NOVARTIS

Novartis Research and Development

LOU064

Clinical Trial Protocol 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

Document type:	Amended Protocol Version
EUDRACT number:	2021-006950-30
Version number:	v02 (clean)
Clinical Trial Phase:	II
Release date:	09-Jan-2024

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
CCI	[redacted]
BCRP	Breast cancer resistance protein
CCI	[redacted]
BTK/ BTKi	Bruton's tyrosine kinase / Bruton's tyrosine kinase inhibitor
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CRA	Clinical research associate
CRO	Contract Research Organization
CSR	Clinical study report
CSU	Chronic spontaneous urticaria
CT	Computed tomography
DBL	Database lock
DBPCFC	Double-blind placebo controlled food challenge
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimate glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medical Authority
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD/IUS	intrauterine device / intrauterine system
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAR	Missing at random
CCI	[redacted]
MCP-MoD	Multiple Comparison Procedures – Modeling
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
msec	milliseconds
MTD	Maximum Tolerated Dose
NOAC	Novel oral anti-coagulants
PA	posteroanterior
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PT	prothrombin time
CCI	[redacted]
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
sIgE	Allergen specific IgE
SmQ	Standardized MedDRA Query
SOP	Standard operating procedure
SPT	Skin prick test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
ULN	Upper limit of normal
WHO	World Health Organization

WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.

Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.

Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 02 (January 2024)

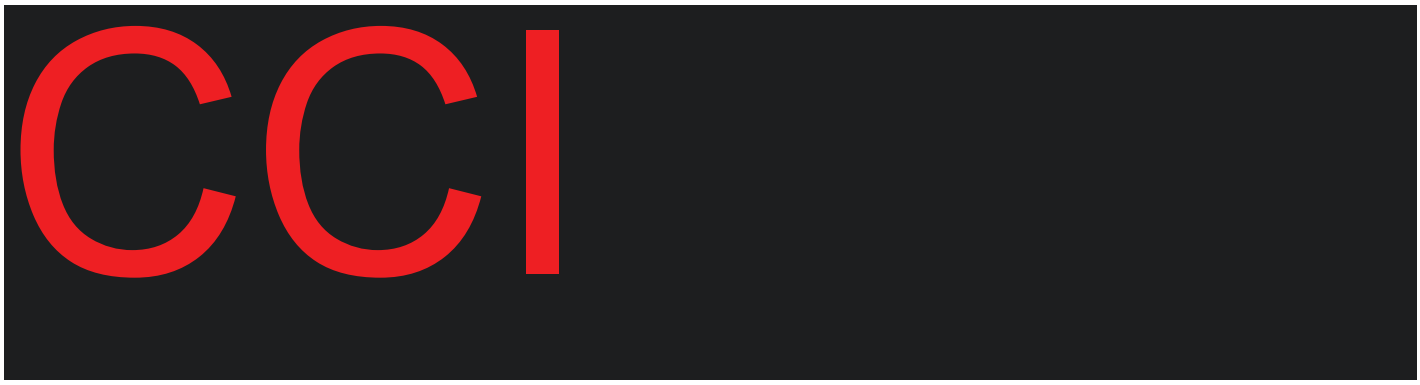
Amendment Rationale

The main purpose of this amendment is to reduce the overall sample size and adapt the randomization ratio to 2:1 as outlined below. These adaptations enable the assessment of the primary study objective with fewer subjects.

- The total sample size is reduced from 110 to 72 participants. The initial assumption for powering the study was to consider a CCI treatment effect (CCI on remibrutinib and CCI on placebo). The recent evidence from the acalabrutinib (BTKi) study (Suresh et al 2023) supports an assumption of an increased remibrutinib true response rate to 80%. Hence, the study is still powered with the reduced sample size, assuming now CCI treatment effect (CCI). It is acknowledged that, in the original version of the protocol, it was incorrectly written in the sample size Section 12.8.1, that the assumed response rate for remibrutinib in the power calculations was CCI in fact an assumed response rate of CCI was used in these original calculations.
- The overall randomization ratio is updated from 1:1:1:1:1 to 2:2:2:1:1 CCI Fewer participants will be assigned to the placebo arm since the trial is still sufficiently powered for its primary objective with the updated assumption for the treatment effect as previously explained (please refer to Section 12.8). The number of participants enrolled to the 1 week arm is also reduced since this information is considered secondary and does not contribute to the primary study objective.
- In addition, placebo response rates from other clinical trials (both available internal and published external data) will be leveraged to estimate the placebo response rate in this trial in a supplementary Bayesian analysis (please refer to Section 12.4.6).
- The protocol is updated to correct inconsistencies concerning the timing of the ECG analysis.
- The protocol is updated further in order to align with the latest information in the IB.

Additionally, this amendment made some other administrative and minor modifications to clarify or correct certain points, improving readability and to assure alignment between different protocol sections.

Changes to the protocol



IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulation prior to implementation. In addition, the changes herein will affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 01 (February 2023)

Amendment Rationale

This protocol amendment addresses the following changes:

Additionally, this amendment made some other administrative and minor modifications to clarify or correct certain points, improving readability and to assure alignment between different protocol sections.

Changes to the protocol

CCI

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulation prior to implementation.

Protocol summary

Protocol number	LOU064I12201
Full Title	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
Brief title	Study of efficacy, safety and tolerability of remibrutinib in adult participants with an allergy to peanuts
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose	To assess the safety, efficacy, and tolerability of remibrutinib at three doses versus placebo in adult participants who have a confirmed IgE-mediated allergy to peanuts.
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 double-blind, placebo-controlled food challenge (DBPCFC) after one month of treatment.
Secondary Objectives	• 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 after one month of treatment • 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 after one month of treatment • 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 after one month of treatment • To evaluate the efficacy of 3 weeks of placebo treatment followed by 1 week of oral remibrutinib CCI [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 after one month of treatment • 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 • To evaluate the safety and tolerability of multiple doses of remibrutinib • To assess the ability of remibrutinib to impact skin mast cells through the assessment of allergen-specific skin prick test (SPT) • To assess the pharmacokinetics (PK) of remibrutinib

Study design	This is a randomized, investigator- and participant-blinded study of remibrutinib compared to placebo, evaluating 5 treatment arms: CCI [redacted] for one month OR placebo for 3 weeks, followed by CCI [redacted] for one week OR placebo for one month in 2:2:2:1:1 ratio. Total study treatment duration is one month.
Rationale	This study design has been used in pivotal phase III studies of food allergy therapies, including the ongoing ligelizumab program and those supporting the recent regulatory approval of Palforzia®. The randomized, participant- and investigator-blinded, parallel-group, placebo-controlled design supports assessment of the ability of the treatment to shift the level of reactivity against the peanut allergen during a DBPCFC.
Study population	The study population includes up to 72 adult male and female participants age 18 - 55 years, inclusive. Participants may have multiple food allergies, but must be peanut allergic in order to be included.
Key Inclusion criteria	• Male or female age 18-55 years inclusive • Documented history of allergy to peanuts or peanut-containing foods • Peanut-specific IgE (sIgE) ≥ 0.35 kUA/L at screening • Positive skin prick test for peanut allergen at screening • Positive DBPCFC test at screening • Must be able to comply with study treatments and assessment schedule
Key Exclusion criteria	• Previous use of BTK inhibitors • Use of investigational drugs within 5 half-lives or 30 days prior to screening • History of hypersensitivity to study drug, its excipients, or drugs of similar class; hypersensitivity or intolerance to any of the matrix materials used in the DBPCFC • History of severe or life-threatening hypersensitivity requiring ICU admission or intubation within 60 days of screening • Reaction to placebo at screening DBPCFC • Uncontrolled asthma • History of mast cell disorder • Any clinically significant disease that, in the opinion of the investigator, would put the safety of the patient at risk through participating, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study, or would compromise patient compliance or preclude completion of the study • History of malignancy in past 5 years • Clinically significant cardiovascular conditions including ECG abnormalities • Significant bleeding risk or coagulation disorders and/or use of anticoagulant medications (except aspirin or clopidogrel monotherapies) • History of clinically significant gastrointestinal bleed • History of splenectomy • Receipt of live or live-attenuated vaccines within 6 weeks of screening • Major surgery within 8 weeks of screening, or planned surgery during study period • Use of prohibited medications, including moderate and strong CYP3A4 inhibitors and inducers within 2 weeks of screening

	• Known active/ongoing, chronic or recurrent infection from viral, bacterial, fungal or helminth etiologies including but not limited to hepatitis B and C and HIV and TB • Active, chronic disease of the immune system (including stable disease with immune therapies) • Female participants must agree to use acceptable forms of birth control for the duration of the study
Study treatment	remibrutinib (LOU064) or placebo
Efficacy assessments	Efficacy will be measured by the double-blind, placebo-controlled food challenge (DBPCFC)
Key safety assessments	Safety assessments will include the following: • Physical examination • Vital signs • Laboratory evaluations • ECG (electrocardiogram) • Pregnancy testing (women of childbearing potential only) • Adverse event/serious adverse event assessment
Data analysis	The primary objective is to determine the difference in the proportion of participants able to tolerate a single dose of ≥600 mg (1044 mg cumulative tolerated dose) of peanut protein after one month of treatment. Logistic regression will be performed for responder analysis.
Key words	remibrutinib, BTKi, food allergy, peanut allergy, adult

1 Introduction

1.1 Background

Food allergy affects people of all ages and nations and, given its prevalence and the costs associated with the disease, it represents an emerging population health priority (Warren et al 2020). An estimated 11% of US adults and approximately 8% of US children are affected by food allergies (Gupta et al 2019). The overall economic cost of food allergy is estimated at approximately $24.8 billion annually (Gupta et al 2019).

The National Institutes of Health (NIH) Food Allergy Expert Panel defines food allergy as a specific IgE-mediated adverse reaction to a given food (Boyce et al 2011). A slightly broader definition by the European Academy of Allergy and Clinical Immunology (EAACI) regards food allergy as an immune mediated adverse reaction to food involving specific IgE-mediated, cell-mediated, or combined IgE and cellular mechanisms (Muraro et al 2014). Peanut allergy is an IgE-mediated disease and, in peanut allergic individuals, ingestion of small quantities of the allergen may lead to severe and potentially life-threatening allergic reactions (Wood 2003).

The underlying pathogenesis of food allergy involves an immunologic mechanism in which IgE is synthesized in response to allergen exposure and binds to high affinity receptors for IgE (FcεRI receptors) via its Fc region on the surface membranes of mast cells and basophils (Sampson et al 2006). Cross-linking of receptor-bound IgE molecules occurs on re-exposure to the allergen and results in cell activation and mediator release (Peavy, Metcalfe 2008). IgE also contributes to the intensity of the reaction by enhancing the expression of FcεRI on mast cells and basophils. Mast cells and basophils play an important role in initiating and amplifying the acute allergic response through the release of preformed chemical mediators of inflammation, as well as newly generated mediators leading to the characteristic symptoms of allergic reaction and anaphylaxis (Vadas et al 2008).

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and member of the TEC kinase family. BTK is expressed in selected cells of the adaptive and innate immune system including B cells, macrophages and mast cells/basophils. BTK is indispensable for signaling through the Fc epsilon receptor (FcεR1 for IgE), the activating Fc gamma receptors (FcγR for IgG), as well as the B cell antigen receptor (BCR), and therefore an important signaling node in the activation/degranulation of B cells, macrophages, mast cells and/or basophils (Rip et al 2018).

BTK inhibitors (BTKi), for example ibrutinib, have been first approved for the treatment of B cell malignancies (Hendriks et al 2014). Due to the above described role of BTK in adaptive as well as innate immune signaling and associated with that, its role in immune-mediated diseases, targeting BTK is regarded as a promising new approach for the treatment of various immune-mediated conditions. Clinical development programs with various BTK inhibitors have been initiated or are ongoing in multiple sclerosis, Sjogren´s syndrome, rheumatoid arthritis, asthma, chronic spontaneous urticaria (CSU), and other immune-mediated diseases.

Mast cells and basophils play a key role in the pathophysiology of FcεR1-mediated disease, including CSU and food allergy, and it has been demonstrated that BTK inhibition leads to blockade of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated allergies (Smiljkovic et al 2017, Regan et al 2017, Dispenza et al 2018). Thus, BTK inhibition is a promising therapeutic concept for the treatment of food allergy.

Remibrutinib (LOU064) is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity (Angst 2020, Gabizon, London 2020). In a Phase 1 trial with healthy volunteers with background atopy, remibrutinib was well-tolerated at all doses without any dose-limiting toxicity and showed encouraging blood and skin pharmacodynamics with a favorable safety profile. These results support further development for diseases driven by mast cells, basophils, and B cells, such as food allergy and chronic spontaneous urticaria (Kaul et al 2019). The CLOU064A2201 Phase 2b clinical trial's primary endpoint analysis demonstrated clinical efficacy and a fast onset of action of remibrutinib in the treatment of CSU patients as well as a favorable safety profile. See the Investigator's Brochure for more information.

Currently the standard of care for food allergy is limited to strict avoidance of the inciting food(s), rescue medication in case of unintentional exposure, and community wide interventions for schools (i.e., peanut-free classrooms) and restaurants (i.e., ingredient alerts) (Jones, Burks 2017). Nevertheless, accidental exposures of food-sensitive individuals to the very antigen they are striving to avoid are frequent. For example, 58% of young children with clinical peanut hypersensitivity followed for up to 5 years experienced adverse reactions from accidental peanut exposure despite best efforts at allergen avoidance (Vander Leek et al 2000). Recently, peanut oral immunotherapy was approved by FDA (Jan-2020) to mitigate allergic reactions during accidental exposure to peanuts, and by EMA (Dec-2020) for the treatment of peanut allergy (Vickery et al 2018). Yet this treatment is not fundamentally changing the unmet medical need in this space as it is only targeting one allergen, is indicated only for a subset of age groups, and might not be suitable for all peanut allergic patients.

Due to rising prevalence of food allergy (including allergy to multiple foods), current limited therapeutic options, and the lifelong disease burden for many patients, there is a recognized unmet medical need to develop novel therapies for food allergy (Sicherer, Sampson 2018). By inhibiting activity of BTK, remibrutinib may be one such novel therapy.

1.2 Purpose

The purpose of this Phase 2 study is to evaluate the efficacy, safety, and tolerability of oral remibrutinib (LOU064) at doses of CCI for one month (4-5 weeks), and oral remibrutinib CCI for 1 week compared to placebo in adult participants (age 18-55 years, inclusive). Assessments will serve to measure protection against allergic reaction by measuring the decrease of sensitivity (e.g.: signs and symptoms of allergic reaction) to oral peanut allergen administered in a double-blind, placebo-controlled food challenge (DBPCFC). Participants will have medically confirmed peanut allergy. Data from this study will be used to support the registration of remibrutinib use in the food allergy population to protect against allergic reactions due to an accidental exposure to peanut.

2 Objectives, endpoints and estimands

Table 2-1 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 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 (Section 16.4, Table 16-7) 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 (Section 2.1 Primary Estimands)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of oral remibrutinib CCI 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 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 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 CCI 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 ≥ 600mg (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)

Objective(s)	Endpoint(s)

• 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

• 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)

CCI

2.1 Primary estimands

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 DBPCFC after one month (4-5 weeks) of treatment and regardless of intake of rescue medication prior to 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 DBPCFC at one month (4-5 weeks). Further details about the population are provided in Section 5.
- **Variable**: 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 (4-5 weeks). The cumulative tolerated dose is the sum of the tolerated doses, not including the reactive dose (Casale et al 2019). Dose-limiting symptoms indicate a true allergic reaction occurring during administration of a single dose of peanut protein at the 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 6.1.3) plus rescue medication (e.g., epinephrine, SABA, and/or anti-histamines) prior to DBPCFC at one month, if needed. Further details about the randomized treatment and rescue medication are provided in Section 6.1 and Section 6.2.
- **Intercurrent events**:
  - Discontinuation of treatment prior to the End of Treatment Assessments on Days 25, 26 and 28: Participants who discontinue treatment prior to the one month DBPCFC part 2A, 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 DBPCFC part 2A due to any reasons other than adverse events
  - Intake of rescue medication prior to DBPCFC conducted at one month
- **Summary measure**: Difference in the proportion of responders between remibrutinib and placebo

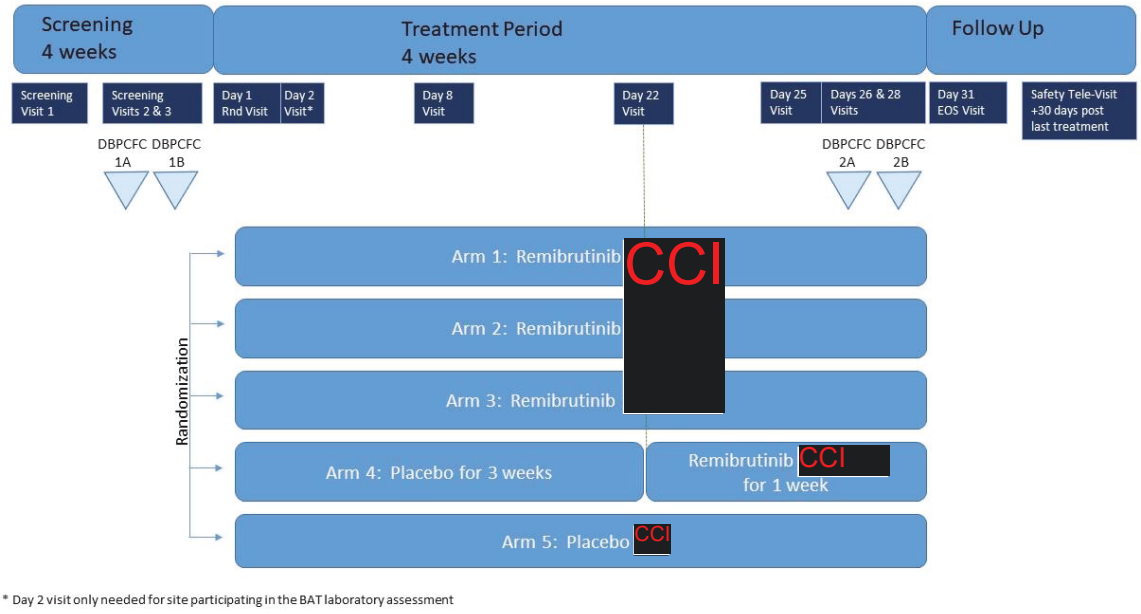
Supplementary estimands to the primary estimand are defined in Section 12.

