NCT: NCT05107115

STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo-controlled, multi center, dose-ranging Phase 2 study of rilzabrutinib followed by an open-label extension phase in patients with moderate-to-severe chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamine treatment**
Protocol number:	**DRI17224**
Compound number (INN/Trademark):	**SAR444671** **Rilzabrutinib/Not applicable**
Study phase:	**Phase 2**
Short Title:	**Rilzabrutinib for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine** RILECSU
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study DRI17224 is based on the protocol amendment 06 dated 21-Sep-2022. There are no major changes to the statistical analysis features in this SAP.

The first participant was randomized on 21-Jan-2022. This SAP is approved before the analyses for core DBL is conducted.

1 INTRODUCTION

1.1 STUDY DESIGN

This study is a 52-week sequential Phase 2 study, comprising a 12-week, randomized, double-blind, placebo-controlled, multi-center, dose-ranging efficacy and safety phase of rilzabrutinib, followed by a 40-week open-label extension (OLE) phase in adult participants with moderate-to-severe CSU who remain symptomatic despite the use of H1 antihistamine treatment.

The total number of participants anticipated in this study is 152. The disease activity of these patients will be at least moderate (see inclusion criteria) despite use of H1-AH. It is expected that ~40% of patients will have concomitant angioedema. Omalizumab naïve patients will be randomized 1:1:1:1 to one of 3 doses of rilzabrutinib (400 mg QPM, 400 mg BID, 400 mg TID) or placebo. Omalizumab-incomplete responders will only be randomized to the 400 mg BID, 400 mg TID and placebo arms, and they will be capped at up to 15% of the patients in that arm. The randomization will be stratified by region and prior use of omalizumab (yes or no).
Note: prior use of omalizumab = yes represents omalizumab-incomplete responders, and prior use of omalizumab = no represents omalizumab-naïve patients.

This study will consist of 3 phases and an optional OLE phase. The phases are as follows:

- Screening period (up to 4 weeks)
- Double-blind IMP treatment period (12 weeks)
- Optional OLE phase (40 weeks): For participants who complete the 12-week double-blind phase, they will be given the option to continue to an OLE phase of the study. It is anticipated that approximately 106 participants will opt into this phase of the study. Participants in the OLE will be given rilzabrutinib 400 mg TID [redacted]
- Follow-up period (4 weeks)

Study primary analysis will be conducted after double-blind treatment period.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of rilzabrutinib in study participants with chronic spontaneous urticaria (CSU) who remain symptomatic despite the use of H1 antihistamines (H1-AH)	• Change from baseline in weekly urticaria activity score (UAS7) at Week 12 (except US and US reference countries) • For US and US reference countries only: change from baseline in weekly itch severity score (ISS7) at Week 12

Objectives	Endpoints
Secondary	
• To demonstrate the efficacy of rilzabrutinib on urticaria activity composite endpoint and itch or hives, separately, at various time points	• Change from baseline in UAS7 at Week 4 • Change from baseline in ISS7 at Week 12 (except US and US reference countries) • For US and US reference countries only: change from baseline in UAS7 at Week 12 • Change from baseline in weekly hives severity score (HSS7) at Week 12 • Proportion of participants with UAS7 ≤6 at Week 12 • Proportion of participants with UAS7 = 0 at Week 12
• To evaluate safety outcome measures	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs) and withdrawals due to TEAEs during the double-blind period and the open label extension
• To assess the plasma PK of rilzabrutinib in participants with CSU	• Plasma PK concentrations of rilzabrutinib in participants with CSU
Tertiary	

[redacted]

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 3. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of SAR444671 vs. placebo.

