NOVARTIS

Clinical Development

LOU064/Remibrutinib

CLOU064I12201 / NCT05432388

A one month, investigator and participant blinded study to investigate the efficacy and safety of remibrutinib (LOU064) at multiple dose levels in adult participants with peanut allergy

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-May-2025	CCI [redacted] before final DB lock	1. remove Fisher exact test from supplementary analyses 2. clarify that supplementary estimand 1 and 3 will not be run 3. remove CTAE grade from table to avoid version conflict 4. on-treatment period has been modified to align across LOU064 trials within program 5. clarify the number for MCMC & bootstrap sampling is 10000 for Bayesian method and frequentist method, respectively 6. adding rules for unscheduled assessments 7. clarify that some analyses will not be performed because they do not target any objective specified in Protocol 8. clarify the method to estimate marginal response rates from Bayesian/frequentist logistic regression 9. clarify that up to and including 3000 mg of peanut protein (instead of 1000 mg, a typo in protocol) will be used to summarize maximum severity of symptoms	1. remove TFLs of Fisher exact test 2. remove TFLs of supplementary 1 and 3 3. NA 4. Update TFLs of safety endpoints 5. Update TFLs of MCPmod 6. NA 7. NA 8. NA 9. Update the table summarizing symptom severity	1. Section 2.5.5 Supplementary analyses 2. Section 2.5.5 Supplementary analyses 3. Section 2.7.3 Laboratory data 4. Section 2.7 Safety analyses 5. Section 2.5.2 Statistical hypothesis model, and method of analysis 6. Section 2.1 Data analysis general information 7. Section 2.6.1 Secondary endpoints 8. Section 2.5.2 Statistical hypothesis, model, and method of analysis 9. Section 2.6.1 Secondary endpoints

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of special interest
AIC	Akaike information criterion
ANCOVA	Analysis of Covariance
AUClast; AUCtau	Area under (the) curve up to last time point; for the dosing interval
CCI	[redacted]
CCI	[redacted]
BMI	Body mass index
Bpm	Beats per minute
CI	Confidence Interval
CM	Concomitant medication
Cmax	Maximum blood concentration
COVID-19	Coronavirus disease (2019)
CRO	Contract Research Organization
CRF	Case Report Form
CRS	Case Retrieval Strategy
CTCAE	Common terminology criteria for adverse event
CV	Coefficient of Variation
DB(L)	Database (lock)
DBPCFC	Double-Blind Placebo Controlled Food Challenge
CCI	[redacted]
ECG	ElectroCardioGram
ED	Effective dose
Emax	Maximum effect
EOS	End of study
HMC	Hamiltonian Monte Carlo
IA	Interim Analysis
ICH-GCP	ICH guideline for good clinical practice
IgE	Immunoglobulin E
IgG	Immunoglobulin G
LLN	Lower level of normal
LLOQ	Lower Limit of Quantification
MAR	Missing At Random
CCI	[redacted]
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MCP-Mod	Multiple Comparison Procedure – Modelling
ML	Maximum Likelihood
MTD	Maximum Tolerated Dose
OFC	Oral food challenge
PK/PD	Pharmacokinetics/Pharmacodynamics
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

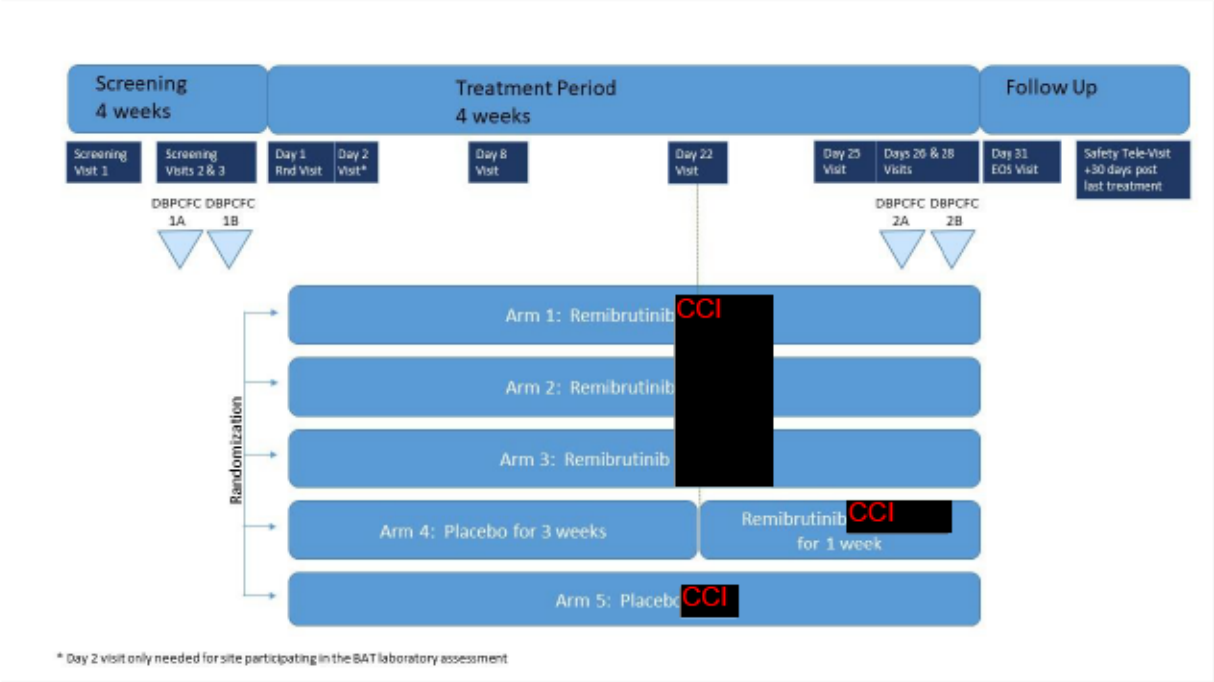
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPT	Skin Prick Test
TFLs	Tables, Figures, Listings
CCI	[redacted]
Tmax	Time to reach maximum blood concentration
ULN	Upper limit of normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organization

1 Introduction

The purpose of this document is to describe the statistical analyses relevant to meeting the objectives mentioned in the version 02 of the Phase 2 study, CLOU064I12201 protocol. All objectives will be covered in this plan with the exception of certain exploratory outputs for biomarkers that will be covered in a separate biomarker analysis plan.