2.2 Secondary estimands

Not Applicable.

3 Study design

Figure 3-1 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

The study will include the following:

1. **Screening period (duration of 4 weeks with 3 required visits)**: Written informed consent will be obtained before any study-related assessments or procedures are performed. Consented participants will be assessed for study eligibility during the Screening Visit 1 and will need to meet all eligibility criteria for this visit in order to progress to Screening Visits 2 and 3 (DBPCFC parts 1A and 1B), conduct of the double-blind, placebo-controlled food challenge.

To minimize bias in reaction for individual participants, sequence in which allergen or placebo material is provided will be determined by IRT. Participants who receive placebo-allergen challenge material during DBPCFC part 1A will receive peanut-allergen challenge material during DBPCFC part 1B; while those who receive peanut-allergen challenge material during DBPCFC part 1A will receive placebo-allergen challenge material during DBPCFC part 1B. The participant and all study staff, except the unblinded pharmacist/staff member who will re-constitute the allergen, will be blinded to which visit administers which (allergen or placebo).

Those participants who meet threshold requirements for allergen challenge (as described in Section 5.1) will proceed to the treatment randomization visit and study treatment period.

To ensure participants meet inclusion/exclusion criteria for exposure to both peanut-allergen and placebo-allergen, unblinding of the food challenge will be disclosed a minimum of 30 minutes following the maximum dose of DBPCFC part 1B at screening visit 3.

2. **Treatment period:** The treatment period is approximately one month long and can range from 4-5 weeks due to the visit windows allowed as well as due to the need to collect end-of-treatment data across 3 visits that have required minimum spacing between them.

Study participants will be seen in the clinic on Day 1 (treatment randomization), Day 8, and Day 22, for on-treatment clinic visits and drug dispensation. Study participants will also be seen in the clinic for three end-of-treatment visits, which collect primary and secondary one month endpoint data, collectively. These will occur on Day 25, Day 26 (DBPCFC part 2A) and Day 28 (DBPCFC part 2B).

The study treatment will begin on Day 1 at the randomization visit and will continue until the CCI of the DBPCFC part 2B end-of-treatment visit. The study treatment is three placebo -matched tablets administered by the participant at home CCI [redacted] CCI [redacted] Participants will continue study drug dosing CCI from Day 1 visit through the CCI dose of their Day 28 (DBPCFC part 2B) visit. The CCI administration of study drug on Day 28 (DBPCFC part 2B) will be the last dose.

There is a minimum of 2 days (48 hours) needed between the DBPCFC parts 1 and 2. Given the need for flexibility to accommodate holidays and weekends, participants will have a window of plus 2 days for all three end-of-treatment visits on Days 25, 26 and 28, which, if maximized, may extend treatment to up to 34 days. Treatment will not exceed 34 days. Participants will be encouraged to try to maintain the visit schedule as written and avoid utilizing windows as much as possible to keep the study treatment period as short as possible.

3. **End of Study Visit and Follow Up Period:** After completion of Day 28 (DBPCFC part 2B) visit, participants will return to clinic 3 days post-last-dose on Day 31 for the end of study visit, which will include post-dose assessments and study evaluations including safety, pharmacokinetics, post-treatment biomarkers, etc. (See Table 8-1). The end-of-study visit should not be earlier than 3 days (72 hours) after the last dose of study drug to facilitate proper PD/biomarker analysis. Additionally, a 30-day post-last-dose safety call will be placed to the participant and will complete participation in the study.

4 Rationale

4.1 Rationale for study design

The randomized, parallel group, participant- and investigator-blinded, placebo-controlled design has been used to assess the ability of other food allergy therapies (to shift the level of reactivity against the peanut allergen during a DBPCFC (Leung et al 2003, Sampson et al 2011). This study design has been used in pivotal phase III studies of food allergy therapies, including the ongoing ligelizumab program and those supporting the recent regulatory approval of Palforzia®. Details of the DBPCFC are provided in Section 8.3.1. The randomized, participant- and investigator-blinded, parallel-group, and placebo-controlled design supports the assessment of efficacy as well as safety by minimizing bias. Unequal randomization ratio (2:1:1) is considered- for the remibrutinib 1-month arms:remibrutinib 1-week arm:placebo. With fewer participants assigned to the placebo arm, the study is still sufficiently powered to detect a dose-response signal. Fewer patients are also enrolled to the 1 week arm given that this information does not contribute to the primary study objective.

The choice of peanut as the main food allergen in this study relates to the following key factors:

- Peanut allergen represents an important unmet medical need as food allergic reactions are most often severe with this allergen (Gupta et al 2013), and is a leading cause of fatal and near-fatal anaphylaxis in the US (Jones, Burks 2017).
- Most patients (> 80%) retain their phenotype into adulthood (Byrne et al 2010) which enables a study across multiple age groups.

The DBPCFC has demonstrated regulatory significance and will support the main efficacy outcome of the study. The embedded biomarkers will provide mechanistic evidence complementing the clinical outcomes, including data relative to known concomitant (non-peanut) food allergies which will characterize a subset of recruited participants. Such data will support the notion that BTK inhibition is a therapeutic approach that is not dependent on the allergen (i.e. “allergen-agnostic”).

Safety analyses will be performed at study visits, as per Table 8-1. At the end-of-treatment visit, in addition to monitoring safety signals CCI [redacted] Further, a follow-up safety phone call will be held with the participant 30 days after cessation of study drug.

4.1.1 Rationale for choice of background therapy

Strict avoidance of the inciting food(s) and symptomatic treatment of allergic symptoms with epinephrine, antihistamines, and/or corticosteroids represent the current standard of care. No other BTKi medication is currently indicated for the prevention of allergic events in patients with peanut allergy. Therefore, the active treatment will be compared to placebo on top of standard of care for acute allergic reactions.

4.2 Rationale for dose/regimen and duration of treatment

The three selected dose levels CCI reflect the clinical dose range expected to maximize the protection with an acceptable safety profile for a maximum number of participants against potentially life-threatening allergic reactions triggered by accidental exposure to food allergens (Kaul et al 2021).

The selection of these three doses will generate data across expected efficacious doses. These data will be used to select the optimal dose to be further investigated in phase 3 and to support registration, as well as generating a broader spread of (lower) exposures aimed to enrich the final PK/PD assessment that will be used for registration purposes. The proposed dose range will support PK/PD modelling for patients <18 years of age and therewith the pediatric dose selection. The dose range will also provide data/insights on the high inter-patient variability in exposure seen in all previous studies and to mitigate potential drug-drug interactions expected at higher doses. Given the improvement in clinical symptoms between week 1 and week 2 of therapy and continued improvement at week 4 of treatment in the Phase 2 CSU trials, a duration of four weeks of therapy was chosen for all three doses in this study, thereby optimizing treatment prior to allergen challenge. The treatment arm with three weeks of placebo followed by one week of remibrutinib CCI treatment will provide insights into the timing of onset of remibrutinib treatment effect.

Based on the safety data from other completed and ongoing remibrutinib trials, the clinical safety profile of remibrutinib is favorable and supports the selected doses for this trial. Analysis of the dose-range finding Phase 2b study CLOU064A2201 evaluating six dosing regimens with doses from CCI found that most adverse events (AEs) were mild or moderate in severity, without patterns of clustering or dose-dependency. CLOU064A2201E1, a long-term extension study of CLOU064A2201, with a 52-week treatment period with CCI remibrutinib CCI did not reveal any significant safety signals, with safety findings in line with observations in CLOU064A2201. In addition, the clinical safety data from the completed Phase 1 studies, which tested single and multiple doses of remibrutinib up to 600 mg QD and 200 mg CCI was favorable and did not raise any concerns. For more detailed information on the safety profile of remibrutinib, please see the Investigator's Brochure.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo is used in this study for the following reasons:

- to minimize bias in the evaluation of safety and efficacy assessments, and
- to allow assessment of the change in sensitivity from DBPCFC when comparing participants taking oral remibrutinib with those continuing solely on food avoidance

4.4 Purpose and timing of interim analyses/design adaptations

CCI

4.5 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in appendices found in Section 16.1 (clinically notable laboratory values and vital signs), Section 16.2 (liver event and laboratory trigger definitions and follow-up requirements), and Section 16.3 (specific renal alert criteria and actions and event follow-up).

This study is placebo-controlled design and approximately one-eighth of participants will receive only placebo by randomization (Section 4.3). Throughout the study, including during the placebo period, participants will be instructed to continue strict avoidance of the inciting food(s) to reduce risk of accidental exposure to allergen(s). The use of symptomatic treatment of allergic symptoms (e.g. epinephrine, antihistamines, and/or corticosteroids) will be allowed as emergency treatment to reduce the risk for the participants.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Double blind, placebo controlled food challenges (DBPCFCs) are the gold-standard method for assessment of food allergies. DBPCFCs have inherent risks including acute allergic reactions with potentially life-threatening anaphylaxis, exacerbation of atopic dermatitis, and emotional distress, particularly in older children, teenagers, and adults who may become more anxious about their food allergy (Feng, Kim 2019). A prior history of a severe allergic event may increase the risk of a severe reaction during the DBPCFC. These participants are excluded from participating in the study. In participants with cardiovascular disease, anaphylaxis or its treatment (e.g., epinephrine) could result in morbidity due to a cardiovascular event. In addition, participants with uncontrolled asthma are at higher risk of dying from anaphylactic events. To further limit the risks associated with this procedure the following measures have been applied:

- The DBPCFC adheres to the principles and recommendations in the PRACTALL Consensus Meeting Report (Sampson et al 2012) and will utilize the well-established CoFAR definition of dose-limiting symptoms (see Section 16.4).
- Only highly trained experts with experience performing DBPCFCs and representing facilities that are equipped and have the expertise to handle potentially life-threatening hypersensitivity events can participate in this study.
- Inclusion/exclusion criteria established to reduce selection of high-risk participants.

The risks to participants in this trial will be minimized by compliance with all of the eligibility criteria and by close clinical monitoring.

The inclusion and exclusion criteria are selected to enroll participants with IgE-mediated peanut allergy and to limit the presence of concomitant morbidities and medications that might increase the risks associated with the DBPCFC, including those related to the rescue medications.

BTK inhibition is a new therapeutic principle for the treatment of food allergy that significantly differs from currently available treatment options in terms of its mode of action and route of administration. Remibrutinib may therefore offer a treatment option for participants with contraindications against or inadequate response to other treatment options under investigation for food allergy, including anti-IgE directed biologics. These participants, for whom a high unmet need for new treatments exists, are part of the eligible patient population of this study. In the Phase 2b trial CLOU064A2201 for CSU participants, remibrutinib showed a rapid onset of action after the first week of treatment. Given the conserved signaling mechanism via BTK in both CSU and food allergy participants, the rapid onset may also prove to be of significant benefit for food allergy participants. Furthermore, the oral route of administration of remibrutinib offers additional convenience compared to injectable biologics.

One possible benefit for study participants is having confirmation of their diagnoses and quantification of the allergen thresholds with the gold-standard DBPCFC.

The safety and tolerability of remibrutinib is supported by the currently available clinical safety experience. As of 10-Mar-2023, CCI [redacted] have been exposed to remibrutinib across a number of Phase 1 and 2 trials with CCI [redacted]. Administration of remibrutinib did not raise any significant safety signals. Most adverse events (AEs) reported were mild in severity, without any patterns of clustering or dose dependency. A maximum tolerated dose has not been identified. Please refer to the Investigator's Brochure for more detailed and updated information.

In the final analysis of the Phase 2b trial CLOU064A2201 in participants with CSU, 309 participants (safety set) received remibrutinib at doses/regimens up to CCI [redacted] for up to 12 weeks. Most adverse events (AEs) were mild in severity, without clustering of specific AEs and no apparent dose related pattern was identified. The most frequent AEs (occurring in ≥ 5% of participants in either any remibrutinib or placebo arm) were:

1. Nasopharyngitis: 8.6% in any remibrutinib arm vs. 7.1% in placebo arm
2. Headache: 9.7% in any remibrutinib arm vs. 14.3% in placebo arm
3. Chronic spontaneous urticaria: 5.2% in any remibrutinib arm vs. 2.4% in placebo arm (the events of chronic spontaneous urticaria were flares primarily reported by participants during the treatment-free follow-up period)

Based on the mode of action of remibrutinib, pre-clinical safety information, drug-drug interaction studies, and the review of currently available literature as well as safety information of approved BTK inhibitors (e.g. ibrutinib, acalabrutinib and zanubrutinib), the following potential risks of remibrutinib have been identified (see below). Of note, many safety risks identified for ibrutinib and acalabrutinib, two BTK inhibitors approved for the treatment of B cell malignancies (mantle cell lymphoma, chronic lymphocytic leukemia, Waldenströem´s macroglobulinemia), are less likely related to the pharmacology of BTK inhibition, but rather to the underlying hemato-oncologic diseases being treated and their associated comedications and complications, such as tumor lysis syndrome, second primary malignancies, etc. Therefore, when comparing the safety risks between the approved BTK inhibitors and remibrutinib, the underlying condition of the treated patient population must be taken into

consideration. Furthermore, ibrutinib and acalabrutinib have a different target selectivity profile compared to remibrutinib (Angst 2020).

- *Infections:* BTK is an important signaling kinase downstream of cell surface receptors and expressed in a number of cell types of the adaptive and innate immune system, including B cells, macrophages, basophils and mast cells. Thus, administration of remibrutinib might be associated with an increased risk for infections and participants should be monitored for signs and symptoms of infections and be evaluated promptly. In the completed and ongoing clinical trials with remibrutinib, infections were well balanced between the remibrutinib and placebo arms. Most of the infections observed were mild to moderate and did not lead to a change in study treatment. In the primary endpoint analysis of the Phase 2b study CLOU064A2201, infections rates were comparable between any remibrutinib arm (22.8%) and the placebo arm (21.4%). Most infections reported in the remibrutinib arms were mild in severity and did not lead to treatment discontinuation.
  - All participants in remibrutinib clinical trials are monitored closely for signs and symptoms of infections while in the trial. Participants with a known history of chronic recurrent or active ongoing infections are excluded from the trial.
- *Response to vaccination*: CCI [redacted]
- *Effect on platelet function - risk for bleeding*: BTK is a signaling kinase in one of several platelet activation pathways. In patients with B cell malignancies (chronic lymphocytic leukemia, Waldenström´s macroglobulinemia, mantle cell lymphoma) treated with the BTK inhibitors ibrutinib or acalabrutinib, major bleeding events (i.e. serious events, gastrointestinal bleeding) were reported. However, the underlying hemato-oncologic diseases of these patients, the prevalence of anti-coagulant/anti-platelet comedication use and the association with such complications should be taken into consideration.
  No relevant increase in bleeding risk has been observed in patients with X-linked agammaglobulinemia, an inborn genetic deficiency of BTK (Quek et al 1998, Futatani et al 2001). Furthermore, BTK inhibition does not have any impact on the plasmatic coagulation system, and plasmatic coagulation was not affected in the human Phase 1 study up to the highest tested dose of CCI [redacted] remibrutinib. In the completed and ongoing trials with remibrutinib, only a few mild and moderate bleeding events were reported. In the primary analysis of the Phase 2b study CLOU064A2201, 13 (4.9 %) non-serious bleeding events were reported on any remibrutinib dose compared to one event on placebo (2.4 %). None of the events reported on remibrutinib was serious or severe. There was a single mild event (gingival bleeding) leading to treatment discontinuation. Participants receiving remibrutinib are closely monitored for any signs and symptoms of bleeding while in the trial. Blood cell counts (including thrombocytes),

hemoglobin and coagulation status are closely monitored throughout the trial. Patients with a known history of bleeding disorders, or with a history of clinically relevant gastrointestinal bleeding and patients requiring anti-platelet or anticoagulant therapy (other than aspirin up to 100 mg/d or clopidogrel) are excluded from the trial; the use of dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel) is prohibited. In case of a significant bleeding event, remibrutinib must be discontinued immediately.

