHQ-8 evaluations are tabulated as described in the CTP Section 14.3.9.6.

5.7 Interim analysis

No interim analysis is planned.

6 Changes to analyses described in the protocol

Panel 22 summarises the changes to the analyses planned in the protocol.

Panel 22. Changes to analyses planned in the protocol

Section in CTP	Description of change	Brief rational
6 Trial objectives, endpoints, and estimands 14.3.7 Analysis of efficacy endpoints	Panel 1 lists the additional exploratory endpoints, • Having PASI 100 response, assessed separately at Weeks 1, 2, 6, 10, 12, and 14, • Having IGA of 0, assessed separately at Weeks 4, and 8, • Having IGA of 0 or 1, assessed separately at Weeks 4, and 8, • Having IGA of 0 or 1 and at least a 2-grade improvement from baseline, assessed separately at Weeks 4, and 8, which are not described in the CTP. Analyses of the above mentioned endpoints have been specified to be carried out in Panel 10.	The additional exploratory endpoints, and the analyses of them, have been specified to obtain additional insights from the collected data on the onset of action for the IMPs.
6 Trial objectives, endpoints, and estimands 14.3.7 Analysis of efficacy endpoints	The explorative endpoints described in the CTP, • Having absolute PASI ≥3, assessed separately at Weeks 4, 8, 16, and 28 • Having absolute PASI ≥5, assessed separately at Weeks 4, 8, 16, and 28, have been replaced by the respective exploratory endpoints • Having absolute PASI ≤3, assessed separately at Weeks 4, 8, 16, and 28 • Having absolute PASI ≤5, assessed separately at Weeks 4, 8, 16, and 28. The above-described replacements have also been implemented in Panel 10.	To align with all other endpoints, where response to the endpoint indicates treatment success.

6 Trial objectives, endpoints, and estimands 14.2 Trial analysis sets	Note 4) to Panel 2 clarifies that the population components of estimands based on PP-PASI or PP-IGA only include subjects with palmoplantar psoriasis. Likewise, the population components of estimands based on sPGA-G only include subjects with genital psoriasis. It has been clarified that analyses of endpoints based on PP-PASI or PP-IGA will be based on the FAS restricted to those subjects who have a positive PP-PASI score at baseline. Likewise for analyses of endpoints based on sPGA-G.	PP-PASI is used to quantify the area and severity of palmoplantar psoriasis, so treatment effects based on this tool are not of interest for subjects without palmoplantar psoriasis. This is also aligned with the protocol-specified procedure that only subjects with palmoplantar psoriasis at baseline will be followed post randomisation. Likewise for PP-IGA and sPGA-G.
14.3.6 Estimand strategy	Prior TNF-α inhibitor use at baseline (≤1, >1) will not be included as a factor in any analysis model. This also means that interactions with prior TNF-α inhibitor use at baseline (≤1, >1) will not be included in the sensitivity analysis model described in Section 5.4.1.2.2.	Amendment 3 of the CTP introduced changes to the eligibility criteria and handled these changes in the analysis by including prior TNF-α inhibitor use at baseline (≤1, >1) as a factor in all analysis models. However, the decision to end the trial ahead of schedule was made shortly after implementing Amendment 3 of the CTP, and very few subjects can be expected to have been randomised under the amended eligibility criteria. In particular, very few randomised subjects can be expected to have used more than one TNF-α inhibitor at baseline, so we do not consider the adjustment for prior TNF-α inhibitor use at baseline (≤1, >1) feasible.