1.1 Study design

Figure 1-1 Study Overview



This is a Phase 2 multi-center, randomized, participant- and investigator-blinded, placebo-controlled study to assess the safety and clinical efficacy of four dosing regimens of oral remibrutinib versus placebo (CCI for one month (4-5 weeks); CCI for one month (4-5 weeks); CCI for one month (4-5 weeks); placebo for 3 weeks followed by remibrutinib CCI for 1-2 weeks; and placebo for one month (4-5 weeks) in adult participants with a medically confirmed diagnosis of IgE-mediated peanut allergy. Approximately 72 participants will be randomized in this study to one of the five arms (randomization ratio of 2:2:2:1:1). Participants initially assigned to the 3-week placebo arm will receive the first dose of blinded remibrutinib treatment at the Day 22 visit. CCI . This is operationally handled by stratification to treatment arms based on CCI participation within the IRT system, and hence, not considered as a design parameter or confounding variable.

The primary analysis will be conducted after all participants complete the end of study visit schedule.

CCI

CCI [redacted]

CCI [redacted]

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of oral remibrutinib CCI [redacted] compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at one month	• Responder status defined as tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at one month
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of oral remibrutinib CCI [redacted] compared to placebo, as measured by the proportion of participants who can tolerate a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at one month	• Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at one month
• To evaluate the efficacy of oral remibrutinib CCI [redacted] compared to placebo, as measured by the proportion of participants who can tolerate a single dose of 3000 mg (5044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC at one month	• Responder status defined as tolerating a single dose of 3000 mg (5044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at one month
• To evaluate the efficacy of oral remibrutinib CCI [redacted] compared to placebo, as measured by the maximum symptom severity at any single challenge dose up to and including 1000 mg of peanut protein during the DBPCFC at one month	• Maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted at one month. Symptom severity will be categorized as 4 levels: None, Mild, Moderate, Severe
• To evaluate the efficacy of 3 weeks of placebo treatment followed by 1 week of oral remibrutinib C [redacted] treatment compared to one month of placebo treatment, as measured by the proportion of participants who can tolerate a single dose ≥ 600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at one month	• Responder status defined as tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at one month (3 weeks of placebo + 1 week of remibrutinib treatment vs. one month of placebo)

• To evaluate the effects of multiple doses of remibrutinib compared to placebo (when applicable), as measured by multiple systemic biomarkers to inform on response to treatment or disease severity	• Change from baseline at Weeks 1 and 4 of:
	  • peanut-specific IgE, including peanut components
	  • peanut-specific IgG4, including peanut components

Objective(s)	Endpoint(s)
• To evaluate the safety and tolerability of multiple doses of remibrutinib	• Treatment-emergent adverse events, vital signs, ECG, and laboratory values, including immunoglobulin levels
• To assess the ability of remibrutinib to impact skin mast cells through the assessment of allergen-specific skin prick test (SPT)	• Change from screening in SPT mean wheal diameters at one month
• To assess the pharmacokinetics (PK) of remibrutinib	• Remibrutinib concentrations in blood and PK parameters (including, but not necessarily limited to: Cmax, AUClast, AUCtau, Tmax)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI [redacted]	

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment). The primary clinical question of interest is to understand the treatment effect of remibrutinib over placebo among participants who have completed actual DBPCFC after one month (4-5 weeks) of treatment and regardless of intake of rescue medication prior to actual DBPCFC at one month.

The primary estimand is described by the following attributes to address the primary clinical question of interest:

- **Population**: Participants aged 18 – 55 years, inclusive, who have been diagnosed with IgE-mediated confirmed peanut allergy and met study inclusion/exclusion criteria and have undergone actual DBPCFC (2A & B) at one month (4-5 weeks).
- **Variable**: Responder status defined as tolerating a single dose of $\geq$ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted at one month (4-5 weeks). The cumulative tolerated dose is the sum of the tolerated doses, not including the reactive dose. Dose-limiting symptoms indicate a true allergic reaction occurring during administration of a single dose of peanut protein at the

actual DBPCFC that should preclude the administration of any further doses in the view of the investigator.

- **Treatment**: The randomized treatment (one of five arms specified in Section 2.1.1.1) plus rescue medication (e.g., epinephrine, short-acting beta agonist, and/or anti-histamines) prior to actual DBPCFC at one month, if needed.
- **Intercurrent events**:
  - Discontinuation of treatment prior to the End of Treatment Assessments on Days 25, 26 and 28: Participants who discontinue treatment prior to actual DBPCFC, or who miss more than 20% of treatment doses throughout the study, or who miss medication doses for ≥ 3 consecutive days in the seven days prior to the one month actual DBPCFC part 2A due to any reasons other than adverse events
  - Intake of rescue medication prior to the actual DBPCFC
- **Summary measure**: Difference in the proportion of responders between remibrutinib and placebo

Supplementary estimands to the primary estimand are defined in Section 2.5.5.

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis or a designated CRO. The most recent version of SAS available in the statistical programming environment will be used for the analysis. The computations with respect to dose-response relationship will be developed and/or validated utilizing the most recent R programming under internally validated systems and environment. Dose-response will be tested and estimated with the MCP-Mod framework implemented in the {DoseFinding} package.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

CCI [redacted]

Unscheduled assessments

The following points summarize the rule for unscheduled assessments:

- Baseline: All unscheduled assessments before the first dose should be included for consideration when calculating the baseline value
- For summary tables by visits, unscheduled assessments should not be included unless they qualify as baseline
- For shift tables, tables of abnormal values, and tables of worse post baseline all unscheduled assessments are included.

Unscheduled assessments will be reported with the scheduled assessments in the listings.

2.1.1 General definitions

2.1.1.1 Study treatment

In this document, 'study medication', 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a participant. Study drug refers to either remibrutinib or placebo.

The treatment arms in this study are as follows.