- *Effects on QT interval*: Remibrutinib is a mild inhibitor of the human ether-a-go-go related gene (hERG) channel (IC50 = CCI unbound Cmax-based average safety margin of CCI based on CCI in humans), without affecting other ion channels in a relevant manner. In the "worst-case" scenario for supratherapeutic exposure for the remibrutinib CCI dose in humans assumed after coadministration with a strong cytochrome P (CYP)3A4 inhibitor (CCI ritonavir), the upper 90% confidence interval bound of the estimated mean QT interval corrected by Fridericia's formula (QTcF) change from screening lies below CCI msec. Participants with a history of major cardiovascular events are excluded from the trial. In addition, triplicate sequential ECG monitoring is implemented in the study to monitor potential effects of remibrutinib on QTc and other ECG parameters.
- *Myelomodulation*: Treatment emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anemia) were reported in participants with hematologic malignancies treated with ibrutinib and acalabrutinib. Again, the underlying hemato-oncologic diseases of these participants and their frequent association with such events should be taken into consideration here. All cytopenias reported in the primary analysis of CLOU064A2201 were mild. Participants are closely monitored for signs and symptoms of cytopenia while in the trial, and those with a history of hematological disorders or with markedly altered hematologic parameters at screening are excluded from the study.
- *Reproductive toxicity*: Remibrutinib is not genotoxic or mutagenic in *in vitro* or *in vivo* studies. CCI [redacted] Highly effective methods of contraception must be practiced. Women of child-bearing potential will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the trial and must agree that in order to participate in the trial they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

For detailed information on potential risks associated with remibrutinib, please refer to the Investigator's Brochure.

This trial will help to improve the understanding of remibrutinib in the management of food allergy and potentially enable the development of a novel, innovative, oral drug that could improve the quality of life of food allergy patients beyond the limited treatment modalities currently available. Potential risks are mitigated as far as possible by compliance with

inclusion/exclusion criteria, study procedures, very close clinical and laboratory monitoring, and study drug discontinuation rules. As with investigational drugs in general, not all safety risks are known. Participants and investigators participating in this trial will be informed should important new safety information become available.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 65 days from each participant as part of the study. The approximate volumes are disclosed in the ICF. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See Section 8.5.3.1 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health Emergency as declared by local or regional authorities e.g., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the Public Health Emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethic Committees prior to implementation of mitigation procedures.

5 Study Population

The population is male and female participants aged 18 - 55 years, inclusive, who have been diagnosed with IgE-mediated peanut allergy, from which approximately 72 participants will be enrolled. Participants with multiple food allergies will be allowed to enroll as long as an allergy to peanut is diagnosed and documented.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to study participation. Participants must be able to understand and provide informed consent.
2. Male or female participants who are 18 to 55 years of age, inclusive, at the time of signing informed consent.
3. Documented medical history of allergy to peanuts or peanut-containing foods.
4. Superseded by 4a.

4a. Positive peanut-specific IgE (peanut sIgE), ≥ 0.35 kUA/L at Screening Visit 1.

5. Positive skin prick test (SPT) for peanut allergen at Screening Visit 1. This is defined as the average diameter (longest diameter and mid-point orthogonal diameter) ≥ 3 mm wheal compared to the negative control.

6. A positive peanut DBPCFC during screening (Screening Visits 2 and 3). A positive peanut result is defined as the occurrence of dose-limiting symptoms at a single dose ≤ 100 mg of peanut protein during the screening DBPCFC.
7. Participants must be able to comply with treatment regimen, participate in the DBPCFC, and must be willing to continue avoiding exposure to peanuts and any other foods that they are allergic to throughout this study.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Previous use of remibrutinib or other BTK inhibitors.
2. Use of other investigational drugs within 5 half-lives or within 30 days (for small molecules) prior to Screening Visit 1, or until the expected pharmacodynamic (PD) effect has returned to baseline (for biologics, see Section 6.4) whichever is longer; or longer if required by local regulations.
3. History of hypersensitivity to any of the following:
   - study drug or its excipients or to drugs of similar chemical classes
   - hypersensitivity or intolerance to any of the matrix components used within the material for the DBPCFC (please refer to the LOU064I12201 Pharmacy Manual for the preparation of the DBPCFC material and for details on the material components)
4. Superseded by 4a.

4a. History of severe or life-threatening hypersensitivity event leading to ICU (intensive care unit) admission or intubation within 60 days prior to Screening Visit 1 or during screening challenge (DBPCFC 1A or 1B).

5. Any occurrence of dose-limiting symptoms to placebo allergen at screening DBPCFC (determined after unblinding of DBPCFC from Screening Visits 2 and 3, described in Section 6.4.2).
6. Participants with uncontrolled asthma (according to GINA guidelines, GINA 2021) who meet any of the following criteria:
   - FEV1 < 80% of participant's predicted normal value at Screening Visit 1
   - Hospitalization for asthma within 12 months prior to Screening Visit 1
7. Current or previous history of a mast cell disorder, including mastocytosis, or tryptase ≥ 20 ng/ml at Screening Visit 1.
8. Have received any live or live-attenuated vaccines (including but not limited to varicella zoster virus or measles, oral polio, nasal influenza) within 6 weeks prior to randomization or requirement to receive these vaccinations less than 4 weeks after the last study drug dose. Refer to Section 4.5 for statement on vaccine administration.
9. History of major surgery within 8 weeks prior to Screening Visit 1, and/or planning or expecting to have surgery during the study or up to 30 days after the last dose.
10. Use of prohibited medication within the interval defined (Table 6-4) prior to treatment randomization (Day 1).

11. Any clinically significant disease that, in the opinion of the investigator, would put the safety of the patient at risk through participating, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study, or would compromise patient compliance or preclude completion of the study.
12. History of malignancy of any organ system within 5 years of Screening Visit 1 [except for basal cell carcinoma; actinic keratoses; Bowen disease (carcinoma in situ) that have been treated, with no evidence of recurrence in the past 12 weeks prior to Screening Visit 1; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed].
13. Presence of clinically significant cardiovascular conditions such as but not limited to myocardial infarction, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, arrhythmia and uncontrolled hypertension within 12 months prior to screening.
14. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
    - Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at Screening Visit 1.
    - Concomitant clinically significant cardiac arrhythmias, e.g. atrial fibrillation, sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointe, cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs
15. History of significant bleeding risk or coagulation disorders.
16. Participants with screening hematology parameters below the following thresh-holds will be excluded:
    - Hemoglobin: < 10 g/dl
    - Platelets: < 100,000/mm3
    - Leucocytes: < 3,000/mm3
    - Neutrophils: < 1,500/mm3
17. Requirement for anticoagulant medication [for example, warfarin or Novel Oral Anti-Coagulants (NOAC)].
18. Requirement for anti-platelet medication, except for acetylsalicylic acid up to 100 mg/d or clopidogrel. The use of dual anti-platelet therapy (e.g. acetylsalicylic acid + clopidogrel) is prohibited.
19. History of gastrointestinal bleeding, e.g. in association with use of nonsteroidal anti-inflammatory drugs (NSAID), that was clinically relevant (e.g. where intervention was indicated or requiring hospitalization or blood transfusion).
20. Patients with history of splenectomy.
21. Known or suspected ongoing, chronic or recurrent infectious disease including but not limited to tuberculosis, atypical mycobacterioses, listeriosis, aspergillosis, or endemic mycoses, and/or known positivity for human immunodeficiency virus (HIV) infection. HIV antibody tests will be performed to determine HIV status with follow-up testing/reporting as required by local regulation.

22. Active systemic bacterial, viral, parasitic or fungal infection that are, in the opinion of the investigator, clinically significant, including but not limited to infections requiring hospitalization or IV antibiotics.
23. Evidence of an ongoing hepatitis C infection (e.g. defined by the detection of hepatitis C ribonucleic acid (HCV-RNA) at screening) and/or an ongoing hepatitis B infection (defined by the detection of hepatitis B virus surface antigen (HBsAg) and/or hepatitis B virus (HBV)-DNA at screening; participants who are positive for anti-hepatitis B core (HBc) antibodies but who are negative for antibodies against HBsAg and HBV-DNA can be included into the study if they agree to monitoring for HBsAg and HBV-DNA reactivation).
24. Active, chronic disease of the immune system (including stable disease treated with immune therapy, e.g. rheumatoid arthritis, systemic lupus erythematosus, etc.) with the exception of well-controlled diabetes or thyroid disorder.
25. History or current hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) levels of more than 1.5 x upper limit of normal (ULN) or International Normalized Ratio (INR) of more than 1.5 at screening.
26. History of renal disease, creatinine level above 1.5x ULN, or estimated Glomerular Filtration Rate (eGFR) <45ml/min (using the Cockcroft-Gault equation) at screening.
27. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to screening.
28. Pregnant or nursing (lactating) females.
29. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for at least 2 weeks after stopping study medication.
    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g. calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

30. Patients who, in the opinion of the Investigator, will not be able to comply with study procedures or visits, adhere to dosing schedule, or other otherwise be in compliance with study requirements.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in the study pharmacy manual.

Study treatment includes investigational drug remibrutinib CCI and placebo. These are placebo-matched, film coated tablets taken orally CCI To ensure blinding to dosing arm, participants randomized to the one month treatment arms will take CCI one of which is active drug, two of which are placebo-matched tablets. Participants randomized to the three week placebo, one week CCI arm will take three placebo-matched tablets CCI for the first three weeks, followed by one week with active CCI tablets and two placebo-matched tablets. The procedure related to DBPCFC is provided in Section 16.4.

Information on the food challenge materials and preparation instructions is provided separately in the pharmacy manual.

6.1.1 Investigational and control drugs

Novartis will supply remibrutinib as film-coated tablets and placebo matching in size, color and shape.

Table 6-1 Investigational and Control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
remibrutinib CCI	Film-coated Tablet	Oral	Double-blind supply, bottles	Global
remibrutinib CCI	Film-coated Tablet	Oral	Double-blind supply, bottles	Global
remibrutinib CCI	Film-coated Tablet	Oral	Double-blind supply, bottles	Global
remibrutinib CCI (placebo)	Film-coated Tablet	Oral	Double-blind supply, bottles	Global
remibrutinib CCI (placebo)	Film-coated Tablet	Oral	Double-blind supply, bottles	Global
remibrutinib CCI (placebo)	Film-coated Tablet	Oral	Double-blind supply, bottles	Global

6.1.2 Additional study treatments

Not applicable.

6.1.3 Treatment arms/group

Participants will be assigned at the visit on Day 1 for study treatment randomization to one of the following five treatment arms to achievea ratio of 2:2:2:1:1 at the end of the study. Each participant will begin taking the prescribed regimen consisting of two placebo and one active tablet OR three placebo tablets CCI starting on Day 1 (randomization) and continuing until Part 2B DBPCFC end-of-treatment visit. The CCI dose on the day of Part 2B DBPCFC end-of-treatment visit will be the last dose administered. The CCI dose will not be administered.

1. Remibrutinib CCI every day on Days 1 through 28
2. Remibrutinib CCI every day on Days 1 through 28
3. Remibrutinib CCI every day on Days 1 through 28
4. Placebo CCI every day on Days 1 through 28
5. Placebo CCI every day for Days 1-21, followed by remibrutinib CCI every day on Days 22 through 28

Treatment duration is approximately one month (4-5 weeks). Participants will receive study drug from the site staff at randomization (Day 1), Day 8 and Day 22 visits. Dispensation of study drug by the site to the participants must be recorded. Participants will administer drug at home, except on clinic days. On clinic days, participants should withhold their CCI dose and take it at the instructed time during the visit (based on assessment schedule and PK draws, etc.). If participant has already taken the dose CCI, this should be noted on patient diary and eCRF. If visit includes PK assessments, participant should be rescheduled to the next available clinic day for the PK visit. Participants' compliance with taking study drug must be

recorded in the source documents and the corresponding electronic Case Report Form (eCRF) to document administration. Dosing information may be collected in eCRF for specific visits (e.g.: visits with PK draws). Study drug reconciliation should be performed at each study visit or per the monitoring plan. The follow-up period is a non-treatment period of 30 days after the last dose of study drug during which neither study treatment will be administered nor study assessments will be performed.

6.2 Other treatment(s)

This study will use a reconstituted peanut allergen and a placebo allergen for the DBPCFC. Instructions on use and components of the consumable product can be found in Section 16.4.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria, medication allowed under certain conditions (listed in Table 6-2) and prohibited medication (listed in Table 6-3). If in doubt, the investigator should contact Novartis before randomizing a participant or allowing a new medication to be started. If a participant is already enrolled and taking a prohibited medication, the investigator should contact Novartis to determine if the participant should continue in the study.

Remibrutinib has been extensively investigated with respect to potential drug-drug interactions (DDI) as victim or perpetrator. As these interactions may lead to significant changes in the exposure of remibrutinib or respective co-medications some drugs are either prohibited or co-administration requires action and must be used with caution.

Oxidative metabolism is the major clearance pathway of remibrutinib and predominantly mediated by CYP3A4 with only minor contribution of other clearance pathways. Therefore, at doses investigated in this study co-administration of strong and moderate CYP3A4 inhibitors are prohibited in this study. Concomitant administration of moderate and strong inducers of CYP3A4 is also prohibited during the study (see Table 6-4). Remibrutinib has been shown in vitro to inhibit some efflux and uptake transporters [such as P--glycoprotein, OATP1B, MATE-1, OAT3, organic cation transporter 1 and breast cancer resistance protein (BCRP)]. Therefore, concomitant administration of remibrutinib with respective BCRP substrates with a small safety margin may be administered with caution (see Table 6-3).

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications are allowed if taken as per below conditions:

Table 6-2 Medications allowed under certain conditions

Medication	Condition under which medication is permitted
Immunotherapy for treatment of allergies in maintenance phase (except food allergies)	Subjects must be on maintenance immunotherapy for at least 3 months prior to Screening Visit 1. For subcutaneous immunotherapy: ensure a minimum of 24 hours between administration of immunotherapy and DBPCFC. For sublingual immunotherapy: Hold immunotherapy dose on days of DBPCFC.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Screening Visit 1
Short acting and long acting antihistamines (e.g., chlorpheniramine, promethazine, diphenhydramine, loratidine, cetirizine)	Not administered within 5 half-lives prior to SPT (skin prick test) and DBPCFC
Short acting beta agonist (SABA)	Not used within 6 hours of all spirometry assessments for asthma participants and within 6 hours prior to start of DBPCFC
Anti-histamine nose spray	Not administered within 12 hours prior to SPT and DBPCFC
Oral H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine)	Not administered within 24 hours prior to SPT and DBPCFC

Table 6-3 Other medications having potential interactions with remibrutinib

Medication or non-drug therapy	Action taken (if taken during study treatment period)
Intestinal BCRP or P-gp substrates which have a narrow therapeutic index Examples (non-exhaustive)[1]: baricitinib, daunorubicin, doxorubicin, mitoxantrone, digoxin, docetaxel, eribulin, everolimus, pazopanib, sirolimus, sorafenib, tacrolimus, talazoparib, tolvaptan, venetoclax	Use with caution. Co-administer in a staggered dosing approach (3 hrs after remibrutinib).
Substrates of **systemic** efflux and uptake transporters OAT3 or OATP1B1 Examples (non-exhaustive):[1] paclitaxel, pemetrexed, topotecan, carboplatin, cisplatin, oxyplatin, sorafenib	Use with caution. Monitor patients and adjust the dose of the concomitant drug(s) as required.
OCT1 substrates Examples (non-exhaustive)[1]: ranitidine, metformin	Use with caution. Monitor patients and adjust the dose of the concomitant drug(s) as required. Metformin: subjects to monitor their blood glucose levels after co-administration with remibrutinib and discontinue remibrutinib treatment in case of uncontrolled blood glucose.

Medication or non-drug therapy	**Action taken (if taken during study treatment period)**
Drugs with known QT prolongation effect Examples (non-exhaustive)[1]: aclarubicin, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, cesium chloride, chloroquine, chlorpromazine, chlorprothixene, cilostazol, cisapride, citalopram, cocaine, domperidone, donepezil, droperidol, escitalopram, flecainide, gatifloxacin, grepafloxacin, halofantrine, haloperidol, hydroxychloroquine, ibogaine, levofloxacin, levomepromazine (methotrimeprazine), levomethadyl acetate, levosulpiride, meglumine antimoniate, mesoridazine, methadone, moxifloxacin, nifekalant, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, propofol, roxithromycin, sertindole, sevoflurane, sparfloxacin, sulpiride, sultopride, terfenadine, terlipressin, terodiline, vandetanib	Use these drugs with caution keeping in mind these risk factors: 1. QT effects of other co-prescribed drugs 2. Electrolyte imbalances (such as hypokalemia, hypomagnesemia) 3. Any impact on their clearance or metabolism (e.g. CYP450 inhibition) Subjects on these medications should be educated to report symptoms like palpitations, light-headedness, or dizziness and ECG should be conducted for such symptoms.