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objective: To demonstrate the efficacy of rilzabrutinib in study participants with CSU who remain symptomatic despite the use of H1 antihistamines (H1-AH)				
Primary endpoint	Change from baseline in UAS7 at Week 12 (except US and US reference countries). Change from baseline in weekly itch severity score (ISS7) at Week 12 (for US and US reference countries only)	Omalizumab-naïve	The intercurrent events will be handled as follows • Discontinuing the study intervention (but not taking selected prohibited and/or rescue medications [b] prior to Week 12): all data collected after discontinuation will be used in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications [b] prior to Week 12: data will be set to missing values after the medication usage, and the participant's worst postbaseline value on or before the time of the medication usage will be used to impute missing endpoint value (for participants whose postbaseline values are all missing, the participant's baseline value will be used to impute the missing endpoint value) (hypothetical strategy). In addition, the missing data imputation rules are as follows: • After discontinuation of the study intervention due to lack of efficacy prior to Week 12: WOCF approach will be used to impute missing data if needed. • After discontinuation of the study intervention due to reasons other than lack of efficacy prior to Week 12: multiple imputation (MI) approach will be used to impute missing endpoint value, and this MI will use all participants excluding participants who have taken the selected prohibited medications and/or rescue medications prior to Week 12 and excluding participants who discontinue due to lack of efficacy prior to Week 12.	Analysis of covariance (ANCOVA) model with intervention groups, region (combined countries) and baseline value of the endpoint as covariates will be used. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) score will be provided. In addition, difference of the rilzabrutinib group against placebo in LS means and the corresponding 95% CI will be provided along with the p-values.

Endpoint Category (estimand)	Estimands			
	Endpoint [a]	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Secondary objective: To demonstrate the efficacy of rilzabrutinib on urticaria activity composite endpoint and itch or hives, separately, at various time points				
Secondary endpoint	Proportion of participants with UAS7 ≤6 at Week 12. Proportion of participants with UAS7 = 0 at Week 12	Omalizumab-naïve	The intercurrent events will be handled as follows: • Discontinuing the study intervention (but not taking selected prohibited and/or rescue medications [b] prior to Week 12): all data collected after discontinuation will be used in the analysis (treatment policy strategy). • Taking selected prohibited medications and/or rescue medications [b] prior to Week 12: Participants will be considered as non-responders for time points after the medication usage (composite strategy). In addition, the missing data imputation rules are as follows: • Having missing data at the analysis time points: Participants will be considered as non-responders.	CMH test adjusted by region (combined countries). The comparison of the proportions of treatment response between rilzabrutinib and placebo will be derived, and the corresponding odd ratios and the 95% CI will be reported.

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (i.e., continuous, proportion) at other weeks

b Selected prohibited medications and/or rescue medications are listed in Table 5

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Omalizumab-naïve	All randomized omalizumab-naïve participants. Participants will be analyzed according to the intervention allocated by randomization. This is the primary analysis population.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants (safety population) without important deviation related to IMP administration, and with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.
Open-label extension (OLE)	All participants who received at least one dose of intervention during the open-label extension phase.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention in the double-blind period, the intervention group for as-treated analyses will be the intervention group as randomized if the participant received at least one administration as randomized.

For participants receiving more than one study intervention in the open-label period, the intervention group for as-treated analyses will be the intervention group that the participant is exposed longer.

The efficacy endpoints analyses in the double-blind period will be primarily based on the omalizumab-naïve population. ITT population will be used as the supplementary analysis for selected efficacy endpoints.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of double-blind IMP. The same baseline value is used for OLE assessments. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

In the double-blind period, unless otherwise specified, efficacy analyses will be primarily based on omalizumab-naïve population according to the intervention group to which the participant is randomized to. ITT population will be used as the supplementary analysis for selected efficacy endpoints according to the intervention group to which the participant is randomized to. All safety analysis will be based on the safety population according to the intervention group to which the participant is actually exposed.

In the open-label extension period, both efficacy and safety analyses will be based on OLE population.

The 3 doses of rilzabrutinib (400 mg QPM, 400 mg BID, 400 mg TID) and placebo will be analyzed separately. A pooled analysis of the 400 mg BID and 400 mg TID doses may be performed as appropriate.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first double-blind IMP administration.
- **Double-blind period**
  - The **double-blind on-treatment period** is defined as the period from the first double-blind IMP administration to earlier of the time of last double-blind IMP administration +1 day and time of first open-label IMP.
  - The **double-blind post-treatment period** is defined as the period from the end of the **double-blind** on-treatment period to the end of study for participants who do not enter the open label period or to time of first open-label IMP for participants who enter the open-label period.
- **Open-label period**
  - The **open-label on-treatment period** is defined as the period from the first open-label IMP administration to the time of last open-label IMP administration + 1 day.

- The **open-label post-treatment period** is defined as the period from the end of the **open-label** on-treatment period to the end of study.

Double-blind treatment-emergent (TE) period includes both **double-blind on-treatment period** and **double-blind post-treatment period**.