14.3.6 Estimand strategy	In procedures for multiple imputation, the CTP specifies the number of imputations to be 1000. Instead, the number of imputations will be 250.	To align with the number of imputations specified for other brodalumab trials, LP0160-1329 and LP0160-1396. 250 imputations substantially exceed the default number of imputations NIMPUTE=25 for PROC MI, and will for sure exceed the percentages of cases with missing values (described as a rule of thumb for the number of imputations in the SAS/STAT 15.2® User's Guide for PROC MI).
14.3.6.2 Estimand strategy for binary endpoints	The procedures for multiple imputation of missing data have been slightly changed: In case of PASI 100 response at Week 16, the CTP describes part of the procedure as a stepwise imputation of underlying PASI scores, sequentially for Weeks 2, 4, 6, 8, 10, 12, 14, and 16. This stepwise process has been changed to also include imputation of underlying PASI scores for baseline and Week 1. A similar change has been made to the analogous stepwise procedure for imputing underlying IGA values.	To handle instances of missing baseline values, to accommodate the above-described addition of the explorative endpoint 'having PASI 100 response at Week 1' and to make use of the data collected at Week 1 in the imputation of missing data.
14.3.6.2 Estimand strategy for binary endpoints	When imputing missing IGA values, full-data imputation will be used as opposed to producing monotone missingness as an intermediate step	To simplify, since full-data imputation based on fully conditional specification methods is readily available in PROC MI.
14.3.6.2 Estimand strategy for binary endpoints	The CTP specifies a supplementary analysis of the primary estimand for binary endpoints, which only uses assessments performed at on-site visits. This supplementary analysis will not be done.	Based on a blind review of data, there have only been very few remote assessments during the trial and, none of the endpoints that are specified to undergo the supplementary analysis have been remotely assessed.

14.3.6.2 Estimand strategy for binary endpoints and 14.3.6.4 Estimand strategy for continuous endpoints	As part of a sensitivity analysis, the CTP specifies imputation of missing data based on a 'retrieved-data' pattern-mixture model if sufficient data exist. This part of the sensitivity analysis will not be performed.	Sufficient data for fitting the 'retrieved-data' pattern-mixture model cannot be expected due to the decision of ending the trial ahead of schedule.
14.3.6.3 Estimand strategy for time-to-event endpoints	The sensitivity analysis with respect to the assumption of non-informative censoring will not be performed	A blind review of data has shown that no event time has been censored for another cause than administrative censoring.

Abbreviations: CTP = clinical trial protocol; IGA = Investigator's Global Assessment; IMP = investigational medicinal product; PASI = Psoriasis Area and Severity Index; PASI 100 = 100% improvement from baseline in PASI score; TNF-α = tumour necrosis factor-α.

7 Supporting documentation

7.1 Appendix 1: Disposition of subjects

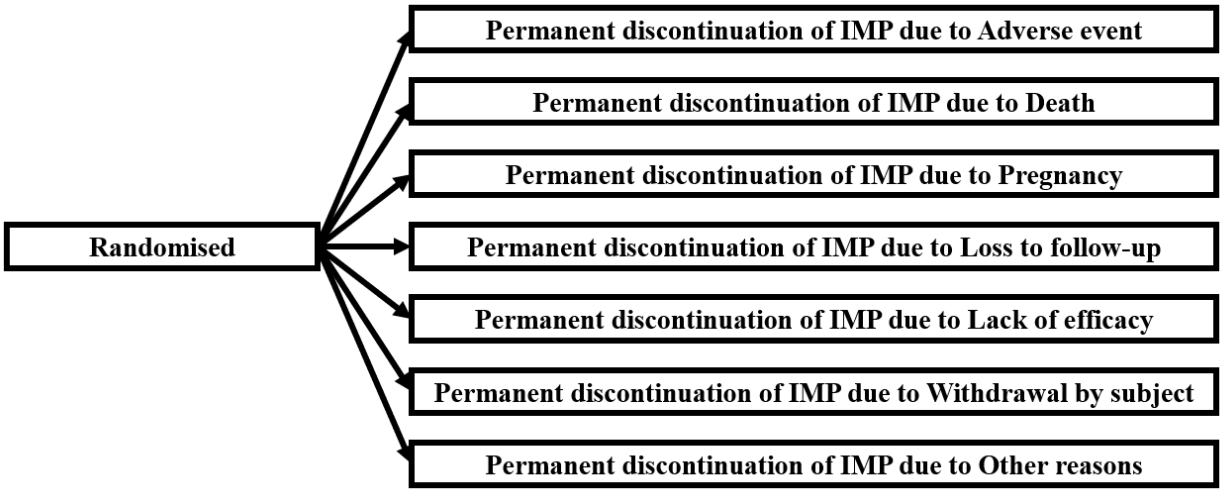
An overall summary of subject disposition will be presented. The disposition summary will include information on the number of subjects screened, randomised, exposed, included in the FAS, permanently discontinuing IMP, and withdrawing from the trial by treatment arm and overall.

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

7.1.1 Time to permanent discontinuation of IMP by treatment arm and reason

The analysis of the time to permanent discontinuation of IMP by treatment arm and reason will be based on the competing risks model illustrated in Panel 23.