[1]The lists provided are not exhaustive. References: University of Washington Drug Interaction database (www.druginteractioninfo.org): Database search October 2021.

6.2.2 Prohibited medication

Use of the treatments displayed below (Table 6-4) is not allowed from Screening Visit 1 to the completion of all three end-of-treatment visits (Day 28). The minimum required period without prohibited treatment before Screening Visit 1 is also shown.

If a participant develops a medical condition that requires use of prohibited treatment or if participant exhibits a behavior of non-compliance regarding prohibited medications at any timepoint from Screening Visit 1 to the end of the completion of all three end-of-treatment visits (Day 28), investigational treatment and DBPCFC must be discontinued (see also Section 9.1.1).

As described above, remibrutinib is metabolized mainly by CYP3A4. Therefore, concomitant administration of remibrutinib with drugs that are strong and moderate CYP3A4 inhibitors is prohibited to avoid increases in the systemic exposure up to 4-fold. Although no DDI study has been conducted so far with CYP3A4 inducers, likewise, concomitant administration of remibrutinib with drugs that are moderate and strong CYP3A4 inducers is prohibited as a published SimCYP model predicts a 90% decrease in remibrutinib blood exposure which can lead to a total loss of efficacy.

Table 6-4 Prohibited Medication

6.2.3 Rescue medication

Any treatment deemed necessary by the investigator can be used to treat adverse events, including allergic reactions. Typically, this includes epinephrine, SABA, anti-histamines, short-term bursts of corticosteroids and saline bolus. Any use of rescue medication must be captured on the designated eCRF.

- Epinephrine: in alignment with treatment guidelines for food allergy, all study participants will be provided with rescue medication epinephrine auto-injector (e.g. EpiPen®) to be used to treat any allergic reactions and potential anaphylactic events that occur throughout the study as needed. If the participant is treated with epinephrine auto-injector (e.g. EpiPen®) outside of a study visit, the participant should contact the study site staff.
- SABA (salbutamol/albuterol): Participants with a documented diagnosis of asthma will also be provided with SABA rescue medication. As listed on Table 6-2, the participant should not use SABA rescue medication within 6 hours of a spirometry assessment and/or DBPCFC.

These two rescue medications are to be provided to the participant locally before discharge from DBPCFC part 1A (Screening Visit 2). Participants should be instructed to bring these medications to each visit.

The counseling of participants on the identification of allergic reactions and symptoms of anaphylaxis, as well as proper instruction for the use of rescue medication must be documented in the source documentation.

Repeat counseling should be provided as needed to ensure complete understanding. Additional supplies of rescue medication should be provided as needed throughout the study.

Rescue medication can either be provided directly at the study center or prescribed to the participants. Please refer to Section 6.3.2 for further information.

6.2.4 Restriction for study participants

6.2.4.1 Dietary restrictions and smoking

Participants may take treatment with or without food, and choice should be recorded on paper patient diary each day. If taken without food, the study medication should be taken with a glass of water [240 milliliters (mL)] at least 2 hours after the last meal and 1 hour before the next meal. Participants must continue to avoid all food(s) to which they have allergies.

On PK assessment days (Day 8 and Day 25), all participants will fast for at least 10 hours (ideally overnight), including no light breakfast or snacks. Staff will inquire about approximate time patient took study treatment on the night prior to PK assessment days. This time will be recorded in eCRF. Participants will then take their study medication on site with water, but without food when instructed by site staff. Participants will continue to fast for at least 4 hours thereafter. No fluid intake other than that given at the time of dosing is allowed from 2 hours before until 2 hours after dosing, as indicated by FDA Bioequivalence Guidance for Industry (Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations; 68 FR 13316, CDER 2003). Participants should have a fluid intake of at least 240 mL every 4 hours during waking hours on PK assessment days in addition to fluid taken with meals and medication.

6.2.4.2 Other restrictions

Not applicable.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1). A unique medication number is printed on the study medication label. Study drug will be dispensed at the treatment randomization (Day 1), Day 8 and at Day 22 visits.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT system and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in the IRT system. The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant’s home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 30 day supply. In this case, regular phone calls or virtual contacts (every week or more frequently if needed) will occur between the site and the participant for instructional purposes,

safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participant can resume visits at the study site.

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (Section 6.1.1). Please refer to the LOU064I12201 Pharmacy Manual for study drug handling and administration.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the product label. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

Because study treatment is administered at home, participants will be asked to return all unused study treatment and packaging at Day 8, Day 22 and Day 28 (DBPCFC part 2B) or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.1.2 Handling of other treatment

All rescue medication, regardless of dispensation method, must be documented in source and closely monitored. Participants should be reminded to bring rescue medication to all study visits. This applies to the following:

- SABA (for participants with a documented diagnosis of asthma)
- epinephrine auto-injector (e.g., EpiPen)

If rescue medication is provided at the study site it must be handled and stored according to the package label, kept in a secured location and dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of dispensing of the above-mentioned treatment in a drug accountability log/inventory log, and source documents. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the study.

Any unused epinephrine and SABA will be disposed of according to local regulation.

6.3.2 Instruction for prescribing and taking study treatment

Every participant should take their assigned regimen consisting of three tablets. Depending on randomization arm, CCI [redacted]

Participants should be instructed to swallow whole tablets and not to chew or break them.

Guidance regarding study treatment and food intake, including on days for PK assessment is provided in Section 6.2.4.1.

If vomiting occurs during the course of treatment, participants should not take the study treatment again before the next scheduled dose.

Participants should be instructed not to make up missed doses. If a participant does not take the full dose within 3 hours of the usual CCI [redacted] dosing time, the dose is considered missed. That dose should be omitted and the participant should make note of the missed dose on the paper diary and continue treatment with the next scheduled dose.

The dose for individual participants will be the same within a treatment arm and will be assigned at treatment randomization (Day 1). All study drug dosages prescribed and dispensed to the participant and all dosing errors or missed administrations during the study must be recorded on the appropriate eCRF. All kits of study treatment assigned by the IRT will be recorded in the IRT.

The investigator must promote compliance by instructing the participants to ensure scheduled visits are made to the site in order to receive the study treatment as per protocol and by stating that compliance is necessary for the participants' safety and the validity of the study.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Participant No. suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a failed screening.

6.4.2 Treatment assignment, randomization

This study will contain **three** separate time-points of randomization via IRT: randomization of the order in which placebo- or peanut-allergen material is given for the DBPCFC will occur for

the screening DBPCFC (Screening Visits 2 and 3) and again at the one month end-of-treatment DBPCFCs (Days 26 and 28), and randomization to study treatment arm will occur on Day 1.

As the DBPCFC is a double-blinded procedure, it consists of two parts: in one part, the participant is challenged with peanut allergen, and in the other part the participant is challenged with placebo. These challenges take place on different days, and the study staff (other than the unblinded pharmacist/staff member who calls IRT and prepares the challenge product) and participant will be blinded as to which day he/she receives which challenge.

Screening Visit 1 - after all inclusion and exclusion criteria are confirmed, but before Screening Visit 2 begins, the site's unblinded staff responsible for preparing the allergen/placebo product for the challenge will call the IRT system to randomize the participant to the order in which they will receive the peanut allergen and placebo during DBPCFC parts 1A and 1B. The participant will complete the DBPCFC parts 1A and 1B. A minimum of 30 minutes after the last dose is given for part 1B, the site can unblind the staff and participant to confirm the final exclusion criteria. Unblinding will enable the site staff to determine if the participant met the exclusion criteria for having a reaction to placebo (see Section 5.2). If no reaction to placebo, the participant may proceed to study treatment randomization, Day 1.

Randomization (Day 1) - Randomization through IRT will take place on Day 1 to randomize the participant to one of five study treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

CCI [redacted]

End-of-treatment DBPCFC part 2A (Day 26) - before this visit begins, the unblinded site member will again contact IRT to obtain the randomization of the order in which the participant will be challenged with placebo or peanut allergen for the end-of-treatment DBPCFC part 2A (Day 26) and DBPCFC part 2B (Day 28). After a minimum of 30 minutes post maximum eliciting allergen dose in DBPCFC part 2B (Day 28) the staff and participant may be unblinded to the allergen/placebo order.

The randomization schemes for participants will be reviewed and approved by a member of the Randomization Office.

6.4.2.1 Replacement policy

For participants discontinued from the study for reasons other than safety, the decision to replace them by equal number of newly enrolled participants will be taken by the Sponsor.

6.5 Treatment blinding

This is a participant- and investigator-blinded study. Participants and investigator study staff will remain blind to the identity of the treatment assignment from treatment randomization (Day 1) until clinical database lock. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- Bioanalyst (PK/PD): to enable identification of samples from the remibrutinib treatment arms of the study to facilitate bioanalysis
- Specific vendors whose role in trial conduct requires their unblinding (e.g. IRT)
- Global Clinical Supply (GCS)
- Novartis associates who are involved in the analysis before final database lock described in Section 4.4

Additionally, participants and investigator study staff will remain blind to the sequence of administration of peanut allergen and placebo allergen during the required DBPCFCs, until unblinding of site staff ONLY to the sequence of allergen and placebo dosing at the completion of DBPCFC part 1B (Screening Visit 3). Both site staff and participant may be unblinded to the sequence of administration following completion of DBPCFC part 2B (Day 28).

The following exception(s) pertain to the blinding of sequence of administration of materials for DBPCFC, allowing unblinding of:

- Site pharmacist or trained staff who will be responsible for randomizing, preparing (reconstituting), dosing and administering the peanut allergen and placebo used during the DBPCFCs
- Global Clinical Supply (GCS)
- Specific vendors whose role in trial conduct requires their unblinding (e.g. IRT)

The following measures must be applied by the study site to keep the participant and study site personnel blinded to the identity of the treatment:

- The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.
- The identity of the peanut allergen/placebo will be concealed by responsible site staff to maintain blinding of the participant, investigator and other site staff not involved with the preparation and administration of the product.

Apart from the study drug facilitator, study site staff should **NOT** handle the Investigational Medicinal Product (IMP) and no information regarding the IMP should be discussed with the site study staff.

Participants should be discouraged from comparing experiences with other study participants.

Unblinding will occur in the case of participant emergencies and at the conclusion of the study. Health authorities will be granted access to unblinded data if needed. The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any participant whose treatment code has been broken for any reason. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to a PK analyst who will keep PK results confidential until final database lock.

Table 6-5 Blinding Schema

Role	Randomization (Treatment)	DBPCFC sequence randomization*	Study drug allocation and Dosing	Safety event(s)	Interim analysis
Participants	B	B	B	B	B
Investigator and site staff	B	B	B	B	B
Site staff for study drug (IMP)	B	B	B	B	B
Site staff unblinded for DBPCFC product preparation	B	UI	B	B	B
Global clinical supply and randomization office	UI	UI	UI	UI	UI
Sponsor CTT	UI	B	B	UI	UI
Pharmacovigi-lance	UI	B	B	UI	UI
Sponsor CRA and CSM	B	B	B	B	B
Sponsor statistician	B	B	B	B	UI
Sponsor PK/PD team	UI	B	B	UI	UI

B- Blinded
UI – Unblinded

* For the peanut/placebo product used during the DBPCF challenges: participants, site staff and sponsor staff will be blinded during the administration of the challenges. Of note, however, participants, site staff and sponsor staff will/may be unblinded after the completion of each set of DBPCFCs (after Screening Visit 2 and after Day 28). Further information on this unblinding is offered in Section 16.4.2.

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted, except if required to manage an adverse event when a participant is deemed to be at a significant safety risk unless administration of investigational treatment is temporarily interrupted. Study drug dose adjustments are not permitted.

Any interruption of study drug administration should be discussed with Novartis or delegate regarding the participant's eligibility to continue investigational treatment.

Any missed or altered study drug administration must be recorded on the appropriate eCRF in order to reconstruct an accurate dosing history for each participant.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Participants will be required to take their prescribed regimen CCI for 28 (up to 34, pending scheduling of end of treatment DBPCFC visits) consecutive days between Days 1 and 28. Participants who: a.) discontinue study treatment prior to the end-of-treatment assessment visits starting on Day 26, OR b.) miss more than 20% of study doses throughout the treatment period, OR c.) miss medication doses for ≥ 3 consecutive days in the in the seven days prior to end-of-treatment DBPCFC, will not undergo the end-of-treatment DBPCFC.

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using tablet counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit, and missed doses should be recorded in the eCRF. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Discontinuation of treatment prior to end-of-treatment assessments: Participants who discontinue treatment prior to Day 26 (DBPCFC part 2A) due to any reasons other than adverse event OR who miss more than 20% of study doses throughout the study treatment period OR who miss ANY medication doses for ≥ 3 consecutive days in the seven days prior to Day 26 (DBPCFC part 2A) will not undergo end-of-treatment DBPCFC part 2A or 2B. Those participants who discontinue treatment after an adverse event, but who resume therapy after discussion between investigator and sponsor, AND who have not missed more than 20% of study doses throughout the treatment period AND have not missed ANY medication doses for ≥ 3 consecutive days in the seven days prior to end-of-treatment DBPCFC part 2A (Day 26) WILL undergo end-of-treatment DBPCFC, part 2A and 2B. Participants who discontinue due to noncompliance of study treatment may be replaced after discussion with Novartis.

6.7.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate eCRF. Any treatment deemed necessary by the investigator for the safety of the participant is allowed. For treatment of severe allergic reactions including anaphylaxis, epinephrine and SABA are typically used with or without antihistamines and corticosteroids. Guidance on clinically notable lab values and vital signs (Section 16.1), monitoring infections (Section 16.1.1), immunizations (Section 16.1.2), as well as liver event definitions and follow up requirements (Section 16.2) and renal alert and actions criteria (Section 16.3) are provided in appendices (Section 16).

Treatments of adverse events should align with prohibited medication (Section 6.2.2, Table 6-4) and medications allowed under certain conditions (Section 6.2.1.1). Medication used to treat adverse events (AEs) must be recorded on the appropriate eCRF.

Please refer to Section 16.4 for the assessment, reporting and management of hypersensitivity reactions observed during the DBPCFC and the post-DBPCFC observation period.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact the investigator or his/ her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any participant whose treatment code has been broken for any reason.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Per Section 4.6 during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by local health authorities.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  CCI
  - A subsection that requires a separate signature for the “Optional Consent for Additional Research” to allow future research on data/samples collected during this study, and for the “Optional consent for activities that may be done outside of the study site”
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

CCI

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the highly effective contraception requirements.

CCI

CCI

A copy of the approved version of all consent/assent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments and study visits. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. If a visit has a specified visit window, all attempts to hold the visit within that specific window is necessary because the assessments are timing-critical for those visits. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to return for the end of study visit as soon as possible and attend the follow-up visits as indicated in the assessment schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits), alternative methods to obtain needed assessments may be implemented by the investigator as the situation dictates. If allowable by a local health authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

The preferred sequence of data collection during study visits that do not include pharmacokinetic sampling is vital signs, spirometry, blood sampling (all labs and biomarkers), SPT, and then DBPCFC, as applicable per visit.

Study drug must be administered prior to DBPCFC at end-of-treatment visits on Days 26 and 28.

For visits that do include pharmacokinetic sampling (Days 8 and 25), every effort will be made to take the pharmacokinetic sample at the protocol specified time points. ECG in triplicate is required pre and post dose on these visits. The order of assessments on PK visit days is: ECG (in triplicate), pre-dose PK blood draw, dosing at 0h followed by ECG after dosing but before 0.5h PK blood draw timepoint.

Please ensure the order of assessments is respected consistently.