Open-label treatment-emergent (TE) period includes both **open-label on-treatment period** and **open-label post-treatment period**.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The primary endpoint is different in US/US reference countries and non-US/US reference countries.

3.2.1 Definition of endpoint(s)

The primary endpoint is change from baseline in UAS7 at Week 12 (except US and US reference countries).

For US and US reference countries, the primary endpoint is change from baseline in ISS7 at Week 12.

The daily UAS is the sum of the daily HSS (ranging from 0 = none to 3 = more than 50 hives) and the daily ISS (ranging from 0 = none to 3 = intense), the 2 key urticaria signs and symptoms which are wheals and itch. The daily UAS scores range from 0 to 6 point/day. Once daily UAS scores are summed over 7-day period to create the UAS7, ranging from 0 to 42, and is composed of the HSS7 and ISS7 components.

For daily e-diary endpoints, the baseline value is the sum of the 7 measurements obtained within the 7 days prior to randomization.

For the Week 12 score, the sum of the 7 days on and prior to the target visit day will be used (i.e., sum of days 79 through 85. Note: if the participant's double-blind EOT visit falls in this window, the score collected on and after this day will be removed from the calculation of Week 12 score given the transition to OLE at EOT visit).

If there are less than 7 but at least 4 non-missing scores available, the weekly score is the sum of the available scores in the 7 days, divided by the number of days that have a non-missing score, multiplied by 7. If there are equal to or more than 4 missing scores, the weekly score is missing.

3.2.2 Main analytical approach

The statistical hypotheses for comparing each of rilzabrutinib groups against placebo on the primary endpoint of change from baseline in ISS7 at Week 12 (for US and US reference countries), and the primary endpoint of change from baseline in UAS7 at Week 12 (for countries except US and US reference countries) are as follows:

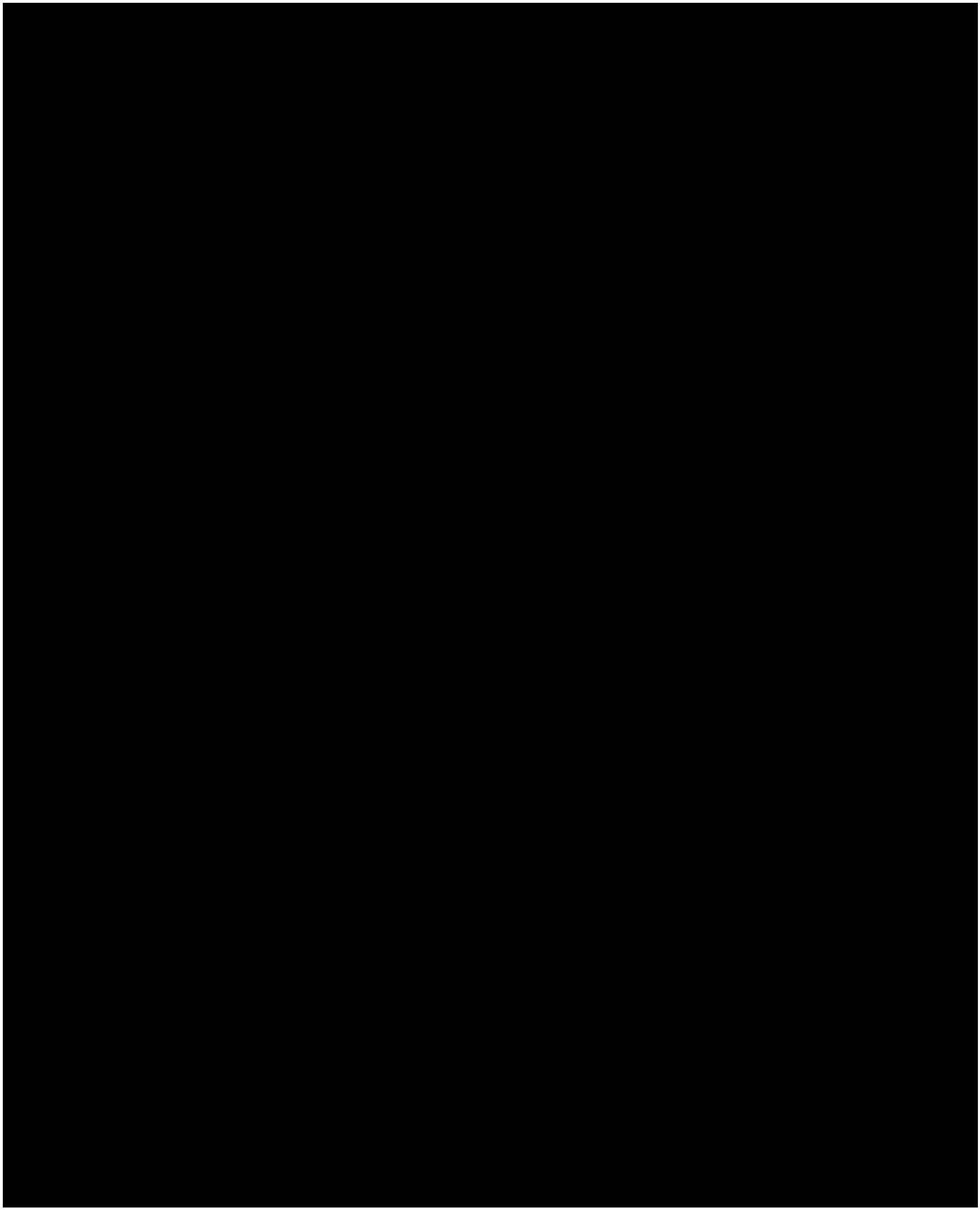
- Null hypothesis H0: No treatment difference between rilzabrutinib and placebo.
- Alternative hypothesis H1: There is a treatment difference between rilzabrutinib and placebo.