- Remibrutinib [redacted]
- Remibrutinib [redacted]
- Remibrutinib [redacted]
- Placebo for 3 weeks followed by remibrutinib [redacted] for 1 week
- Placebo

2.1.1.2 Study day

Study day will be defined as the number of days since the date of first dose of study drug. The date of first dose of study drug will be defined as Day 1 and the day before the first dose of study drug will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

for dates on or after the first date of treatment,

Study day = Assessment date – Date of first dose of study drug + 1;

for dates prior to the first date of treatment,

Study day = Assessment date – Date of first dose of study drug.

2.1.1.3 Baseline definition

In general, baseline is defined as the last measurement taken before the first dose of study drug. Details on baseline calculations if different from this general definition will be provided in the later sections.

2.1.1.4 Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of study drug.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

If not stated otherwise for efficacy analyses, on-treatment values are defined as values taken post-baseline but no later than 1 day after last dose of treatment. Off-treatment values are defined as post-baseline values taken more than 1 day after last dose of treatment.

Details on calculation of post-baseline values are provided in the later sections.

If not stated otherwise, visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows.

2.2 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety set will include all participants who received at least one dose of the actual study drug (either remibrutinib or placebo) received though the actual treatment received does not match the randomized treatment. Safety set will be utilized for all safety summaries and analyses (Note: The wording "Safety set will be utilized for all safety/efficacy summaries and analyses" in Protocol v02 Section 12.1 is inconsistent with "PD population will be used for primary analysis" specified in Protocol v02 Section 12.4.2. To resolve the conflict, the PD analysis set instead of the Safety analysis set will be used for efficacy analysis).

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received study drug (remibrutinib) and with no protocol deviations that impact on PK data.

The PD analysis set will include all participants with available PD data and no logistics/assay/analytical issues that may have impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Subjects without a signed informed consent obtained prior to participation in the study (INCL01) will be excluded from any analyses. All the protocol deviation codes and the details are included in Table 2-1.

Table 2-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Participants are excluded from specified analysis sets		
INCL01A	Signed informed consent not obtained	Exclude participants from all analysis sets
INCL06	Subjects not meeting positive DBPCFC at screening	Exclude participants from PD analysis set
OTH33	ICH-GCP non-compliance	Exclude participantss belonging to these sites from PK analysis set and PD analysis set
EXCL07	Participant has current or previous history of a mast cell disorder, including macrocytosis or tryptase > or = 20 ng/ml	Exclude participants from PD analysis set
Participants are not excluded from analysis sets, but data being impacted by protocol deviation is treated as missing value:		

Category Deviation code	Text description of deviation	Data exclusion
TRT12	Each dose (peanut/pacebo) administration at DBPCFC was not separated by at least minimum of 15 minutes	DBPCFC results will be treated as missing values for efficacy analysis
OTH20	DBPCFC stopped though participant did not experience any Dose Limiting Symptoms	DBPCFC results will be treated as missing values for efficacy analysis
OTH24	The sequence of the amounts of 1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 600 mg, 1000 mg, and 3000 mg of peanut protein and corresponding placebo was not followed at end-of-treatment DBPCFCs	DBPCFC results will be treated as missing values for efficacy analysis

Any updates to the above table will be updated via SAP amendment prior to final DBL as required.

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Participant disposition

Safety set will be used for the summary and listing of participant disposition.

The overall number of participants who completed, and discontinued the study will be summarized including the reasons for discontinuation.

Number of participants with protocol deviations will be tabulated by category (e.g., selection criteria not met, subject not withdrawn as per protocol, treatment deviation, prohibited concomitant medication, other) and deviation.

The number of participants included in each analysis set will be tabulated. Participant exclusion from analysis sets will be listed for all participants with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by study arm based on safety set.

Demographics include age, sex, race, ethnicity, weight, height and Body Mass Index (BMI). For age and BMI, both categorical and continuous summaries will be presented.

The categories for BMI are as follows:

- BMI (< 25, $25 \leq 30$, ≥ 30)

Disease related baseline characteristics include:

- Peanut specific IgE/IgG4
- Total IgE/Total IgG4
- Size of wheal diameter (SPT)
- History of allergies to other foods
- History of anaphylactic reaction to peanut

- Age at diagnosis of peanut allergy
- History of peanut desensitization therapy
- Co-morbid allergic diseases (i.e., asthma, allergic rhinitis, atopic dermatitis)

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment arm. Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The duration of exposure to study drug in days to each study arm will be summarized using descriptive statistics.

Duration of exposure to study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (Duration of exposure = (date of last known study treatment – date of first known study treatment)).

In addition, the number of doses, total cumulative dose and number of missed doses will be presented. Categorical data (in weeks) will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented.

Compliance will be calculated as the percentage of the number of days where study drug was administered as per protocol (CCI [redacted]) divided by the duration of exposure (i.e., the number of days between first and last dose).

Overall compliance will be categorized by <80% and 80% - 100% and summarized by treatment group. In addition, compliance during last week before the actual DBPCFC will be summarized as <45% and 45% - 100%

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, and preferred term by treatment arm. Any allergy related medications taken during the study treatment period will be listed separately.

2.5 Analysis supporting primary objective(s)

The primary objective of this study is to characterize the dose-response relationship between remibrutinib treatment after one month of treatment (CCI [redacted]) and placebo with respect to the responder rate as the primary endpoint. The consecutive steps are therefore (1) to confirm an overall dose response signal, (2) to estimate the dose-response curve to support selecting dose(s) for the Phase 3 studies. The Multiple Comparison Procedures – Modeling (MCP-Mod) methodology (Bretz et al 2005) will be used to address these goals.

CCI [redacted] final analysis will be performed upon end of study.

2.5.1 Primary endpoint(s)

The primary endpoint is responder rate, where responder rate is defined as the proportion of participants tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted after one month of study treatment.

2.5.2 Statistical hypothesis, model, and method of analysis

CCI [redacted]

Primary endpoint – Responder rate

The statistical analysis will be based on the PD analysis set.

The null hypothesis of a no dose-response relationship for responder rate will be tested at a significance level of 10% against the one-sided alternative hypothesis of a dose-response relationship using the MCP-Mod methodology (Bretz et al 2005, Pinheiro et al 2014).