Table 8-1 Assessment Schedule

Period	Screening			Treatment								End of Treatment Assessment Visits							
Visit Name	**Screening Visit 1**	**Screening Visit 2 (Part 1A DBPCFC)[2]**	**Screening Visit 3 (Part1B DBPCFC)[2]**	**Randomization (Start of Treatment)**	**Day 2[3]**	**Day 8[3]**					**Day 22**	**Day 25[3]**						**Day 26 (Part 2A DBPCFC)[2]**	**Day 28 (Part 2B DBPCFC)[2]**
Visit Numbers[1]	**1**	**20**	**30**	**100**	**110**	**120**					**130**	**140**						**150**	**160**
Days	**-30 to -15**	**-21 to -7**	**-10 to -3**	**1**	**2**	**8**					**22**	**25 -0 +2**						**26 -0 +2**	**28 -0 +2**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**-**
Clinic visit	X	X	X	X	X	X						X	X						X	X
Medical history/current medical conditions	X																			
Demography	X																			
Concomitant Medications	X	X	X	X	X	X						X	X						X	X
Informed consent	X																			
CCI																				
Inclusion / Exclusion criteria	X	X	X	X																
Adverse Events	X	X	X	X	X	X						X	X						X	X
Vital Signs	X	X	X	X		X						X	X						X	X
Body Height	S																			
Body Weight	X	X	X	X		X							X						X	X
Physical Examination	X	S	S	S		S						S	S						S	S
Electrocardiogram (ECG)[4]	X					X	X						X	X						
Spirometry[5]	X	X	X																X	X
Pregnancy and assessments of fertility[6]	S	S	S	S		S						S	S						S	S

Period	**Screening**			**Treatment**									**End of Treatment Assessment Visits**							
Visit Name	**Screening Visit 1**	**Screening Visit 2 (Part 1A DBPCFC)[2]**	**Screening Visit 3 (Part1B DBPCFC)[2]**	**Randomization (Start of Treatment)**	**Day 2[3]**	**Day 8[3]**						**Day 22**	**Day 25[3]**						**Day 26 (Part 2A DBPCFC)[2]**	**Day 28 (Part 2B DBPCFC)[2]**
Visit Numbers[1]	**1**	**20**	**30**	**100**	**110**	**120**						**130**	**140**						**150**	**160**
Days	**-30 to -15**	**-21 to -7**	**-10 to -3**	**1**	**2**	**8**						**22**	**25 -0 +2**						**26 -0 +2**	**28 -0 +2**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**-**
Urinalysis	X			X		X							X							
Hematology	X			X		X							X							
Clinical Chemistry	X			X		X							X							
Coagulation Panel	X			X		X							X							
Hepatitis and HIV Screen	S																			
Liver function test[7]				X		X							X							
Outpatient PK visits						X	X	X	X	X	X		X	X	X	X	X	X		
PK blood collection	See table below																			
Total IgE; Peanut CCI IgE & IgG4; CCI	X												X							
Blood collection for specific immunoglobulin	X												X							
CCI																				
Skin Prick test	X																		X	

Period	**Screening**			**Treatment**									**End of Treatment Assessment Visits**							
Visit Name	**Screening Visit 1**	**Screening Visit 2 (Part 1A DBPCFC)[2]**	**Screening Visit 3 (Part1B DBPCFC)[2]**	**Randomization (Start of Treatment)**	**Day 2[3]**	**Day 8[3]**						**Day 22**	**Day 25[3]**						**Day 26 (Part 2A DBPCFC)[2]**	**Day 28 (Part 2B DBPCFC)[2]**
Visit Numbers[1]	**1**	**20**	**30**	**100**	**110**	**120**						**130**	**140**						**150**	**160**
Days	**-30 to -15**	**-21 to -7**	**-10 to -3**	**1**	**2**	**8**						**22**	**25 -0 +2**						**26 -0 +2**	**28 -0 +2**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**0min**	**30min**	**1h**	**2h**	**3h**	**4h**	**-**	**-**
Double Blind Placebo Controlled Food Challenge (DBPCFC)[2]		X	X																X	X
Unblinding of Allergen/Placebo for DBPCFC part 1B and part 2B[10]			X																	X
Study drug dispensation				X		X						X								
Study drug administration[11]				X		X						X	X						X	X
Study drug accountability				S		S						S	S						S	S
Providing rescue medication, counseling, training & accountability[12]	S			S																

Period	**Post-Treatment Follow-Up**	
Visit Name	**Day 31 End of Study**[13]	**Post Study Safety Tele-Visit**
Visit Numbers[1]	**1999**	
Days	**31 -0 +2**	**Last treatment +30 days ±5**
Time (post-dose)	**-**	**-**
Clinic visit	X	
Medical history/current medical conditions		
Demography		
Informed consent		
CCI		
Inclusion / Exclusion criteria		
Adverse Events	X	X
Vital Signs	X	
Body Height		
Body Weight		
Physical Examination	S	
Electrocardiogram (ECG)[4]		
Spirometry[5]		
Pregnancy and assessments of fertility[6]	X	
Tuberculosis test		
Urinalysis	X	
Hematology	X	
Clinical Chemistry	X	
Coagulation Panel	X	
Hepatitis and HIV Screen		
Liver function test[7]	X	
Outpatient PK visits		
PK blood collection	See table below	

Period	**Post-Treatment Follow-Up**	
Visit Name	**Day 31 End of Study**[13]	**Post Study Safety Tele-Visit**
Visit Numbers[1]	**1999**	
Days	**31 -0 +2**	**Last treatment +30 days ±5**
Time (post-dose)	**-**	**-**
Total IgE; Peanut CCI IgE & IgG4; CCI	X	
Blood collection for specific immunoglobulin	X	
CCI		
Skin Prick test		
Double Blind Placebo Controlled Food Challenge (DBPCFC)[2]		
Unblinding of Allergen/Placebo for DBPCFC part 1B and part 2B[10]		
Study drug dispensation		
Study drug administration[11]		
Study drug accountability		
Providing rescue medication, counseling, training & accountability[12]		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit structure given for internal programming purpose only
[2] The DBPCFC has two parts: Parts A and B for both the screening DBPCFC and the End of Treatment DBPCFC will be done at least 2 days apart, but will not exceed 7 days apart, IRT will be called on day of Part1A and Part 2A to randomize participant to order of placebo/allergen dosing.
[3] Blood work at this visit is to be drawn prior to CCI dose. Participants should be instructed to hold their CCI dose until the end of the clinic visit.
[4] Triplicate ECGs will be conducted on days of PK blood draws. Triplicate ECGs should be performed at two timepoints: timepoint 0h before PK has been drawn but before dosing of study drug, and then again after dosing but before PK timepoint 0.5 h
[5] Only to be performed in participants diagnosed with asthma.
[6] Serum pregnancy test required at 1st screening visit for appropriate subjects and End of Study visit. Urine pregnancy test required at all other visits.
[7] Hepatitis B reactivation monitoring will be performed as needed: only in participants who are positive for HBcAb and negative for HBsAg and HBV-DNA at screening: HBsAg, HBV-DNA
[8] CCI
[9] CCI .
[10] Unblinding with call to IRT occurs a minimum of 30 minutes after last dose of allergen/placebo administration. Determination of final exclusion criteria regarding reaction/no reaction to placebo can be met with this unblinding.
[11] Study drug will be dosed at home CCI by patient from Day 1 throughout the study. On days with clinic visits, study drug will NOT be taken at home in the CCI The participant will take their CCI dose at the clinic at the specified time (based on assessment schedule for the visit).
[12] Assessment to be recorded in the source documentation only.
[13] End of treatment visit must be a minimum of 3 days after DBPCFC Part 2B. This visit may not be sooner than 72 hours from last study dose.

Table 8-2 PK blood collection

Period	Visit Name	Visit Numbers	Days	Time (post-dose)	PK blood collection
Screening	Screening Visit 1	1	-30 to -15	-	
	Screening Visit 2 (Part 1A DBPCFC)[1]	20	-21 to -7	-	
	Screening Visit 3 (Part1B DBPCFC)[1]	30	-10 to -3	-	
Treatment	Randomization (Start of Treatment)	100	1	-	
	Day 2[2]	110	2 to 2	-	
	Day 8[2]	120	8 to 8	0min	X
				30min	X
				1h	X
				2h	X
				3h	X
				4h	X
	Day 22	130	22 to 22	-	
End of Treatment Assessment Visits	Day 25[2]	140	25 -0 +2	0min	X
				30min	X
				1h	X
				2h	X
				3h	X
				4h	X
	Day 26 (Part 2A DBPCFC)[1]	150	26	-	
	Day 28 (Part 2B DBPCFC)[1]	160	-0 +2 28 -0 +2	-	

Period	Visit Name	Visit Numbers	Days	Time (post-dose)	PK blood collection
Post-Treatment Follow-Up	Day 31 End of Study[3]	1999	31 -0 +2	-	
	Post Study Safety Tele-Visit		Last treatment +30 days -5 +5	-	

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] The DBPCFC has two parts: Parts A and B for both the screening DBPCFC and the End of Treatment DBPCFC will be done at least 2 days apart, but will not exceed 7 days apart, IRT will be called on day of Part1A and Part 2A to randomize participant to order of placebo/allergen dosing.
[2] Blood work at this visit is to be drawn prior to CCI dose. Participants should be instructed to hold their CCI dose until the end of the clinic visit.
[3] End of treatment visit must be a minimum of 3 days after DBPCFC Part 2B. This visit may not be sooner than 72 hours from last study dose.

8.1 Screening

Screening

In order to enroll in the study, participants must meet all inclusion and none of the exclusion criteria (Section 5.1 and Section 5.2). Participants will have up to a 4 week screening period to establish study eligibility. During the screening period, participants will be required to attend three visits; Screening Visit 1, Screening Visit 2 (DBPCFC part 1A) and Screening Visit 3 (DBPCFC part 1B). When scheduling the three screening visits, note that spacing of the visits is important as there are important considerations related to allergen exposure and wash-out before the next visit day:

- Screening Visit 2 and 3 should be a minimum of 2 days (48 hours) apart and a maximum of 7 days apart
- Screening Visit 3 and Day 1 should be a minimum of 3 days apart and a maximum of 7 days apart

At the first visit, all inclusion and exclusion criteria will be reviewed other than the DBPCFC criteria, and all lab work will be collected as required for screening. Participants must meet all eligibility criteria, and lab results must be acceptable prior to progressing to Screening Visit 2 (DBPCFC part 1A). Prior to the Screening Visit 2 (DBPCFC part 1A), screening can be extended one additional week if any information concerning eligibility to proceed to the DBPCFC is outstanding. Additionally, prior to Screening Visit 2, in the case where any required laboratory or assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to Screening Visit 2. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study. The DBPCFC parts 1A and 1B should be the last assessments conducted in the screening period after all other criteria are confirmed. Any participant that failed screening due to IgE inclusion criteria may be screened again once for inclusion in the study.

Screening Visit 2 will be part 1A of the screening DBPCFC. Upon arrival and confirmation all other inclusion and exclusion criteria are met, the IRT system should be called by the unblinded pharmacist/site staff who will be reconstituting the DBPCFC product. The participant will be randomized to receive a certain sequence of allergen/placebo administration. All efforts should be taken to maintain blinding of the participant and site staff as to whether the participant is receiving allergen or placebo at each visit. At Screening Visit 3 (DBPCFC part 1B), the IRT system may be called a minimum of 30 minutes after the last dose of allergen/placebo product in order to unblind the staff to confirm the final inclusion/ exclusion criteria related to the results of the screening DBPCFC. Once confirmed, the participant may proceed to the randomization visit (Day 1).

Note there is a minimum 3 day (72 hour) period between Screening Visit 3 (DBPCFC part 1B) and the randomization visit (Day 1). This serves as a food allergen wash-out period after the DBPCFC and must be adhered to so that dosing and on-treatment assessments are started after the appropriate wash-out period. The randomization visit should not occur less than 72 hours after Screening Visit 3. If, according to the assessment schedule, the Screening Visit 3 (DBPCFC Part 1B) is scheduled for a day that would require the Randomization Visit (Day 1)

to be on a weekend or holiday, the Day 1 visit should be scheduled for the first available clinic day after the 72 hour window. Screening Visit 3 should be conducted as close as possible to Day 1 after the 3 day (72 hour) minimum delay between visits.

Rescreening will be allowed only once for participants who failed initial screening (Screening Visit 1). Participants who meet eligibility criteria at Screening Visit 1, but discontinue or screen fail for whatever reason, including AE/SAE, during or after the DBPCFC (Screening Visits 2 and 3) may not be re-screened. Any participants who are going to be rescreened for the study should be discussed with the sponsor before resigning the consent form/starting rescreening. If a participant rescreens for the study, the participant must sign a new informed consent and will be issued a new Participant No. (Section 6.4.1). Informed consent for a rescreened participant must be obtained prior to performing any study-related assessments or collecting any data for the new screening visit(s). Care should be taken to review the prohibited medications in Section 6.2.1 and Table 16-7 for the time periods specified prior to screening testing (i.e., SPT and DBPCFC).

8.1.1 Eligibility screening

Participants will be screened for all inclusion and none of the exclusion criteria using patient interview and past medical records available to the site at the time of the visit. Participants will be asked about recent participation in investigational trials, use of investigational products, and also use of other BTKi products. A complete medical history including current medications, vitamins and supplements, as well as chronic and acute conditions will be collected. A complete physical exam will be conducted. Lab work will be collected and pertinent results reviewed before proceeding in the study. Tuberculosis testing may be performed at the discretion of the Investigator during the screening period at the site's local laboratory. If TB test is performed, negative results must be available before proceeding to Screening Visit 2.

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for hepatitis B surface antigen (HBsAg), HBV DNA and, if standard local practice, hepatitis B core antigen (HBcAg). Screening for hepatitis C will be based on measurement of HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the local laboratory site (e.g. by Western blot). Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

These results will be recorded as source data only by the use of an "S" for the corresponding criteria in Table 8-1 of the protocol.

8.1.1.2 Alcohol test, Drug screen, Urine cotinine

Not applicable.

8.1.1.3 Spirometry

For participants with a documented diagnosis of asthma, spirometry testing should be performed at screening (Screening Visit 1) to assess the participant's eligibility for study participation (see Section 5.2, exclusion criterion 8).

Furthermore, spirometry is performed prior to the DBPCFCs at Screening Visits 2 (part 1A) and 3 (part 1B) and end-of-treatment visits on days 26 (part 2A) and 28 (part 2B).

For each spirometry measurement, the accurate participant data (e.g., age, gender and height) should be used for the calculation of FEV1% predicted normal value at the site.

The spirometry assessment should be performed in accordance with the standard practice at the site including the quality check and will follow the ATS/ERS standard (ATS/ERS Task Force: Standardization of Lung Function Testing, Graham et al 2019).

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered as a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, inclusion/exclusion pages, disposition, total IgE and peanut specific IgE, medical history, DBPCFC and SPT must also be collected for screen failure participants, if these data were obtained. No further data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (Section 10.1.3). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized. Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographics and baseline characteristics will be collected at Screening Visit 1, as specified in the assessment schedule.

Data collected will include age; sex; race; ethnicity; height and weight; relevant medical history, and prior and concomitant medications. A detailed medical history (including family medical history) and current medical conditions present before signing of informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the eCRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Participant race and ethnicity are collected and analyzed to

identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities. See assessment schedule for full list of assessments completed at the Screening visits (Table 8-1).

8.3 Efficacy

Efficacy will be measured with the DBPCFC results, outlined in the primary objective description found in Table 2-1. Details regarding the conduct of the DBPCFC can be found in Section 16.4.

Pharmacodynamic samples will be collected at the timepoints defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

Pharmacodynamic (PD) samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

8.3.1 Appropriateness of efficacy assessments

The procedures of DBPCFC have been endorsed in principle by the Adverse Reactions to Foods Committee of the American Academy of Allergy and Immunology, and there are well established guidelines such as the PRACTALL protocol (Cox, Nowak-Wegrzyn 2018, Sampson et al 2012) and the CoFAR definition of dose-limiting symptoms (Section 16.4.6). The DBPCFC is the state-of-the-art technique to confirm or refute histories of adverse reactions to foods. It is the "gold standard" by which all studies of food allergy should be judged (Bock et al 1988).

Threshold doses can only be determined using DBPCFCs with low doses of the offending food. This approach has been previously used in a clinical study to determine the ability of an anti-IgE monoclonal to shift the dose-response curve of a peanut DBPCFC (Leung et al 2003).

Although the average amount of peanut consumed in an accidental exposure has not been accurately quantified, it is generally believed to be no more than one or two peanuts, or the equivalent of approximately 160 mg to 325 mg of peanut protein. Therefore, as proposed in this study, an increase in the threshold of peanut flour required to provoke symptoms should serve as a proxy to estimate the level of protection against unintended ingestion.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on adverse event (AE) collection and reporting, refer to AE section: Section 10.1.

Safety assessments will include the following, as described in Table 8-3 below:

- Physical examination
- Vital signs
- Laboratory evaluations
- ECG (electrocardiogram)
- Pregnancy testing (women of childbearing potential only)

- Adverse event/serious adverse event assessment

Additional safety assessments may be conducted should these be requested by the local regulatory authority. Any new or worsening clinically relevant findings from such additional assessments, meeting definition of an AE or serious AE, should be recorded as an AE/SAE.