Panel 23. Competing risks model for analysis of the time to permanent discontinuation of IMP by reason



Abbreviations: IMP = investigational medicinal product.

Permanent discontinuation of IMP due to Adverse event will be taken to have occurred if the data recorded in the 'End of treatment' eCRF form fulfil both of the following (and similarly for the other competing events shown in Panel 23).

- 'Has the subject completed the treatment period?' is answered 'No'
- 'Primary reason for permanent discontinuation from IMP?' is answered 'Adverse event',

The timing of the event will be taken as the reported 'Date of last administration of IMP'. This analysis will consider the following as potential right-censoring events.

- **Completion of treatment**. This potential right-censoring event will be taken to have occurred if 'Has the subject completed the treatment period?' is answered 'Yes' on the 'End of treatment' eCRF form. The timing of the event will be taken as the reported 'Date of last administration of IMP'.
- **Withdrawal from trial**. This potential right-censoring event will be taken to have occurred if 'Did the subject complete the trial?' is answered 'No' on the 'End of trial' eCRF form. The timing of the event will be taken as the reported 'Date of last contact'.

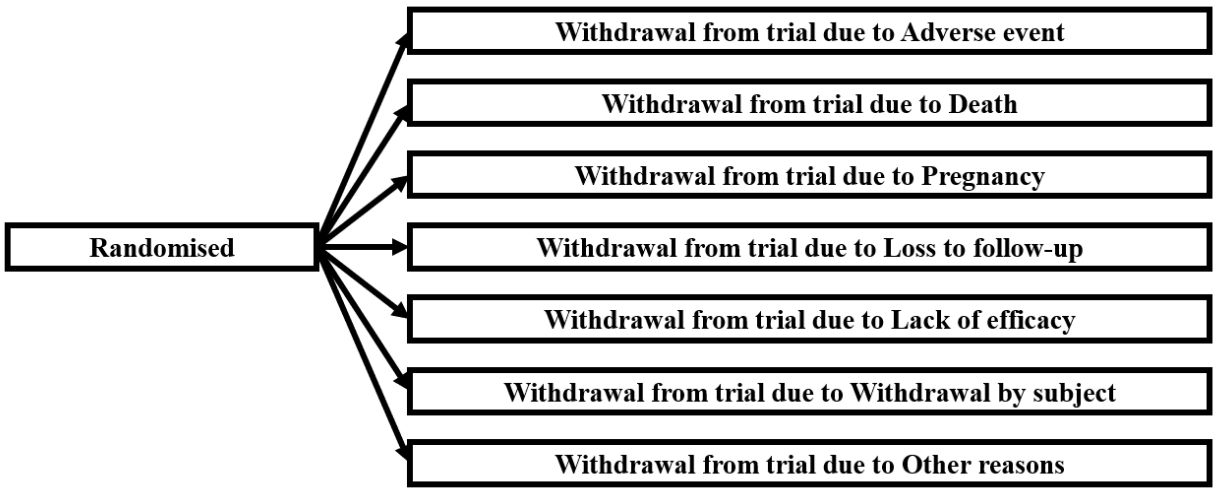
We refer to these as 'potential' right-censoring events, since they will only lead to right-censoring if, by the time of their occurrence, none of the seven events illustrated on Panel 23 have happened. Right-censoring based on withdrawal from trial could, for instance, happen if a subject withdraws from the trial prior to having been administered any IMP. If a potential right-censoring event happens on the same date as one of the events illustrated on Panel 23, the latter will be assumed to have happened first.

The cumulative incidence functions associated with the seven event types of the model will be estimated based on the Aalen-Johansen estimator.

7.1.2 Time to withdrawal from trial by reason

The analysis of the time to withdrawal from trial will be based on the competing risks model illustrated in Panel 24.

Panel 24. Competing risks model for analysis of the time to withdrawal from trial by reason



Withdrawal from trial due to Adverse event will be taken to have occurred if the data recorded in the 'End of trial' eCRF form fulfil both of the following (and similarly for the other competing events shown in Panel 24).

- 'Did the subject complete the trial?' is answered 'No'
- 'Primary reason for withdrawal from trial' is answered 'Adverse event',

The timing of the event will be taken as the reported 'Date of last contact'. This analysis will consider the following as a potential right-censoring event.