The primary endpoint will be analyzed based on logistic regression model, including treatment arm as a categorical variable (all remibrutinib doses and placebo) and including, but not limited to, log-transformed baseline total IgE and baseline tolerated peanut allergen dose as covariates. The logistic regression model is defined as follows. The response y_{ij} for subject i in dose group j receiving dose d_j is modelled as $y_{ij} \sim Bin(1, p_{ij})$ with $p_{ij} = \text{logit}^{-1}(\delta_j + x_{ij}^T\beta)$,, where x_{ij} are covariates of subject i in dose group j, δ_j are dose-specific intercepts and β are parameters associated with the covariates, common across dose groups. Any missing values in the covariates will be replaced with the median value for that variable. All covariates will be standardized to have a mean of 0 and a standard deviation of 0.5, so they are on the same scale as the binary input (Gelman, 2008)

In case of complete separation, the Maximum Likelihood estimate of the logistic regression does not exist. If this problem is encountered, we will replace the logistic regression by a Bayesian logistic regression with weakly informative priors. The Bayesian logistic regression model follows the same model equation as above, but incorporates weakly informative priors for the model's parameters. Priors are specified as follows: for parameters associated to the

treatment arm, δ_j, a student-t distribution with a mean of 0, standard deviation of 2, and 5 degrees of freedom is employed. This choice of prior, conveys some information through its 0 mean while having a large variance (considering that the model parameters are on logit scale) to allow the data to dominate the posterior distribution. For parameters associated with the remaining standardized covariates, a normal prior is chosen with a mean of 0 and standard deviation of 2, indicating a lack of strong prior beliefs or specific information about these parameters. The Bayesian logistic regression model is fitted with the brms package on R 4.3.1, using the adaptive Hamiltonian Monte Carlo (HMC) sampler (Carpenter, et al., 2017) with 4 chains for 3,000 iterations including 500 iterations of warm-up. Convergence of the HMC will be assessed using the following diagnostics: the trace plot, the lower number of effective sample size and the highest R hat value.

Odds ratio and 80% confidence intervals (CI) will be presented comparing each remibrutinib dose to placebo with respect to the proportions of response. Similarly, marginal difference in response proportions will also be presented. If frequentist method will be used, marginal difference in responder rates with one-sided p-value and corresponding 80% CI will be estimated from the logistic regression model using the methodology described in (Ge, et al., 2011) with sandwich variance estimator (Liu & Xi, 2024) If Bayesian method will be used, marginal difference in responder rates with posterior probability of marginal difference above 0, and 80% credible interval will be provided. The posterior distribution of the marginal difference in response probabilities between dose group j and placebo (i.e., Dose=0) will be obtained based on the following formula:

$$\frac{1}{n}\sum_{i=1}^{n} P(Y = 1|Dose = j,\ X_i = x_i^T) - \frac{1}{n}\sum_{i=1}^{n}(Y = 1|Dose = 0,\ X_i = x_i^T)$$
$$= \frac{1}{n}\sum_{i=1}^{n} \text{logit}^{-1}(\delta_j + x_i^T\beta) - \frac{1}{n}\sum_{i=1}^{n} \text{logit}^{-1}(\delta_0 + x_i^T\beta)$$

Where

- $Y = 1$ represents responder
- n is the total number of participants in the study
- x_i^T are covariates of subject i
- δ_j are dose-specific intercepts (j = 0 corresponding to placebo)

β are parameters associated with the covariates, common across dose groups. With a MCMC sample from the posterior distribution for δ_j, δ_0, β, the posterior distribution for the mean difference in marginal response rates can be derived as well as the posterior mean and 80% credible interval and the probability of marginal differences above 0 could be derived.

Generalized MCP-Mod (Pinheiro et al 2014) will be applied based on the estimates and SE of the proportion of responders from the frequentist logistic regression model. The CCI 1-week treatment regimen will not be included in the dose response model fit. To perform generalized MCP-Mod trend test, the adjusted values of the proportion of responders for remibrutinib versus

placebo arm and associated covariance matrix will be obtained from the model. If the Bayesian logistic regression is used, we will adopt the Bayesian MCP-Mod framework proposed by.(Fleischer, et al., 2022).To perform the Bayesian MCP step, we use the optimal contrast vectors calculated from the regular MCP-Mod that is, ignoring any information from the prior. For each model shape, the posterior probability will be calculated such that the underlying contrast is greater than 0. The Bayesian Mod step follows the same procedure as the frequentist Mod Step, except that MCMC samples are used instead of bootstrap samples.

For each candidate model a contrast test statistic, based on a linear combination of the treatment estimates per dose will be derived. The contrast coefficients will be chosen to maximize the power to detect pre-specified candidate models. For that purpose, beta model, E_{max} and sigmoid E_{max} dose-response shapes will be selected. For the E_{max} model ($E_0+E_{max}*d/(d+ED_{50})$), two shapes with ED_{50}= CCI will be used, while for the sigmoid E_{max} model ($E_0+E_{max}*d^h/(d^h+ED_{50}^h)$) two shapes with ($ED_{50}$, h) = (CCI and (CCI) will be utilized, where E_0 is the expected placebo effect, E_{max} is the maximum change in effect over placebo, ED_{50} is the dose at with which 50% of E_{max} is achieved and h is Hill parameter, and a betamod $f(d, \theta) = E0 + EmaxB(\delta1, \delta2)(d/scal)^{\delta1}(1 - d/scal)^{\delta2}$ shape with (scale, δ1, δ2)=(CCI) to capture the nonmonotone dose-response relationship (Figure 2-1).

Figure 2-1 CCI

CCI

Optimal contrasts will be derived for the remibrutinib CCI dose regimen dose-response curves according to the model shapes above .

The global test decision is based on the maximum of all contrast test statistics from the proposed candidate shapes. A critical value q controlling the type I error rate can be derived from the fact that the contrast test statistics approximately follow an asymptotic multivariate normal distribution. If the maximum contrast test statistic exceeds the critical value q, the overall null

hypothesis of a constant dose-response curve is rejected and proceeds to the estimation steps to determine the dose-response curve.

Dose response curve and target dose estimation (dose-finding step)

Once statistically significant dose-response relationship is established, the dose-response modeling will be performed with a combination of bootstrapping and model averaging based on the choice of candidate models.