Table 8-3 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will be performed as specified in the Table 8-1, and includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded as an AE, see Section 10.1.
Vital signs	Vital signs include blood pressure and pulse measurements. After the participant has been sitting for 5 minutes, with back supported and both feet placed on the floor uncrossed, systolic and diastolic blood pressure will be measured using an automated validated device e.g. OMRON, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in the Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section (see Table 8-4 below) unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits). Safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory, Novartis will ensure the results reported are equivalent to central laboratory collection and analysis.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant. Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. In all cases, the investigator

must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening, a decision regarding whether the result is of clinical significance or not shall be made by the investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

Clinically notable laboratory findings are defined in Section 16.1.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, [in the case of clinically significant anemia the following parameters will be assessed: Erythrocyte Mean Corpuscular Hemoglobin (MCH), Erythrocyte Mean Corpuscular Hemoglobin Concentration (MCHC), Erythrocyte Mean Corpuscular Volume (MCV)], Platelets, Erythrocytes, Leukocytes, and Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine Kinase (CK), Direct Bilirubin, Indirect Bilirubin (in case of clinically significant elevation), Total Bilirubin, Total Cholesterol, Low Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, C-reactive protein (CRP), estimated Glomerular Filtration Rate (eGFR), Glucose (either fasting or non-fasting).
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Hepatitis markers	Hepatitis B screening: Antibodies against hepatitis B core antigen (HBcAb); antibodies against hepatitis B surface antigen (HBsAb); hepatitis B surface antigen (HBsAg, only in participants who are positive for HBcAb), and hepatitis B-Deoxyribonucleic acid (HBV-DNA, only in participants who are positive for HBcAb). Hepatitis C screening: hepatitis C virus antibodies (anti-HCVAb) and hepatitis C-Ribonucleic acid (HCV-RNA, only in participants who are positive for anti-HCVAb)
Hepatitis B re-activation monitoring	Only in participants who are positive for HBcAb and negative for HBsAg and HBV-DNA at screening: HBsAg, HBV-DNA
HIV testing	HIV test performed at screening
Additional tests	Immunoglobulins (total IgE, IgG, IgA, IgM) Follicle-stimulating hormone (FSH) (for female participants with unclear fertility status)
Pregnancy Test	Serum / Urine pregnancy test for women of childbearing potential (refer to 'Pregnancy and assessments of fertility' Section 8.4.3)

Test Category	Test Name
Urinalysis	A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Performed on site (unless prohibited by local guidelines, then sample to be sent to central laboratory) Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If dipstick measurement results are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the eCRF.

8.4.2 Electrocardiogram (ECG)

ECGs will be measured at Screening Visits 1, and on Days 8 and 25. Refer to Table 8-1.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. Refer to Section 8 for order of assessments.

To provide additional cardiac safety data on remibrutinib, particularly regarding QT prolongation, ECGs will be performed in triplicate. At all visits where PK samples are collected (Days 8 and 25), pre and post-dose ECG assessments should be collected. Pre dose should be collected before the PK blood draw. Post dose assessment should be measured between the 0h and 0.5h PK sampling timepoints (i.e. after first PK sample and study drug dosing at 0h but before the second PK sample at 0.5h) and the mean QTcF value for each timepoint will be calculated from the triplicate ECGs for each participant.

Triplicate 12-lead ECGs are to be collected approximately 2 minutes apart for central analysis with ECG machines supplied by the core laboratory. Each ECG will be sent electronically for central review directly from the ECG machine. For all ECG tracings, a certified copy on non-heat-sensitive paper (e.g. appropriately signed and dated photocopy of the original ECG tracing) must be archived at the study site. The participant's number, the date, actual time of the tracing, and study code must appear on each page.

The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. The Fridericia QT correction formula (QTcF) should be used for clinical decisions (e.g. at the screening visits to assess eligibility). The investigator must calculate QTcF if it is not auto calculated by the ECG machine.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at screening before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

In the event that a clinically significant ECG abnormality is identified at the site [e.g. severe arrhythmia, conduction abnormality of QTcF > 450 msec (males)/460 msec (females)], a copy of the assessment is sent to the core central reader for expedited review if applicable, and the ECG is repeated to confirm the diagnosis.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At Screening Visit 1, all pre-menopausal female participants who are not surgically sterile will have serum β-hCG collected. Only those who are confirmed not pregnant will be permitted to continue in the study.

At Screening Visit 2 DBPCFC part 1A and subsequent study visits, all pre-menopausal female participants who are not surgically sterile will have urine pregnancy testing performed. A positive urine test needs to be confirmed with a central lab serum test prior to study drug administration. If positive, the participant must be discontinued from study treatment.

At the End-of-study Visit (Day 31), a serum pregnancy test should be performed.

Clear instruction should be given that in case of a positive test, the participant **must contact** the investigator immediately.

If participants cannot visit the site to have serum pregnancy tests during a Public Health Emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits), urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.3.1 Assessment of fertility

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use laboratory testing (FSH) and medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.4 Appropriateness of safety measurements

The selected safety monitoring assessments (including laboratory assessments covering clinical chemistry, hematology, coagulation status and immunoglobulins, as well as clinical and physical assessments, triplicate ECG monitoring and general AE assessments) are reliable and well-established standard measures which allow valid and close safety monitoring of the trial's patient population, with regards to their disease, to the compound they are treated with, remibrutinib, and also to their overall medical safety.

In addition to safety assessments that are standard in this population, participants are not eligible to join the study if they have a history of a severe or life-threatening hypersensitivity event needing an ICU admission or intubation within 60 days prior to Screening Visit 1 or uncontrolled asthma at Screening Visit 1. Spirometry is performed in asthmatic participants before each DBPCFC for safety purposes.

Also, study treatment will be discontinued if the participant experiences a life-threatening hypersensitivity event needing an ICU admission or intubation OR a serious hypersensitivity event suspected to be related to study treatment.

8.5 Additional assessments

8.5.1 CCI

CCI

8.5.2 Pharmacokinetics

PK samples will be collected at the visits and timepoints defined in the assessment schedule (Table 8-1).

PK assessment will be limited to 6 time points at each visit to characterize peak exposures of remibrutinib (0, 0.5, 1, 2, 3, 4 hours after intake of study medication, respectively). Samples should be taken as close to the given time (0, 0.5, 1, 2, 3, 4 hours post dose) as possible and the sampling time must be recorded. CCI

PK samples will be obtained and evaluated in all participants on active treatment. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment.

All samples will be given a unique sample number as per lab manual. The actual sample collection date and time will be entered on the appropriate eCRF page.

CCI

If participants cannot visit the site for protocol specified PK assessments (per Section 4.6), an alternative collection method (e.g. home nursing) may be used if available. Samples should then be sent to site for processing and shipment as per a normal site visit.

Remibrutinib blood concentrations will be determined by a validated Liquid Chromatography-Mass Spectrometry (LC-MS/MS) method. Concentrations will be expressed in mass per volume units (ng/mL) and will refer to the free base. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

The number of samples/blood draws collected will not exceed those stated in the protocol.

A non-validated method will be used for metabolite investigations as needed.

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol. The following PK parameters will be determined from the blood concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast, AUCtau. Additional PK parameters may be determined as needed.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf, Vz/F and CL/F. Therefore, and due to the limited sampling up to 4 hours these PK parameters may not be determined.

8.5.3 CCI

8.5.3.1 Use of residual biological samples

Any residual blood samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis related to the purpose of this study. CCI

8.5.4 Skin Prick test

An allergen specific skin prick test (SPT) is a commonly used diagnostic tool. In this study a titration SPT using peanut allergen will provide additional information on the impact of BTK suppression on skin mast cells.

In performing the test, the skin of the participant's back is the preferred site of testing, alternatively the forearm may be used. For consistency it is important to perform the SPT at the same location throughout the study. Skin reactions are to be recorded after 15 minutes of applying allergen to the pricked location. Section 16.5 lists medications that affect tests results and must be avoided prior to performance of SPT.

This study specifies the use of both a titration SPT (TSPT) and non-TSPT. All participants will perform TSPT to peanut. Skin prick testing is scheduled according to Table 8-1. The size of the wheal and flare (the longest diameter and the midpoint orthogonal diameter) at each site will be recorded in the eCRFs.

The SPT may rarely cause serious allergic reactions, including anaphylaxis, and the site should be prepared to provide immediate treatment should that occur. If the participant experiences a systemic allergic reaction and/or an event which is judged by the investigator as an adverse reaction, it should be reported on the designated eCRF. The SPT procedure is detailed separately in Section 16.5.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator. The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant decision
- Pregnancy
- Any SAE, with the exception of anaphylaxis unrelated to study drug, and which does not require hospital admission for ≥ 24 hours.
- Any severe AE that is assessed to be at least possibly related to study drug
- Any moderate to severe infection
- Participant requires use of prohibited treatment as per Section 6.2.2
- Participant failure to comply with the study protocol results in potential risk to the participant
- Participant experiences a moderate or severe hypersensitivity event unrelated to the DBPCFC and suspected to be related to study treatment
- Confirmed QTcF > 500 msec
- Abnormal liver laboratory results requiring discontinuation (see Section 16.2)
- Abnormal renal laboratory results requiring discontinuation (see Section 16.3)
- Platelets < 75,000/mm^3
- Clinically significant spontaneous bleeding events
- Any other adverse event or laboratory abnormality that in the judgment of the investigator prevents the participant from safely continuing in the study
- Any protocol deviation or other situation that results in a significant risk to the participant's safety

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information. If treatment code has been broken as noted in Section 6.5 and Section 6.7.3, and site personnel and sponsor determine discontinuation of study treatment is indicated, this information should be recorded. The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

All participants who discontinue from study treatment prematurely should complete the End of Study visit at the time of treatment discontinuation.

Participants who discontinue from study treatment and agree to participate in the post-study televisit, should be contacted as indicated in the Assessment Schedule (Table 8-1).

If the participant cannot or is unwilling to participate in the post-study televisit, the site staff should make every effort to maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should at a minimum information on new/concomitant treatments and adverse events /serious adverse events should be obtained.

Participants who discontinue study treatment will no longer undergo any DBPCFC that may be planned on the remaining visit(s).

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

Discontinuation of treatment prior to completion of the three end-of-treatment assessment visits: Participants who discontinue treatment prior to Day 26 (DBPCFC Part 2A) due to any reasons other than adverse event OR who miss more than 20% of study doses throughout the study treatment period OR who miss ANY medication doses for ≥ 3 consecutive days in the seven days prior to Day 26 (DBPCFC Part 2A) will not undergo end-of-treatment DBPCFC part 2A or 2B. Those participants who discontinue treatment after an adverse event, but who resume therapy after discussion between investigator and sponsor, AND who have not missed more than 20% of study doses throughout the treatment period AND have not missed ANY medication doses for ≥ 3 consecutive days in the seven days prior to end-of-treatment DBPCFC Part 2A (Day 26) WILL undergo end-of-treatment DBPCFC, Part 2A and 2B. Participants who discontinue due to noncompliance of study treatment may be replaced after discussion with Novartis.

If the participant agrees, the three end-of-treatment visit(s) and/or the end-of-study visit should be conducted at the time of the participant’s study discontinuation, as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g.

dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new personal data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study stopping rules

Dependent on regional guidance, any restart following a temporary hold due to stopping rules being met will require prior submission and approval of a substantial CTA amendment to the competent authorities.

Overall study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs cumulatively across all of the cohorts:

- One or more drug related-SAEs;
- Two or more participants experience hypersensitivity reactions of moderate to severe intensity unrelated to DBPCFC;

- Two or more participants experience a similar AE which was assessed as severe in intensity and are considered as potentially related to the study treatment;
- The sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the investigator and sponsor agree it is safe to proceed.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant completes the End-of-study visit (Day 31). This includes any repeat assessments associated with this visit with full documentation and follow-up by the investigator or, in the event of an early study termination decision, the date of that decision.

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination may include but are not limited to:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) or regulatory authorities after review of safety and efficacy data
- Discontinuation of study drug development
- Practical reasons (including slow enrollment)

In taking the decision to terminate, Novartis will always consider the participant's welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Expected adverse events

For the study-mandated procedures/requirements listed below, only the signs and symptoms listed under each procedure will be considered outside normal range and will be recorded as an

adverse event (AE) (see Section 10.1.2 for definition of AE). For all other study-mandated procedures/requirements not listed in this section, all AEs will be recorded.

Skin Prick Test: The following events related to SPT will be considered AEs if they occur within 48 hours of the SPT:

- Prolonged (>24 hours) pruritus at the SPT site
- Induration/swelling at the SPT site larger than 10 mm in diameter and lasting more than 24 hours
- Allergic or anaphylactic reaction that requires the use of rescue medications

DBPCFC: The following events related to an DBPCFC will be considered AEs:

- Severe dose-limiting symptoms as defined by

As moderate dose-limiting symptoms are the usual threshold at which an DBPCFC will be considered positive to a food (allergen), almost every positive DBPCFC would be recorded as an AE, which will dilute the true incidence of AEs for this trial. To avoid artificially increasing the AE incidence from DBPCFCs, only severe dose-limiting symptoms as defined by Section 16.4.6 will be considered AEs. However, all reactions that occur during a DBPCFC will be captured in the appropriate eCRF.

10.1.2 Adverse events

An adverse event (AE) is any untoward medical occurrence [e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease] in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participants and identifying adverse events. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

In general, the occurrence of adverse events must be sought by non-directive questioning of the participants at each visit during the study. Additionally, the investigator should proactively query the participants about the occurrence of specific adverse events related to the administration of study drug, and in the event of accidental food ingestion. Adverse events also may be detected when they are volunteered by the participants during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.3):

1. The severity grade:
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy can only be evaluated meaningfully by an analysis of cohorts, not on a single participant;
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported;
4. Whether it constitutes a SAE (Section 10.1.2 for definition of SAE) and which seriousness criteria have been met;
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Drug interrupted/permanently discontinued
   - Dose increases or reductions are not permitted
6. Its outcome: not recovered/ not resolved; recovered/ resolved; recovering/ resolving; recovered/ resolved with sequelae; fatal or unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse event monitoring should be continued until the end of study visit or for at least 30 days following the last dose of study treatment, whichever is longer.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

Please refer to Section 16.4 for the assessment, reporting and management of hypersensitivity reactions observed during the DBPCFC and the post-DBPCFC observation period.

10.1.3 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (Section 10.1.5).

10.1.4 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail). Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified in local regulations. Any SAEs reported up to the participant's last visit will be reported in the eCRF. SAEs beyond that date will only be recorded in the Novartis Safety database. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form (eSAE) (with paper backup if required); all applicable sections of the form must be completed in order to provide a clinically thorough report.

1. Screen Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis with 24 hours of learning of its occurrence.
2. Randomized OR Treated Participants: SAEs collected between time participant signs ICF until 30 days after the participant has discontinued from study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: if more stringent, local regulations regarding reporting timelines prevail) of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the investigational treatment, a Chief Medical Office and participant Safety (CMO&PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Hypersensitivity reactions during DBPCFC are expected. These events will not be reported as AE/SAE. Please refer to Section 16.4 for the assessment, reporting and management of serious hypersensitivity reactions observed during the DBPCFC and the post-DBPCFC observation period.

10.1.5 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Subject Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of the study treatment to any pregnancy outcome. The follow-up should be for up to 12 months following the birth of the baby. Any SAE experienced during pregnancy must also be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (Committee for Medicinal Products for Human Use (CHMP) Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty, CHMP 2014).

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

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 and Table 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease, imaging such as abdominal US, CT or MRI, as appropriate, obtaining a history of exposure to environmental chemical agents.

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to screening during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Section 16.3. Additional details on actions required in case of renal events are outlined in Table 16-4 and Table 16-5.

10.2.3 Adverse Events of Special Interest

Avoiding exposure to the relevant allergens is a cornerstone of the standard of care for management of food allergy. Nonetheless, accidental exposures and subsequent food allergy reactions are known to occur. These adverse events are of special interest because they relate to the primary outcome, which is increase in the eliciting dose of known food allergen. This study will collect data regarding all likely food allergy reactions.

Additional adverse events of special interest related to remibrutinib, CCI [redacted] will be collected also.

10.2.4 Hematologic safety monitoring

Once a participant is exposed to study treatment, hematologic laboratory alert values should be assessed during the study period:

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

Abnormal hematologic laboratory findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, hematologic laboratory alerts or hematologic safety events (e.g., significant bleeding) should be monitored and followed up by the investigator or designated trial staff as summarized in Section 16.1.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Statistical summaries will be generated by treatment arm and overall for disposition, demographics and any baseline characteristics. Unless specified otherwise, all endpoints relevant to efficacy, safety, PK, PD and biomarkers will be summarized by treatment arm (i.e., LOU064 or placebo).

12.1 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 any study drug. Safety set will be utilized for all safety/efficacy summaries and analyses.

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 any study drug 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.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group and overall utilizing the safety set.

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

Relevant medical histories and current medical conditions at baseline will be listed by treatment arms.

12.3 Treatments

The Safety set will be used for the analyses below. 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.

The duration of exposure (in weeks) by treatment arm will be summarized using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment arm.

12.4 Analysis supporting primary objectives

The primary objective of this study is to characterize the dose-response relationship among remibrutinib treatment after one month of treatment CCI and placebo with respect to the responder rate as the primary endpoint, and to select appropriate dose(s) in Phase 3 studies. The consecutive steps are therefore (1) to confirm an overall dose--response signal, (2) to estimate the dose-response curve to enable 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.

12.4.1 Definition of 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 treatment.

12.4.2 Statistical model, hypothesis, and method of analysis

Primary endpoint – Responder rate

The statistical analyses will be based on the PD population.

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 categorical variable (remibrutinib doses and placebo) after one month/ 1 week of treatment dosing period and not limited to but also including log-transformed baseline total IgE, and baseline peanut allergen tolerated dose as covariates. Odds ratio and 80% confidence intervals (CI) will be presented comparing each remibrutinib dose to placebo with respect to the proportions of response. The Odds ratio of the effect of the CCI four week treatment relative to CCI 1 week treatment will also be calculated. From this logistic regression the model estimates of the proportion of responders by dose will be determined together with the corresponding standard error. These estimates will be used in the dose response fitting.