- **Completion of trial**. This potential right-censoring event will be taken to have occurred if 'Did the subject complete the trial?' is answered 'Yes' on the 'End of trial' eCRF form. The timing of the event will be taken as the reported 'Date of last contact'.

We refer to this as a 'potential' right-censoring event, since it will only lead to right-censoring if, by the time of its occurrence, none of the seven events illustrated on Panel 24 have happened.

The cumulative incidence functions associated with the seven event types of the model will be estimated based on the Aalen-Johansen estimator.

7.2 Appendix 2: Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for the ITT analysis set by treatment arm and overall. In addition, demographics and baseline characteristics will be presented by baseline body weight stratum (≤100 kg, >100 kg).

Demographics include age, sex, race, and ethnicity. Baseline characteristics include height, weight, body mass index, smoking status, alcohol use, duration of psoriasis, and previous psoriasis therapy including prior biologic use. In addition to the above specified baseline characteristics, the following baseline measures of disease severity will be presented: PASI, IGA, PP-PASI, PP-IGA, sPGA-G, DLQI, SF-36v2, and the baseline weekly average pruritus and pain as assessed by the NRS. SF-36v2 will be presented in terms of the Physical and Mental Component Summary measures. In addition, baseline PASI will be summarised in terms of the severities "Moderate (PASI score < 20)" and "Severe (PASI score ≥ 20)" for subjects in the ITT analysis set.

7.3 Appendix 3: Treatment compliance

Treatment compliance will be presented from data listings. Subjects not receiving the scheduled dose will be listed by sites, sorted by treatment group, subject number, and visit. Subjects being administered IMP via remote visits will be listed by sites, sorted by treatment group, subject number, and visit. The number and percentage of IMP administration visits with 'Full dose', 'Partial dose' and 'No dose' will also be summarised by protocol-defined visit week based on the SAF. For this summary, subjects who permanently discontinued IMP will contribute to the IMP

administration visits they completed while being on treatment, to the entire treatment period up to the time of permanent discontinuation of IMP, and are excluded from the IMP administration visits after the time of permanent discontinuation of IMP.

7.4 Appendix 4: Protocol deviations

Important subject-level protocol deviations will be tabulated by country for screened subjects.

7.5 Appendix 5: Medical history (prior and current medical history)

Summarisations of medical and surgical history prior to baseline by SOC and PT, concurrent illness and procedures at baseline by SOC and PT, and trial disease-specific medical history at baseline will be done based on the ITT analysis set. Concurrent procedures during the trial will be tabulated by SOC and PT based on the SAF.

7.6 Appendix 6: Prior and concomitant medication

Summarisations of trial disease treatments prior to baseline and concomitant medication at baseline by ATC level will be done based on the ITT analysis set. Concomitant medication during the trial will be tabulated by ATC level based on the SAF.

7.7 Appendix 7: PRO scoring algorithms

References to the scoring algorithms of the PROs are specified in Panel 25.

Panel 25: PRO scoring algorithms

DLQI	Scored according to: https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/dermatology-life-quality-index.
SF-36v2	Scored by QualityMetric Health Outcomes(tm) Scoring Software 5.0 Q provided with license. Norm-based scores will be used for analysis.
Pruritus NRS	Subjects will assess their worst itch over the past 24 hours using an 11-point NRS with 0 indicating 'no itch' and 10 indicating 'worst possible itch'.
Pain NRS	Subjects will assess their worst pain over the past 24 hours using an 11-point NRS with 0 indicating 'no pain' and 10 indicating 'worst possible pain'.
C-SSRS	The C-SSRS is a rater-administered, standardised, and validated instrument developed for the assessment of the severity and frequency of SIB (4) (5)
PHQ-8	The PHQ-8 is a validated and widely used 8-item version of the Patient Health Questionnaire depression scale designed to clinically assess subjects for symptoms and signs of depression (6)

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; NRS = numeric rating scale; PHQ-8 = Patient Health Questionnaire-8; SF-36v2 = 36-item Short Form Health Survey version 2, acute recall.

8 References

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2. Summary of product characteristics for guselkumab (Tremfya®).

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4. Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and validation of a computer-automated Columbia-Suicide Severity Rating Scale using interactive voice response technology. J Psychiatr Res. 2010;44(16)**:**1224-1228.

5. K P, GK B, B S, DA B, KV Y, MA O, GW C, GA M, L G, S S, JJ M. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12)**:**1266-1277.

6. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009;114(1-3)**:**163-173.