Dose-response estimation for a sigmoid E_{max} or beta model, if selected, will be fit by fixing the CCI for the sigmoid Emax model, and fixing the location of the maximum effect for the beta model (keeping the ratio $\delta1/(\delta1+\delta2)$ fixed).

As different models contribute to the bootstrap resamples, the approach can be considered more robust than simple model selection (Schorning et al 2016) in the generalized MCP-Mod framework.

First, we draw bootstrap samples repeated 10000 times from the multivariate normal distribution of the estimates originating from the first-stage model. Next, for each bootstrapped data set we fit our candidate models, select the one with lowest AIC and save the corresponding estimated quantities of interest. This selection step implies that the bootstrap samples potentially come from different models.

Median from all the bootstrapped means and confidence limits for each dose-level around model-averaged predictions will be obtained using a non-parametric bootstrap procedure repeated at least 10,000 times.

Results of the model-averaged analysis will be presented for each dose, including the placebo-adjusted estimates of the responder rate and its associated 80% CI.

2.5.3 Handling of intercurrent events

The primary analysis will account for different intercurrent events as described below.

1. The primary analysis will be performed with completers only assuming dropouts occur completely at random. A completer is defined as a participant who completes DBPCFC after one month of study treatment or three weeks of placebo plus one week of study treatment. In other words, treatment policy strategy is applied here. Missing outcomes due to treatment discontinuation/interruption are assumed to occur at random and ignored.
2. Intake of rescue medication prior to DBPCFC conducted before one month: ignorable (treatment policy strategy, reflected in the Treatment attribute)

2.5.4 Sensitivity analyses

To show treatment effect without the benefit of prohibited medications as a sensitivity analysis, the primary analysis will be repeated with DBPCFC results took after the relevant use of prohibited medication (i.e., having protocol deviation coded as COMD01 – participant took prohibited medication mentioned in Protocol V2 Table 6-4 or took medication that was not allowed under certain conditions during study mentioned in Protocol V2 Table 6-2) being treated as missing values.

2.5.5 Supplementary analyses

In addition to completer analysis as the primary, the below estimands will be considered:

1. (Note: Given that the sample size has been largely reduced from 110 to 72, and responder rate to peanut protein is only measured at one single post-dose time point (i.e., at one month), supplementary estimands 1 and 3 that implement multiple imputation will not be performed. Supplementary estimand 1: Participants who do not undergo DBPCFC at one month. due to any reason [including operational complications caused by public health emergency (i.e., COVID-19)] other than AEs will be imputed under Missing at Random (MAR) assumption. The interest lies in the responder status after one month of treatment that would be observed if participants had not discontinued study due to reasons other than AEs before one month of treatment (hypothetical strategy).
2. Supplementary estimand 2: Composite strategy will be considered in addition to hypothetical strategy assuming any participant missing DBPCFC other than due to public health emergency (i.e., COVID-19) or participant missing doses >20% as non-responders.
3. Supplementary estimand 3: Treatment policy will also be considered to show the treatment effect in real-world conditions. Missing DBPCFC outcome in participants who discontinue remibrutinib or who miss more than 20% of study doses throughout the study treatment period or who miss doses ≥ 3 consecutive days in the 7 days prior to end-of-treatment visit on Day 26 for reasons other than adverse events before Part 2 DBPCFC visit will be imputed based on copy reference.
4. Supplementary estimand 4: to show treatment effect if treatment failure had not occurred, participants who had dose-limiting symptoms at any dose of the post-treatment blinded OFC to placebo will be considered as non-responders

Intake of rescue medication prior to DBPCFC conducted at end of study after one month of treatment: consider ignorable (treatment policy strategy, reflected in the treatment attribute) for all estimand strategies.

In addition to the primary analysis, we will analyze primary endpoint under primary estimand with Bayesian logistic regression model utilizing historical data on the placebo arm. The priors are the same as the Bayesian logistic regaression with weakly informative described in the Section 2.5.2, except for the dose-specific intercept, δ_j, that corresponds to the placebo arm (i.e., for $d_j = 0$), which will include information of historical data by using robustified meta-analytic predictive prior (MAP). Placebo information was obtained from both internal and external historic data is presented in Table 2-2. The MAP is derived from historical data using a hierarchical Binomial model as implemented in the RBesT package. The placebo's response probability in the logit scale is the sum of an intercept and trial-specific random effects. For the prior on the intercept, we use a normal distribution with a mean of –2.94 (= logit(0.05)) and a standard deviation of 2. We use the recommended conservative Half-Normal with mean 0 and standard deviation 1 for the prior of the between-trial heterogeneity parameter. The MAP prior on the placebo's response probability in the logit scale, represented numerically using a large MCMC simulation sample, is approximated by a mixture of normal distributions. To further robustify the prior for potential differences across the historical data and the trial data, a non-informative component is added to the mixture prior with a weight of 50% (Schmidli, et al., 2014).The Bayesian MCP-Mod framework is applied as described in Section 2.5.2. Similar outputs as primary analysis will be generated.

Table 2-2 Historical trial placebo data from external publications and internal studies

Table	External data	Number of participants	Responders
Palforzia PII	Yes	26	0
Palforzia PIII	Yes	138	7
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary efficacy endpoints will be analyzed as follows:

- Responder status defined as tolerating a single dose of ≥ 1000 mg (2044 mg cumulative tolerated dose), and 3000 mg (5044 mg cumulative tolerated dose) peanut protein without dose-limiting symptoms after three weeks placebo plus one week study treatment plus OR after one month of treatment dosing period. The proportion of responders will be analyzed for 1000 mg and 3000 mg peanut protein dose separately utilizing the same logistic regression model proposed for the primary analysis. Proportion of responders and 80% CI will be presented for 1000 mg and 3000 mg peanut protein dose, respectively.
- Categorical summaries will be generated for maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 3000 mg during the actual DBPCFC conducted after three weeks placebo plus one week study treatment and after one month of treatment dosing period. Symptom severity will be categorized as 4 levels: None, Mild, Moderate, Severe. Proportion of participants will be summarized descriptively by severity levels for the corresponding allergen dose and symptoms.
- (Note: Analysis specified in this bullet point will not be performed because it does not target any objective listed in Protocol) Change in maximum tolerated dose (MTD) of peanut protein without dose-limiting symptoms during the actual DBPCFC after one month of treatment compared to after 1 week of treatment for remibrutinib CCI [redacted] treatment arms: MTD (log-transformed scale) after one month along with changes from baseline and changes from after 1 week of treatment will be summarized descriptively.