Handling of the use of prohibited and/or rescue medications:

For efficacy analysis, Table 5 presents the prohibited and rescue medications where data may be considered as intercurrent events if the last column indicates as 'Yes'. Blinded medical review of these selected treatments will be implemented before database lock to confirm that the medication has the potential to impact the efficacy assessment by considering the type of medication, indication, reason, and timing. [redacted]

Table 5 - Selected prohibited and/or rescue medications impact on efficacy

[redacted]



[redacted]

The primary endpoint will be based on the Omalizumab-naïve population. The intercurrent events handing strategy for the primary estimand is the treatment policy/hypothetic approach.

The primary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with the baseline value of the primary endpoint, intervention group and region as covariates, with intercurrent events and missing data being handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation. For participants taking selected prohibited medications and/or rescue medications (see Table 5), their data after the medication start date will be set to missing, and the worst postbaseline value on or before the time of the medication usage will be used to impute missing Week 12 value (for participants whose postbaseline values are all missing, the baseline will be used to impute). Participants who discontinue the study intervention prematurely are encouraged to follow the planned clinical visits and in these participants who did not take the selected prohibited medications and/or rescue medications, all data collected after the study intervention discontinuation will be used in the analysis. For these participants, missing data may still happen despite all efforts to collect the data after intervention discontinuation. For participants who discontinue study intervention due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a WOCF approach will be used to impute missing Week 12 value if needed (i.e., due to study discontinuation). For participants who discontinue study intervention not due to lack of efficacy, all data collected after discontinuation will be used in the analysis, and a multiple imputation approach will be used to impute missing Week 12 value if needed (i.e., due to study discontinuation). This multiple imputation will use all participants excluding participants who have taken the selected prohibited medications and/or rescue medications on or before Week 12 and excluding participants who discontinue due to lack of efficacy on or before Week 12.

Each of the imputed complete data will be analyzed by fitting an ANCOVA model as described above. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) mean changes (and standard error) score will be provided. In addition, difference of the rilzabrutinib group against placebo in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

See Section 5.5 for the sample SAS code for the imputation and how the analysis model will be built.

3.2.3 Sensitivity analysis

The following sensitivity analyses will be performed targeting the same estimand as in the primary analysis to assess the impact of the missing data handling strategy.

Pattern mixture model with copy increment from placebo

All data after taking the selected prohibited/rescue medications will first be set to missing. The primary endpoint will be analyzed with imputed missing Week 12 values using a pattern mixture model with copy increment from placebo (1). This copy increment from placebo implies that when participants discontinue study intervention early or take selected prohibited/rescue medications, they continue to take advantage of their previous therapy, but they progress in the same way as participants in the placebo group.

The imputed dataset will be analyzed by fitting an ANCOVA model same as the one in the primary analysis. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided along with the p-values.