Generalized MCP-Mod (Pinheiro et al 2014) will be applied based on the estimates and SE of the proportion of responders from the 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.

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 12-1).

Figure 12-1 CCI

Optimal contrasts will be derived for the remibrutinib BID 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).

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.

The details of the bootstrapping and model averaging techniques will be provided in the Statistical Analysis Plan (SAP).

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% confidence interval.

12.4.3 Handling of intercurrent events of primary estimand

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
2. Intake of rescue medication prior to DBPCFC conducted before one month : ignorable (treatment policy strategy, reflected in the Treatment attribute)

12.4.4 Handling of missing values not related to intercurrent event

12.4.5 Sensitivity analyses

Not applicable.

12.4.6 Supplementary analysis

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

Participants who discontinue study before one month of treatment, OR who miss more than 20% of study doses throughout the study treatment period, OR who miss ANY medication doses for ≥ 3 consecutive days in the 7 days prior to DBPCFC Part 2A, will not undergo DBPCFC at one month due to any reason [including operational complications caused by public health emergency (i.e., COVID-19)] other than adverse events 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).

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.

Treatment policy will also be considered to show the treatment effect in real-world conditions. 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.

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.

The response rates will also be analyzed using a Bayesian logistic regression model. The covariates of interest will be included similar to the primary model. A prior will be implemented to borrow placebo response rates from the existing knowledge of the historical trials and a noninformative prior on the remibrutinib response rates. Further details will be described in the SAP.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic 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% Confidence Interval (CI) will be presented for 1000 mg and 3000 mg peanut protein dose, respectively.

Maximum severity of symptoms occurring at any challenge dose of peanut protein up to and including 1000 mg during the DBPCFC conducted after three weeks placebo plus one week study treatment plus OR/ 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 allergic dose and symptoms:

- Change in maximum tolerated dose (MTD) of peanut protein without dose-limiting symptoms during the DBPCFC after one month of treatment compared to after 1 week of treatment for remibrutinib CCI 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. 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 will be analyzed utilizing the proportional odds model. 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.
- 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 after one week of treatment (3 weeks of placebo + 1 week of remibrutinib treatment vs. placebo). Proportion of responders and 80% CI 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.

12.5.2 Safety endpoints

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.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of pre-dosing 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 adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

12.5.2.1 Adverse Events

All adverse events summarized will be displayed by treatment group and overall. All adverse events 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.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) 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 adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation. In case of sparse events in any of these categories occur, only a listing will be provided if deemed adequate.

Adverse events of special interest for remibrutinib treatment CCI [redacted] will also be summarized for all participants.

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

12.5.2.2 Vital signs

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

12.5.2.3 Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and, if normal ranges are available, abnormalities will be flagged. 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.

12.5.2.4 12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced by treatment group.

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.

12.5.3 Pharmacokinetics

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.

12.5.4 PK/PD relationships

The PK and PD properties of remibrutinib and its effect on relevant biomarker changes (CCI 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.

12.6 Analysis of exploratory endpoints

12.6.1 CCI

CCI

CCI

12.6.2 CCI

CCI

12.7 Interim analyses

CCI

12.8 Sample size calculation

A total of 72 participants will be enrolled in this study. The discontinuation rate is expected to be around 10%. Assuming an approximately 2:2:2:1:1 randomization ratio (2:1 ratio between 1-month remibrutinib treatment arms vs 1-week remibrutinib treatment arm and placebo arm), the anticipated number of completers in each of the remibrutinib 1-month treatment arms is expected to be around 14 to 16 participants and 7 to 8 in the 2 remaining arms.

12.8.1 Primary endpoint(s)

Dose-response relationship

The primary objective of this study is to characterize the dose-response relationship among remibrutinib doses (CCI 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 signal for a one-sided type-I error at 10%, assuming a true maximum treatment effect of CCI responder rate and placebo treatment effect of CCI responder rate.

CCI

CCI

Table 12-1 CCI

CCI

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

Angst D, Gessier F, Janser P, et al (2020) Discovery of LOU064 (Remibrutinib), a potent and highly selective covalent inhibitor of Bruton's Tyrosine Kinase. Journal of Medicinal Chemistry; 63(10):5102-18.

Bock SA, Sampson HA, Atkins FM, et al (1988) Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. Journal of Allergy and Clinical Immunology; 82(6):986-97.

Boyce JA, Assa'ad A, Burks AW, et al (2011) Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. Journal of the American Academy of Dermatology; 64(1):175-92.

Brazier JE, Mulhern BJ, Bjorner JB, et al (2020) Developing a new version of the SF-6D health state classification system from the SF-36v2: SF-6Dv2. Medical care; 58(6):557-65.

Bretz F, Pinheiro JC, Branson M (2005) Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics; 61(3):738-48.

Byrne AM, Malka-Rais J, Burks AW, et al (2010) How do we know when peanut and tree nut allergy have resolved, and how do we keep it resolved? Clinical & Experimental Allergy; 40(9):1303-11.

Casale, TB, Haselkorn T, Ciaccio, et al (2019) Harmonization of terminology for tolerated and reactive dose in food allergy immunotherapy. The Journal of Allergy and Clinical Immunology: In Practice; 7(2):389-92.

CDER (2003) Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations.68 FR 13316. (Internet) Available at: <https://www.govinfo.gov/app/details/FR-2003-03-19/03-6491/summary> (Accessed 29-Mar-2022).

Chinthrajah RS, Jones SM, Kim EH, et al (2022) Updating the CoFAR Grading Scale for Systemic Allergic Reactions in Food Allergy. Journal of Allergy and Clinical Immunology.

Committee for Medicinal Products for Human Use (CHMP) Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. (2014). (Internet) Available at: <https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-mcp-mod-efficient-statistical-methodology-model-based-design-analysis-phase-ii_en.pdf> (Accessed 29-Mar-2022).

Cox AL, Nowak-Wegrzyn A (2018) Innovation in food challenge tests for food allergy. Current allergy and asthma reports; 18(12):1-12.

Dispenza MC, Pongracic JA, Singh AM, et al (2018) Short-term ibrutinib therapy suppresses skin test responses and eliminates IgE-mediated basophil activation in adults with peanut or tree nut allergy. Journal of Allergy and Clinical Immunology; 141(5):1914-6.

Feng C, Kim JH (2019) Beyond avoidance: the psychosocial impact of food allergies. Clinical reviews in allergy & immunology; 57(1):74-82.

Futatani T, Watanabe C, Baba Y, et al (2001) Bruton's tyrosine kinase is present in normal platelets and its absence identifies patients with X-linked agammaglobulinaemia and carrier females. British journal of haematology; 114(1):141-9.

Gabizon R, London N (2020) A fast and clean BTK inhibitor. Journal of Medicinal Chemistry; 63(10):5100-1.

Graham BL, Steenbruggen I, Miller MR, et al (2019) Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med; 200(8):e70-e88.

Gupta R, Holdford D, Bilaver L, et al (2013) The economic impact of childhood food allergy in the United States. JAMA pediatrics; 167(11):1026-31.

Gupta RS, Warren CM, Smith BM, et al (2019) Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw Open; p. e185630.

Hendriks RW, Yuvaraj S, Kil LP (2014) Targeting Bruton's tyrosine kinase in B cell malignancies. Nature Reviews Cancer; 14(4):219-32.

Jones SM, Burks AW (2017) Food Allergy. N Engl J Med; 377(12):1168-76.

Kaul M, End P, Cabanski M, et al (2021) Remibrutinib (LOU064): A selective potent oral BTK inhibitor with promising clinical safety and pharmacodynamics in a randomized phase I trial. Clinical and translational science; 14(5):1756-68.

Kaul M, Storim J, End P, et al (2019) LBPD1718| LOU064: A highly selective and potent covalent oral BTK inhibitor with promising pharmacodynamic effects in skin. Allergy; 74:332-75.

Leung DY, Sampson HA, Yunginger JW, et al (2003) Effect of anti-IgE therapy in patients with peanut allergy. New England Journal of Medicine; 348(11):986-93.

Maruish M, Kosinski M, Bjorner J, et al (2011) User’s manual for the SF36v2 Health Survey.

Muraro A, Werfel T, Hoffmann-Sommergruber K, et al (2014) EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy; 69(8):1008-25.

Niggemann B, Beyer K (2007) Diagnosis of food allergy in children: toward a standardization of food challenge. Journal of Pediatric Gastroenterology and Nutrition; 45(4):399-404.

Peavy RD, Metcalfe DD (2008) Understanding the mechanisms of anaphylaxis. Curr Opin Allergy Clin Immunol; 8(4):310-5.

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. Statistics in medicine; 33(10):1646-61.

Quek LS, Bolen J, Watson SP (1998) A role for Bruton's tyrosine kinase (Btk) in platelet activation by collagen. Current biology; 8(20):1137-S1.

Regan JA, Cao Y, Dispenza MC, et al (2017) Ibrutinib, a Bruton's tyrosine kinase inhibitor used for treatment of lymphoproliferative disorders, eliminates both aeroallergen skin test and basophil activation test reactivity. Journal of Allergy and Clinical Immunology; 140(3):875-9.

Rip J, Van Der Ploeg EK, Hendriks RW, et al (2018) The role of Bruton's tyrosine kinase in immune cell signaling and systemic autoimmunity. Critical Reviews™ in Immunology; 38(1).

Sampson HA, Van Wijk RG, Bindslev-Jensen C, et al (2012) Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology PRACTALL consensus report. Journal of Allergy and Clinical Immunology; 130(6):1260-74.

Sampson HA, Leung DY, Burks AW, et al (2011) A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. Journal of Allergy and Clinical Immunology; 127(5):1309-10.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Journal of Allergy and Clinical Immunology; 117(2):391-7.

Schorning K, Bornkamp B, Bretz F, et al (2016) Model selection versus model averaging in dose finding studies. Statistics in medicine; 35(22):4021-40.

Sicherer SH, Sampson HA (2018) Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J. Allergy Clin. Immunol; 141(1):41-58.

Smiljkovic D, Blatt K, Stefanzl G, et al (2017) BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. Allergy; 72(11):1666-76.

Suresh RV, Dunnam C, Vaidya D, et al (2023) A phase II study of Bruton's tyrosine kinase inhibition for the prevention of anaphylaxis. J Clin Invest; 133(16):e172335.

Taylor SL, Hefle SL, Bindslev-jensen C, et al (2004) A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clinical Experimental Allergy; 34(5):689–95.

Vadas P, Gold M, Perelman B, et al (2008) Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. N Engl J Med; 358(1):28-35.

Vander Leek TK, Liu AH, Stefanski K, et al (2000) The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J. Pediatr; 137(6):749-55.

Vickery BP, Vereda A, et al (2018) AR101 Oral Immunotherapy for Peanut Allergy. N. Engl. J. Med; 379(21):1991-2001.

Warren CM, Jiang J, Gupta RS (2020) Epidemiology and Burden of Food Allergy. Curr Allergy Asthma Rep; 20(2):6.

Wood RA (2003) The natural history of food allergy. Pediatrics; 111(6 Pt 3):1631-7.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following specific criteria have been identified for this study. Should these criteria be met, a re-test must be done within 5 days after the first assessment. 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 eCRF.

Refer to Section 16.2 for clinically notable laboratory values for hepatotoxicity.

Refer to Section 16.3 for clinically notable laboratory values for nephrotoxicity.

For ECGs, a notable QTc value is defined as a QTc (Fridericia's) interval of greater than 450 msec for males or greater than 460 msec for females – all such ECGs will be flagged by the central CRO's cardiologist and require assessment for clinical relevance by the investigator. Confirmed QTcF > 500 msec requires discontinuation of study treatment.

16.1.1 Guidance on monitoring infections

All infections that develop during the study will be reported as AEs on the respective AE eCRF pages. Treatment and additional evaluations (e.g. WBC/Lymphocyte) or other needed investigations / assessments to monitor for signs and symptoms of infection will be performed at the discretion of the Investigator.

The Investigator should remind the participant of the risk of infections and instruct them to promptly report any symptoms of infections to the Investigator. The participants must also be reminded to always carry their Participant Information Card (with site contact information and which identifies them as participants in a clinical study with investigational and control agents with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the Investigator be contacted.

In the case of suspected or confirmed serious or atypical infection, study drug interruption should be considered. The Investigator should inform the Sponsor of any such cases.

When evaluating a participant with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR).

The Investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof in consultation with infectious disease experts, as appropriate. The Investigator should inform the Sponsor of any such cases.

16.1.2 Guidance on immunizations

Administration of live or live-attenuated vaccines (including live or live-attenuated SARS-CoV-2 (COVID-19)) should be avoided 6 weeks before and during treatment with remibrutinib and for 4 weeks after the last study drug dose. Further, participants are encouraged to perform necessary last dose of **non-live** vaccines (including for COVID-19) at least 4 weeks before randomization, if available, and according to local practice.

The safety of and ability to generate a primary or anamnestic response to immunization with live, live-attenuated, or inactivated vaccines during remibrutinib treatment has not been investigated. The response to vaccination (including non-live vaccines) could be impaired when B-cells are inhibited.

It is recommended that the Investigator review the participant's immunization history as part of the initial screening procedure for a participant being considered for treatment with remibrutinib.

Vaccination of the participant (including COVID-19 vaccine), in compliance with local area vaccination guidelines for the patient population being treated, is recommended prior to administration of remibrutinib.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law* cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline AND > 5 x ULN

*Treatment-emergent elevations in AST or ALT (>3x ULN or increase of >3x above baseline visit levels, if >ULN at baseline) in combination with total bilirubin >2x ULN (or >2x above baseline visit levels, if >ULN at baseline visit) or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 5 x ULN for more than two weeks OR ALT > 8 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin and CK in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study treatment can be restarted if liver enzymes return to baseline.
	If elevated at baseline: ALT > 3 x baseline AND > 5 x ULN for more than two weeks OR ALT ≥ 5 x baseline AND ≥ 8 x ULN			
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated*	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
	If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN			

* This situation suggests liver injury based on (i) elevation of ALT, and (ii) the presence of symptoms of liver injury. Even if bilirubin is normal, the presence of liver symptoms indicates potentially severe liver injury.

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Stop treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Stop study treatment • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate eCRF	Investigator discretion

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow -up within 2 days; increase fluid intake before assessment if appropriate • Repeat follow-up (every 2-5 days) until creatinine is <125% of baseline value
Serum creatinine increase ³ 50 % [1]	• Consider causes and possible interventions and initiate renal investigation • Repeat assessment within 24-48 h if possible • Stop study drug if repeat assessment shows similar increase • Close follow-up (every 24-48 h), consider participant hospitalization and specialized treatment until creatinine is <125% of baseline value
New onset dipstick proteinuria ≥ 3+ When urine proteins are measured as a follow-up of positive urine dipstick measurements: Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Stop study drug unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• Assess and document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[1] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. (Note: in exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the Renal Safety Group to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, eg, dehydration due to delirium, tumor lysis

Table 16-5 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in the eCRF: • Urine dipstick and sediment microscopy evidence of Drug-Induced Nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the eCRF
Monitor participant regularly (frequency at investigator's discretion) until: • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

16.4 Appendix 4: Double-blind Placebo-Controlled Food Challenge (DBPCFC)

16.4.1 Background

The DBPCFC represents the gold standard to diagnose food allergy. It is also the most objective method to clinically estimate threshold doses for allergenic foods in highly sensitive individuals (Taylor et al 2004). In this study the DBPCFC is based upon two available guidelines, PRACTALL (Sampson et al 2012) and the CoFAR Grading Definition of Dose-Limiting Symptoms. The double-blind aspect of the DBPCFC markedly reduces any potential bias of participant and/or supervising health care professionals that could interfere with its appropriate interpretation. The test itself corresponds most closely to the natural ingestion of food.

The DBPCFC is to be strictly performed under medical supervision to document the dose of allergen that provokes a reaction and, if needed, to administer symptomatic treatment which could potentially require the management of anaphylaxis. Participants must be in good health before proceeding with the food challenge and should be advised to avoid physical exercise at least one hour prior to the start of the procedure. A light breakfast is optional on the day of the DBPCFC, in line with local practice. Additionally participants should be on minimal or no symptomatic medication before starting the DBPCFC (Table 6-2 and Table 6-3). Due to the inherent risk of a severe reaction, participants who have experienced a severe or life-threatening hypersensitivity event leading to ICU admission or intubation within 60 days prior to Screening Visit 1 are excluded from study participation.

Intravenous access may be set up before the DBPCFC at the investigator's discretion (e.g., participant at high risk of reaction or severe reaction based upon prior history and medical history).

At the start of the DBPCFC a small dose of peanut allergen is administered. This dose is intentionally lower than any dose expected to induce a reaction (Niggemann, Beyer 2007). While monitoring the participant for any allergic symptoms, the allergen dose is gradually increased until a cumulative dose at least equivalent to the portion of allergen as defined in the objectives (Section 2) is ingested (refer to the LOU064I2201 Pharmacy Manual).

16.4.2 DBPCFC Dosing schedule

This study includes two DBPCFCs: the first at Screening (Visits 2 and 3), the second at the end-of-treatment (one month) (Day 26 and 28).