  An analysis of covariance (ANCOVA) model for change from baseline in log transformed MTD for actual DBPCFC administered after post-treatment will be fit with terms including, treatment arm, log-transformed baseline total IgE, and log-transformed maximum tolerated allergen dose at baseline. Model adjusted means and 80% CIs will be presented for each of the treatment arms over placebo.
- (Note: Analysis specified in this bullet point will not be performed because it does not target any objective listed in Protocol) Responder status defined as tolerating a maximum single dose of peanut protein without dose-limiting symptoms after 1week or after one month of treatment.

  The proportion of responders for the allergen dose defined as ordinal categorical variable ranging from 0-3000 mg will be analyzed utilizing the proportional odds model. The model will include treatment arm, log-transformed baseline total IgE, and log-transformed

maximum tolerated allergen dose at baseline. Proportion of responders and 80% CI will be presented for each of the peanut allergen dose challenge administered to the participants.

A Kaplan-Meier plot with responder rate vs. peanut allergen dose after one month or after 1 week of treatment will be presented to show any differences across treatment arms (i.e., remibrutinib doses, placebo).

- Change from baseline in peanut-specific IgE and IgG4 after one week/after one month of treatment: Summary statistics, including geometric means and geometric standard deviations, will be presented for peanut-specific IgE and IgG4 along with changes from baseline by time point and treatment group. Change from baseline in log-transformed levels of peanut specific-IgE and peanut specific-IgG4 after one week/one month of treatment will be analyzed using an ANCOVA model with terms for treatment arm, and log-transformed baseline peanut specific-IgE or peanut specific-IgG4.

  Ratio of peanut specific IgE to IgG4 for all participants at baseline and post-baseline will be plotted by treatment arm and the descriptive summaries of this ratio will be reported.
- Responder status defined as tolerating a single dose of $\geq$ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the DBPCFC conducted after one week of treatment (3 weeks of placebo + 1 week of remibrutinib treatment vs. placebo). Proportion of responders and 80% CI over placebo will be presented with the same logistic regression model as defined for the primary analysis.
- Change from baseline in wheal size diameters from SPT after one week/after one month of treatment will be analyzed using ANCOVA with baseline wheal size as a covariate and the change from baseline will also be summarized descriptively. Model adjusted means and 80% confidence intervals will be presented for each of the treatment arms over placebo.

2.7 Safety analyses

For all safety analyses, the safety set will be used. All listings will be presented by treatment group and tables will be presented by treatment arm and overall. For the 3 weeks Placebo followed by remibrutinib CCI for 1 week arm, the AEs will be listed by the placebo period and remibrutinib period separately to differentiate the AEs that occurred during the respective period.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of baseline data from Screening Visits 1, 2 and 3 which will also be summarized where appropriate (e.g. change from screening summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period.

The on-treatment period lasts from the date of first administration of study treatment (Day 1) to 28 days after the end of treatment.

2.7.1 Adverse events (AEs)

All AEs summarized will be displayed by treatment group and overall. All AEs listings will be presented by treatment arm and participant.

All events that the investigator classifies as reactions associated to the DBPCFC or SPT must be captured on the designated eCRF and will not be reported on the AE eCRF. These events will be reported separately and not included in reporting of treatment-emergent AEs (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term).

The number (and percentage) of participants with treatment emergent AEs will be summarized in the following ways:

1. by treatment, primary system organ class and preferred term
2. by treatment, primary system organ class, preferred term and maximum severity
3. by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study medication related AEs, death, serious adverse events (SAEs), and other significant AEs leading to discontinuation. In case of sparse events in any of these categories occur, only a listing will be provided if deemed adequate.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

For the legal requirements of clinicaltrials.gov, two required tables on treatment-emergent AEs which are not SAEs with an incidence greater than a certain threshold based on the final database and on treatment-emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and PT on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

a. a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
b. more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

AEs of special interest (AESI) are defined in the latest version of the compound electronic Case Retrieval Strategy (eCRS). The classification reflects the safety topics of interest identified in the current version of the remibrutinib Development Safety Profiling Plan, and may be updated based on review of accumulating data. The number and percentage of participants with treatment emergent AEs of special interest will be summarized by risk category, PT and treatment.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest. The most recent list of adverse events

of special interest at the time of database lock will be used. CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

2.7.2 Deaths

All deaths in the clinical database that occur during the treatment period will be listed.

2.7.3 Laboratory data

All laboratory data will be listed by treatment group, participant, and visit/time and, if normal ranges are available, abnormalities will be flagged. The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

Summary statistics will be provided by visit/time for treatment group, and overall. Shift tables using the low/normal/high/(low and high) classification will be used to compare baseline to the worst on-treatment value.

The laboratory parametersin Table 2-3 will be analyzed with respect to numerical Common Terminology Criteria for Adverse Event (CTCAE) grades (according to the most recent version)

Table 2-3 Laboratory parameters

Abnormality	Lab parameter
Hematology	
Anemia	Hemoglobin (g/L)
Platelet count decreased	Platelets (thrombocytes) (10^9/L)
White blood cell decreased	Leukocytes (WBCs) (10^9/L)
Neutrophil count decreased	Absolute neutrophil count (10^9/L)
Lymphocyte count decreased	Absolute lymphocyte count (10^9/L)
Lymphocyte count increased	Absolute lymphocyte count (10^9/L)
Chemistry	
Liver function	
Alanine aminotransferase increased	ALT (SGPT) (U/L)
Aspartate aminotransferase increased	AST (SGOT) (U/L)
Blood bilirubin increased	Bilirubin (µmol/L)
GGT increased	Gamma-glutamyl transferase (GGT) (U/L)
Alkaline phosphatase increased	Alkaline Phosphatase (U/L)

Abnormality	Lab parameter
Renal function	
Creatinine increased*	Creatinine (µmol/L)
Blood urea Nitrogen (BUN) increased	Urea
INR increased**	International normalized ratio
Lipids	
Cholesterol high	Cholesterol Total (mmol/L)
Hypertriglyceridemia	Triglycerides (mmol/L)

The number and percentage of participants with new or worsening laboratory abnormalities based on CTCAE grade in each visit-window and at any time post baseline will be presented. Participants with specific laboratory abnormalities (defined by CTCAE grade 3 and 4) will be listed. A case is considered as newly occurring abnormality if the value is not notable or missing at baseline but is notable thereafter. A case is considered as worsening abnormality if the value is notable at baseline and at least one post-baseline value during is worse than baseline.