Each DBPCFC consists of two Parts, active allergen (peanut) challenge and placebo challenge. Each challenge is to be performed on a separate day (part 1A and 1B during screening, and part 2A and 2B at end-of-treatment period). The active allergen challenge is either given on the first day or the second day. To ensure and preserve the double-blind nature of the challenge, independent (unblinded) study site staff need to prepare the material for each challenge prior to administration. Study staff/investigator administering the challenge and Participants undergoing the challenge remain blinded to the identity of the challenge on the two test days (i.e. if peanut allergen or placebo is tested on the first or the second day). The time interval between each challenge is two to seven days; there must be a minimum of two full days and a maximum of 7 days between part 1A or 2A and part 1B or 2B DBPCFCs. There must be at least

72 hours between the completion of the DBPCFC part 1B and the first administration of study treatment at the randomization visit.

16.4.2.1 Allergen dose escalation

At each DBPCFC, participants will be exposed to increasing amounts of allergen, either peanut protein or corresponding placebo in a randomized fashion, with each dose administration separated by at least 15 minutes (Table 16-6).

Randomization will be done via IRT system by the unblinded site staff who will be reconstituting/preparing the content for the DBPCFC. Unblinded staff must try diligently to maintain the blind of whether the participant is receiving allergen or placebo for all parts of the DBPCFCs. The placebo will match in texture and color and both allergen and placebo powders will be mixed into a dessert-like challenge material for consumption.

At screening DBPCFCs, the amounts of 1 mg, 3 mg, 10 mg, 30 mg, and 100 mg of peanut protein and corresponding placebo will be tested. At the end-of-treatment DBPCFCs, 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 the corresponding placebo will be tested.

16.4.2.2 Maximum dose

Within the DBPCFC, incremental allergen (or placebo) dose increases continue until the highest dose for the challenge has been reached or until the participant displays (a) dose-limiting symptom(s) (Section 16.4.5).

300 mg peanut protein is estimated to correspond to the amount of allergen generally associated with accidental exposure, while 3000 mg corresponds to the highest peanut protein dose used within this protocol.

16.4.3 Dosing Schedule

No.	Peanut Protein/Placebo (mg)	Cumulative Dose (mg)
1	1	1
2	3	4
3	10	14
4	30	44
5	100	144
6	300	444
7	600	1044
8	1000	2044
9	3000	5044

After each administered dose of allergen (or placebo) participants are to be monitored for any reaction. In the presence of an allergic reaction, and at the investigator's discretion, the interval between escalating doses can be increased or the challenge can be stopped. (Section 16.4.5).

The minimum observation time between doses is 15 minutes, the maximum observation time is 30 minutes. If needed, an additional 30 minutes of observation is permitted for further evaluation of symptoms. If continuation of the DBPCFC is still in question after 1 hour of observation, the challenge should be considered positive and should be stopped.

During and up to at least one hour after the completion of the DBPCFC, vital signs should be monitored at minimum:

- Start of challenge
- End of challenge
- With administration of epinephrine or any rescue medications
- Vital signs should be taken every 15 minutes after dosing for up to at minimum 1 hour after last dose of rescue medication(s)
- At any time deemed clinically necessary or relevant

Additionally, the participant should be, at minimum, observed every 15 minutes by a study team member after the last dose is given for signs and symptoms of reaction as well as AEs. These observation findings should be documented in source documents.

In the event of an allergen dosing error, the site should contact Novartis.

16.4.4 Allergen material

Novartis will supply the Oral Food Allergen Peanut Flour Chocolate Meal Base and its placebo globally in an open-label fashion.

- high dose: 20%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (20%w/w Peanut Choc)
- low dose: 0.67%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (0.67%w/w Peanut Choc)
- Placebo: 0%w/w Peanut Flour Chocolate Flavour Challenge Meal Base (0%w/w Peanut Choc)

Pharmaceutical Dosage Form: Granules for oral suspension

Route of Administration: Oral

The food challenge material and preparation instructions are described in detail in the LOU064I12201 Pharmacy Manual provided separately.

As previously noted, there should be an independent, unblinded staff member, or other appropriately trained study site staff to prepare (i.e. NOT TO ADMINISTER) the unblinded material for the DBPCFC after obtaining the assigned test sequence through the IRT system Section 16.4.2.

16.4.5 Preparing for the DBPCFC

Prior to DBPCFC material preparation, independent **unblinded** study site personnel need to access the IRT system to obtain the assigned DBPCFC test sequence (peanut allergen or placebo).

16.4.6 Evaluation parameters of the DBPCFC

Objective symptoms exhibited by participants should be evaluated through physical examination. Complaints arising from the participant without observable changes will be classified as subjective.

The DBPCFC will be **positive** with the occurrence of any dose-limiting symptom(s). Dose-limiting symptoms indicate a true allergic reaction occurring during administration of a single dose that should preclude the administration of any further doses. Investigators must adhere to Table 16-6 (CoFAR grading scale) for definition of dose-limiting symptoms (Chinthrajah et al 2022). According to the CoFAR grading scale, symptoms are classified as mild, moderate or severe. Investigators must not deviate from the severity score when deciding to continue or discontinue the DBPCFC in order to ensure the precision of the procedure and to preserve the safety of the participants.

The DBPCFC is positive when the occurrence of any dose limiting symptom(s) is/are detected as below:

- Any moderate and severe symptom(s) as defined in Table 16-6 (CoFAR grading scale)
- Any symptom(s) that require administration of any rescue medication (e.g., SABA, epinephrine or other)
- A combination of mild symptoms during a single dose as defined in Table 16-6, at the discretion of the investigator

Once any of the dose limiting symptom(s) described above are observed, the next dose of DBPCFC must not be administered.

All findings that the investigator classifies as reactions to the DBPCFC should be recorded in source documentation and on a designated eCRF. These events should not be reported on the Adverse Event eCRF unless they constitute an SAE according to the investigator's judgement.

The details and start time of any treatment and/or medication provided to treat DBPCFC-related allergic reactions should be recorded on the respective eCRF. The DBPCFC will be considered **negative** if a participant does not exhibit dose-limiting symptom(s) by the end of the challenge.

Table 16-6 Definition of Dose-Limiting Symptoms (per the CoFAR grading scale)

MILD (not typically dose limiting)	MODERATE (dose limiting)	SEVERE (dose limiting)
· Skin – limited (few) or localized hives, swelling (e.g., mild lip edema), skin flushing (e.g., few areas of faint erythema) or mild pruritus (e.g., occasional scratching) • Respiratory – rhinorrhea (e.g., occasional sniffling or sneezing), nasal congestion, occasional cough, throat discomfort	· Skin – systemic hives (e.g., numerous or widespread hives), swelling (e.g., significant lip or face edema), pruritus causing protracted scratching, more than a few areas of erythema or pronounced erythema • Respiratory – throat tightness without hoarseness, persistent cough, wheezing without dyspnea	• Skin – severe generalized urticaria/angioedema/erythema • Respiratory – laryngeal edema, throat tightness with hoarseness, wheezing with dyspnea, stridor • GI – severe abdominal pain/cramping/repetitive vomiting • Neurological – change in mental status

MILD (not typically dose limiting)	**MODERATE (dose limiting)**	**SEVERE (dose limiting)**
• GI – mild abdominal discomfort (including mild nausea with or without decreased activity), isolated emesis thought to be secondary to gag	• GI – persistent moderate abdominal pain/cramping/nausea with decreased activity, vomiting	• Circulatory – clinically significant hypotension

16.4.7 Completion of the DBPCFC

At the completion of the DBPCFC (post-administration of the last dose of allergen), participants must remain under observation at the study site for a minimum of 2 hours unless after unblinding the participant was found to have received placebo challenge on that day. In the event of a positive challenge participants must remain under observation at the study site for a minimum of 1 hour after allergic symptoms have improved to a level compatible with safe discharge. Observation beyond this timepoint remains at the Investigator's discretion and could potentially include hospital overnight observation.

Treatment of positive reactions

Epinephrine, SABA, anti-histamines and saline bolus are typically used to treat allergic reactions. Treatment in line with local clinic provisions/ guidelines is at the investigator's discretion. All treatment must be documented in the corresponding eCRF.

Discharge procedures

Upon discharge from the study site post-DBPCFC participants should be provided with a 24 -hour emergency telephone contact. Furthermore, participants should be advised to avoid physical exercise within 2 hours after having received the last dose of the DBPCFC.

Delayed or late-onset reactions to the DBPCFC are defined as reactions occurring after the participant was discharged from the clinic. Since a delayed reaction to the DBPCFC cannot be predicted prior to discharge, all participants should be briefed about the signs and symptoms of anaphylaxis and provided with rescue medication [epinephrine auto-injector and short acting beta-agonists (asthma participants only)]. Participants should also receive specific information on how to recognize a late reaction and how and when to use rescue medication. Delayed or late- onset reactions will not be considered dose-limiting and will be captured on a designated eCRF.

Post-discharge, participants who need to use epinephrine due to a suspected reaction should immediately go to the closest emergency room for additional assessment, and contact the investigative site.

Adverse event reporting

If the participant experiences an allergic reaction associated with the DBPCFC (immediate, delayed or late-onset) that meets the criteria for a serious adverse event in the investigator's judgment, it should be captured on the designated CFR and reported as described in Section 10.1.3 SAE Reporting.

16.5 Appendix 5: Skin Prick Test

16.5.1 Background

This study includes a Skin Prick Test (SPT) targeting peanut allergen. CCI [redacted]

16.5.2 SPT materials

Preparation for the reagent of titration SPT (also described in Lab Manual)

- ~ 5ml Vials (can be purchased from any supplier)
- Diluent (saline) (also purchased from any supplier)
- Pipette with disposable pipette tip (able to measure 0.1 to 0.9 ml)
- Add 0.9 mL of diluent to each of 5 vials (~ 5 mL in size). Label them from 1:10, 1:100, 1:1'000, 1:10'000, 1:100'000; and include the name of the allergen, the lot number, and the date on which the dilutions were made.
- Take 0.1 mL of the undiluted peanut stock and add to vial 1:10. Mix well.
- Take 0.1 mL from the 1:10 vial and add to vial 1:100. Mix well.
- Take 0.1 mL from the 1:100 vial and add to vial 1:1'000. Mix well.
- Take 0.1 mL from the 1:1,000 vial and add to vial 1:10'000. Mix well.
- Take 0.1 mL from the 1:10,000 vial and add to vial 1:100'000. Mix well.

Only a very small volume of allergen is needed per test – one "drop". The prepared dilutions should not be used for more than one week after reconstitution.

16.5.3 Start SPT

Location of SPT: The skin of the participant's back is the preferred site of testing, alternatively the forearm may be used. For consistency purposes it is important for individual participants to perform the SPT at the same site during the study.

Test time: Skin reactions should be recorded 15 minutes after placement of SPT.

Positive/negative control: The SPT should be repeated x 1 if the appropriate valid positive (≥ 3 mm wheal) and negative (no response) control results were not obtained.

Prohibited/washout medications prior to SPT

Table 16-7 Prohibited period of medication prior to SPT

Medication	Prohibited period
Short and long acting anti-histamines (e.g., chlorpheniramine, promethazine, diphenhydramine, loratadine, cetirizine)	≥5 half-lives
Antihistamine nose spray	12 hours
Oral H2-receptor antagonist (e.g., cimetidine, ranitidine, famotidine, roxatidine, lafutidine)	24 hours
Systemic corticosteroids (including short-term burst of OCS)	≥5 half-lives

16.5.4 Conduct SPT

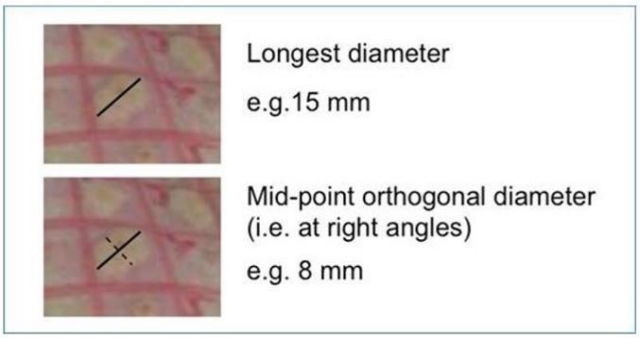
1. Clean the area of skin with 70% alcohol and allow to dry
2. Use a pen (which can be washed off with an alcohol wipe) to mark the skin with the sites where SPT will be performed. Put a mark beside the area where a particular solution will be placed; or draw boxes on the skin

- Label allergen: undiluted and diluted peanut stock for TSPT (from 1:10 to 100'000)
- Label histamine (positive control) and diluent-saline (negative control)

3. Place one drop of test solution at the appropriate labelled site as above and "prick" the skin with provided metal lancet: Starting from saline, positive control, then allergen (for TSPT, from the lowest concentration) using a different lancet for controls and allergens.
4. Start a timer for 15 minutes. Record times in source documents.
5. After pricking the skin, immediately blot the skin with tissue paper to absorb excess liquid; avoid letting the liquid run from one site to another
6. After 15 minutes measure the size of the wheal at each site: 1) Start with the site you first pricked and then work your way in the same order in which the pricks were applied. The time taken to do this will be approximately the time it took to apply the solutions and prick them, 2). Measure and record the longest diameter at each site (record in eCRF), 3) Measure and record the midpoint orthogonal diameter (record in eCRF).

For the eligibility check, the average of longest wheal diameter and the corresponding midpoint orthogonal diameter will be used, e.g. 11.5 mm = (15+8)/2

Figure 16-1 Measurement of skin reaction



16.5.5 Complete SPT

After measurement of skin reaction and recording results in the source document, clean the skin with alcohol to remove the ink from marker pen on the skin.

Rarely, SPT can cause a generalized allergic reaction (e.g., hives itchy, runny nose, asthma) or even anaphylaxis. Therefore, at the completion of SPT, the participants should remain under observation at the site as per the investigator's discretion.

Adverse event reporting

If the participant experiences a systemic allergic reaction suspected to be triggered by the SPT, the event should be captured in the designated eCRF (see Section 10.1.1). Adverse events meeting the criteria for a SAE should be reported as described in Section 10.1.4 SAE Reporting.

16.6 Appendix 6: List of Moderate CYP3A4 inhibitors, strong CYP3A4 Inhibitors and strong CYP3A4 Inducers

The lists provided in the tables below are non-exhaustive.

Reference: University of Washington Drug Interaction database (www.druginteractioninfo.org): Database search December, 2021

Table 16-8 Moderate inhibitors and inducers of CYP3A4*

CYP3A4	Concomitant Medication Name	Action
Moderate **inhibitors** of CYP3A4	aprepitant, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, ferula asafetida resin (*herbal product*), fluconazole, isavuconazole, netupitant, schisandra sphenanthera (*herbal product*), tofisopam, verapamil, duvelisib, letermovir, lefamulin, ravuconazole, istradefylline, voxelotor, atazanavir, ritonavir, darunavir, ACT-539313, darunavir, fedratinib, letermovir, GSK2647544, lefamulin, amprenavir, faldaprevir, imatinib, ravuconazole, netupitant, nilotinib, istradefylline, tofisopam, berotralstat, ACT-178882, voxelotor, FK1706	Avoid **moderate CYP3A4 inhibitor** if alternative available.
Moderate **inducers** of CYP3A4	semagacestat, efavirenz, tipranavir, ritonavir, dabrafenib, cenobamate, lesinurad, bosentan, thioridazine, rifabutin, metamizole, lorlatinib, nafcillin, talviraline, phenobarbital, lopinavir, sunaprevir, beclabuvir, daclatasvir, modafinil, PF-06282999, pexidartinib, etavirine, elagolix, sotorasib, lersivirine, telotristat ethyl	Avoid **moderate CYP3A4 inducer** if alternative available.

* The list is not exhaustive; concomitant medication used for fungal treatment in the list only apply to oral/parenteral medication

Table 16-9 Strong inhibitors and inducers of CYP3A4

CYP3A4	**Concomitant Medication* Name**	**Action**
Strong **inhibitors** of CYP3A4	clarithromycin, conivaptan, itraconazole, ketoconazole, mibefradil, nefazodone, posaconazole, telithromycin, troleandomycin, voriconazole, mifepristone, ombitasvir, paritaprevir, ritonavir, dasabuvir, indinavir, tipranavir, cobicistat, danoprevir, elvitegravir, saquinavir, lopinavir, LCL161, josamycin, lonafarnib, posaconazole, grapefruit juice, conivaptan, tucatinib, nefazodone, deritinib, nelfinavir, ribociclib, boceprevir	Avoid **strong CYP3A4 inhibitor** if alternative available.
Strong **inducers** of CYP3A4	apalutamide, avasimibe, carbamazepine, enzalutamide, rifampin, mitotane, phenobarbital, phenytoin, rifabutin, St. John's wort (herbal product), lumacaftor, rifapentine, ivosidenib	Discontinue **strong CYP3A4 inducer** if medically justifiable and closely monitor for potential associated adverse events.

*Concomitant medication used for fungal treatment in the list only apply to oral/parenteral medication