Shift tables will be provided on CTCAE grades to compare baseline relative to the worst grade. These summaries will be split into hematology and chemistry, and will be presented by treatment group.

Potential drug-induced liver injuries will be evaluated by means of newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-4. A case will be considered as newly occurring if a criterion is not met or missing at baseline but is met thereafter. A case is considered as worsening abnormality if the value is notable at baseline and at least one post-baseline value during is worse than baseline.

For criteria defined by the combination of abnormal parameters in Table 2-3, the identification of cases will be based on a time window between the individual abnormal values of up to end of treatment period. Modified eDISH plots will be generated for potential Hy's law cases.

Liver function tests will also be presented graphically as matrix plots of each of the parameters (ALT, AST, TBL, ALP) maximum post-baseline/upper limit of normal (ULN) normalized.

Table 2-4 Liver enzyme abnormalities

Parameter	**Criterion**
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1xULN; >1.5xULN; >2xULN; >3xULN
ALP	>1.5xULN; >2xULN; >5xULN
(ALT or AST) & TBL	>3xULN & (TBL>1.5xULN; >2xULN)
(ALT or AST) & INR	>3xULN & INR>1.5
ALP & TBL	>3xULN; >5xULN & TBL>2xUL
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law)**.

Similary, participants meeting specific renal alert criteria at any post-baseline will be summarized according to Table 2-5.

Table 2-5 Specific renal alert criteria

Parameter	Notable criterion
Serum creatinine	increase 25% – 49% (%change from baseline), increase ≥ 50%
Dipstick proteinuria	≥ 3+ (Newly occurring)
Dipstick hematuria (occult blood)	≥ 3+ (Newly occurring)

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

ECG data will be collected at scheduled visits in single ECGs or triplicate ECGs. If triplicate ECGs are performed, then average of the non-missing values of the 3 measurements will be used in the analysis. Clinically significant findings from ECG evaluations will be reported as AEs and included in the analysis of AEs. ECG parameters include max heart rate, mean PR duration, mean QT duration, mean QRS duration, and QT corrected using Fridericia's correction formula. Descriptive statistics of each ECG parameter will be provided by treatment group and by visit.

The number and percentage of participants meeting the criteria defined in table below will be provided for each criterion by treatment group and by visit.

Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits (Table 2-6) in terms of absolute QT/QTc intervals or changes from baseline will be presented.

All ECG data will be listed by treatment group, participant and visit/time, and abnormalities will be flagged. Summary statistics and graphical presentations (e.g. boxplots) will be provided by treatment and visit/time.

Table 2-6 Criteria for relevant ECG absolute or change from baseline values

Absolute values criteria	
QT interval	>500 msec
QTcF:	>450 msec (males)
	>460 msec (females)
PR:	>200 msec
QRS complex:	>120 msec
Changes from baseline criteria	
QRS complex :	increase >25% compared to baseline
QTcF	increase >60 msec compared to baseline

2.7.4.2 Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and, if ranges are available, abnormalities (Table 2-7) (and relevant orthostatic changes) will be flagged. Summary statistics and graphical presentations (e.g. boxplots) will be provided by treatment and visit/time.

Table 2-7 Clinical notable criteria for vital signs

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 90	≥ 140
Diastolic blood pressure (mmHg)	< 60	≥ 90
Pulse rate (bpm)	< 50	> 100
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease > 7% from baseline	Increase > 7% from baseline

2.8 Pharmacokinetic endpoints

Descriptive statistics of remibrutinib blood concentration data will be provided by treatment arm, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Relevant PK parameters will be listed by treatment arm and participant. Descriptive summary statistics for PK parameters will be provided by treatment arm. An exception to this is Tmax where median, minimum and maximum will be presented. PK analysis set will be utilized for all summaries and figures.

2.9 PD and PK/PD analyses

The PK and PD properties of remibrutinib and its effect on relevant biomarker changes (SPT) that will impact the clinical endpoints (i.e., responder rate at various peanut allergen doses) will be explored graphically and via longitudinal models (i.e., Mixed model) as appropriate. Details of the modeling plan will be documented in a separate PK/PD analysis plan.

2.10 CCI

CCI

CCI

2.11 Interim analysis

CCI [redacted]

3 Sample size calculation

The primary objective of this study is to characterize the dose-response relationship among remibrutinib doses (CCI [redacted]) and placebo with respect to the primary endpoint, responder rate after one month of treatment. The sample size was determined with DesignMCPMod (v0.1.2) application

Approximately 14 completers per remibrutinib 1-month treatment arm and 7 completers on the placebo arm provides at least 80% power (power over the different chosen candidate models assumed) to detect a dose-response relationship for a one-sided alpha of 10%, assuming a true maximum treatment effect of CCI [redacted] responder rate and placebo treatment effect of CCI [redacted] responder rate.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 3-1 CCI [redacted]

CCI [redacted]

4 Change to protocol specified analyses

No changes proposed from the protocol specified analyses.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation of missing/partial start or end study drug date. If missing, the time of study end date will be imputed to 00:00:00.

5.1.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, then the imputed end date should be set to the earliest of the study end date, 31DECYYYY or date of death.
- If the AE end date day is missing, then the imputed end date should be set to the earliest of the study end date, last day of the month or date of death.
- If AE year is missing or AE is ongoing, then the end date will not be imputed.

Rules for imputing the AE start date:

1. If imputing end dates, then this should be done prior to calculating imputed start dates.

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date, then AE start reference date = min(informed consent date, earliest visit date).
- Otherwise, AE start reference date = treatment start date.

Impute AE start date:

- If the AE start date year value is missing, then the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, then the imputed AE start date is set to NULL.

- If the AE start date year value is less than the treatment start date year value, then the AE started before treatment. Therefore:
  - If AE month is missing, then the imputed AE start date is set to the mid-year point (01JULYYYY).
  - Otherwise, if AE month is not missing, then the imputed AE start date is set to the mid-month point (15MONYYYY).
- If the AE start date year value is greater than the treatment start date year value, then the AE started after treatment. Therefore:
  - If the AE month is missing, then the imputed AE start date is set to the year start point (01JANYYYY).
  - Otherwise, if the AE month is not missing, then the imputed AE start date is set to the later of month start point (01MONYYYY) or AE start reference date + 1 day.
- If the AE start date year value is equal to the treatment start date year value:
  - If the AE month is missing, then the imputed AE start date is set to the AE reference start date + 1 day.
  - If the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
  - Otherwise, if the AE month is equal to the treatment start date month or greater than the treatment start date month, then the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date (including on-going records):

a) If imputing end dates, this should be done prior to calculating imputed start dates.
b) When the medication is ongoing at the end of the study, no numeric end date is derived.
c) If the end date is completely missing no numeric end date is derived.

1. If CM end day is missing and CM month/year are non-missing, then impute CM date as the minimum of study end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing, then impute CM date as the minimum of study end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the complete CM start date, use the complete CM start date as the imputed CM end date.

Rules for imputing the CM start date:

If imputing end dates, then this should be done prior to calculating imputed start dates.

- If the CM start date year value is missing, then the imputed CM start date is set to one day prior to Treatment start date (TR01SDT).

  - If the CM start date year value is less than the *Treatment start date (TR01SDT)* year value, then the CM started before treatment. Therefore;
  - If the CM month is missing, then the imputed CM start date is set to the mid-year point (01JULYYYY).
  - Else if the CM month is not missing, then the imputed CM start date is set to the mid-month point (15MONYYYY).
- If the CM start date year value is greater than the *Treatment start date (TR01SDT)* year value, the CM started after treatment. Therefore;
  - If the CM month is missing, then the imputed CM start date is set to the year start point (01JANYYYY).
  - Else if the CM month is not missing, then the imputed CM start date is set to the month start point (01MONYYYY).
- If the CM start date year value is equal to the *Treatment start date (TR01SDT)* year value;
  - And the CM month is missing or the CM month is equal to the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to one day prior *Treatment start date (TR01SDT).*
  - Else if the CM month is less than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the mid-month point (15MONYYYY).
  - Else if the CM month is greater than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the complete (imputed) CM end date, then imputed CM start date should be set to the complete (imputed) CM end date.

If there is no end date and ongoing check is not ticked, the CM will be considered as ongoing and included in the summary table.

5.2 Laboratory parameters derivations

Refer to Section 16.2 of the protocol for clinically notable laboratory values for hepatotoxicity.

Refer to Section 16.3 of the protocol for clinically notable laboratory values for nephrotoxicity

- Discontinuation of the study treatment should be considered if the abnormal hematology parameter is confirmed:Hemoglobin: < 10 g/dL
- Platelets: < 75 000/mm^3
- Leukocytes: < 3 000/mm^3
- Neutrophils: < 1 500/mm^3

For all other laboratory assessments, the Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report (which the investigator should review and sign-off) and the investigator will report any values considered clinically significant in the CRF.

5.3 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.4 Laboratory parameters derivations

The following table shows the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Table 5-1 Directions of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Hemoglobin	Low
Hematocrit	Low
Erythrocytes	Low
WBC	Low and high
Basophils	High
Eosinophils	High
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high

B. Chemistry	
Albumin	Low
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High
Potassium	Low and high
Magnesium	Low and high
Calcium	Low and high
LDH	High
Phosphorus	Low and high
Sodium	Low and high
CRP	High
Fibrinogen	High
HbA1c	Low and high

5.5 Statistical models

The proportion of participants tolerating a single dose of ≥ 600 mg (1044 mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms during the actual DBPCFC after remibrutinib treatment will be analyzed using a logistic regression model. The model will include terms for treatment arm, baseline peanut allergen tolerated dose and log-transformed baseline total IgE as continuous covariates.

The SAS procedure PROC GLIMMIX will be used. Odds ratios will be presented with associated 80% confidence intervals for treatment comparison of each treatment arm vs. placebo.

Multiple imputation for primary estimand:

The following steps will be used for imputation of missing response status under hypothetical strategy (Supplementary estimand 1):

- The missing response status will be imputed using multiple imputation method under MAR assumption. Missing values will be imputed separately for each treatment group using a logistic model log-transformed baseline total IgE , log-transformed maximum tolerate peanut dose at baseline, as continuous covariates based on fully conditional specification (FCS) method for 100 times. This results in 100 imputed datasets. SAS procedure PROC MI can be used to generate the multiple imputed datasets with seed for the random function set to 73468 for this study.
- The final imputed dataset where all the missing values are filled will be analyzed using a logistic regression model utilized for primary analysis.
- In the next step, the estimates and standard errors of the log(odds ratio) based on the 100 imputed datasets will be combined by applying Rubin's rules for multiple imputed data sets, see Little and Rubin (2002). The SAS procedure PROC MIANALYZE will be used for combining the results considering the linear scale and then we will take exponential of combined result to obtain the odds ratio and 80% CI.

Proportional odds model:

The proportion of responders for the allergen dose defined as ordinal categorical variable ranging from 0-3000 mg will be analyzed utilizing the proportional odds model with dose categories, [0-300], (300-600], (600-3000].

The SAS procedure PROC GENMOD will be used for analysis. A cumulative logit link function will be used. Odds ratio will be presented with associated 80% confidence intervals for treatment comparison of each treatment arm versus placebo.

5.6 Rule of exclusion criteria of analysis sets

Table 5-2 Criteria leading to exclusion

Analysis Set	Criteria that cause subjects to be excluded
Safety	Not randomized and/or no study drug taken/or no consent signed
PD	Not randomized and/or no study drug taken and/or no consent signed and/or ICH-GCP non-compliance and/or violation of key eligibility criteria

6 References

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