3.2.4 Supplementary analyses

The following supplementary analysis will be performed:

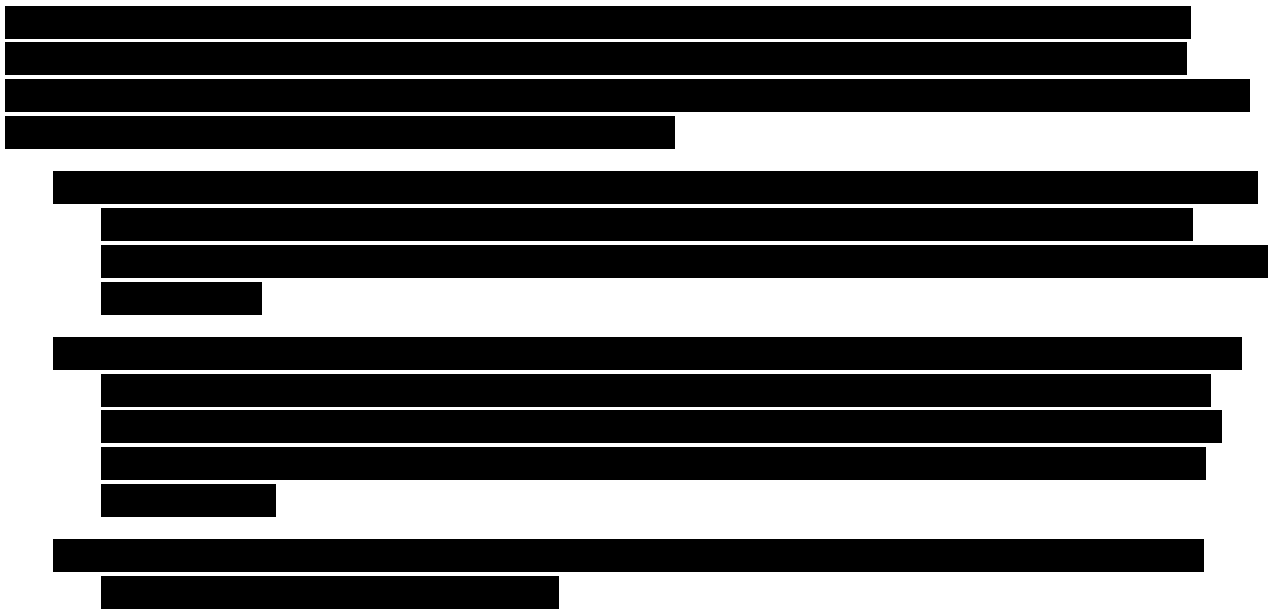
As-observed analysis (Including all data after taking selected prohibited and/or rescue medications)

The data collected after taking the selected prohibited medications and/or rescue medications will be included in the supplementary analysis. The intercurrent event of taking selected prohibited medications and/or rescue medications will be handled in treatment policy strategy. This strategy may better reflect actual real-world outcomes where prohibited medications and/or rescue medications would likely be given when lack of efficacy is seen. For missing data, a multiple imputation approach will be used to impute missing Week 12 value, and this multiple imputation will use all participants.

Additional prohibited/resuce medication analysis (WOCF after taking the corresponding prohibited and/or rescue medications)

Two additional prohibited/rescue medication analyses will be performed: 1) the data collected after taking selected prohibited and/or rescue medications with high/medium/low impact on efficacy will be set to missing and imputed by WOCF, other missing data handling strategy are the same as the primary analysis. 2) the same intercurrent event handling strategy will be applied to the use of selected prohibited and/or rescue medications with high impact on efficacy.

The primary endpoint will also be analyzed based on ITT population. In addition, descriptive statistics for omalizumab-incomplete responders will be provided.



3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are efficacy endpoints. Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE) and Section 3.7.1.1 (PK).

3.3.1 Definition of endpoint(s)

The continuous secondary endpoints are presented below:

- Change from baseline in UAS7 at Week 4
- Change from baseline in UAS7 at Week 12 (for US and US reference countries)
- Change from baseline in ISS7 at Week 12 (except US and US reference countries)
- Change from baseline in HSS7 at Week 12

The responder secondary endpoints are presented below:

- Proportion of participants with UAS7 $\leq$6 at Week 12
- Proportion of participants with UAS7 = 0 at Week 12

3.3.2 Main analytical approach

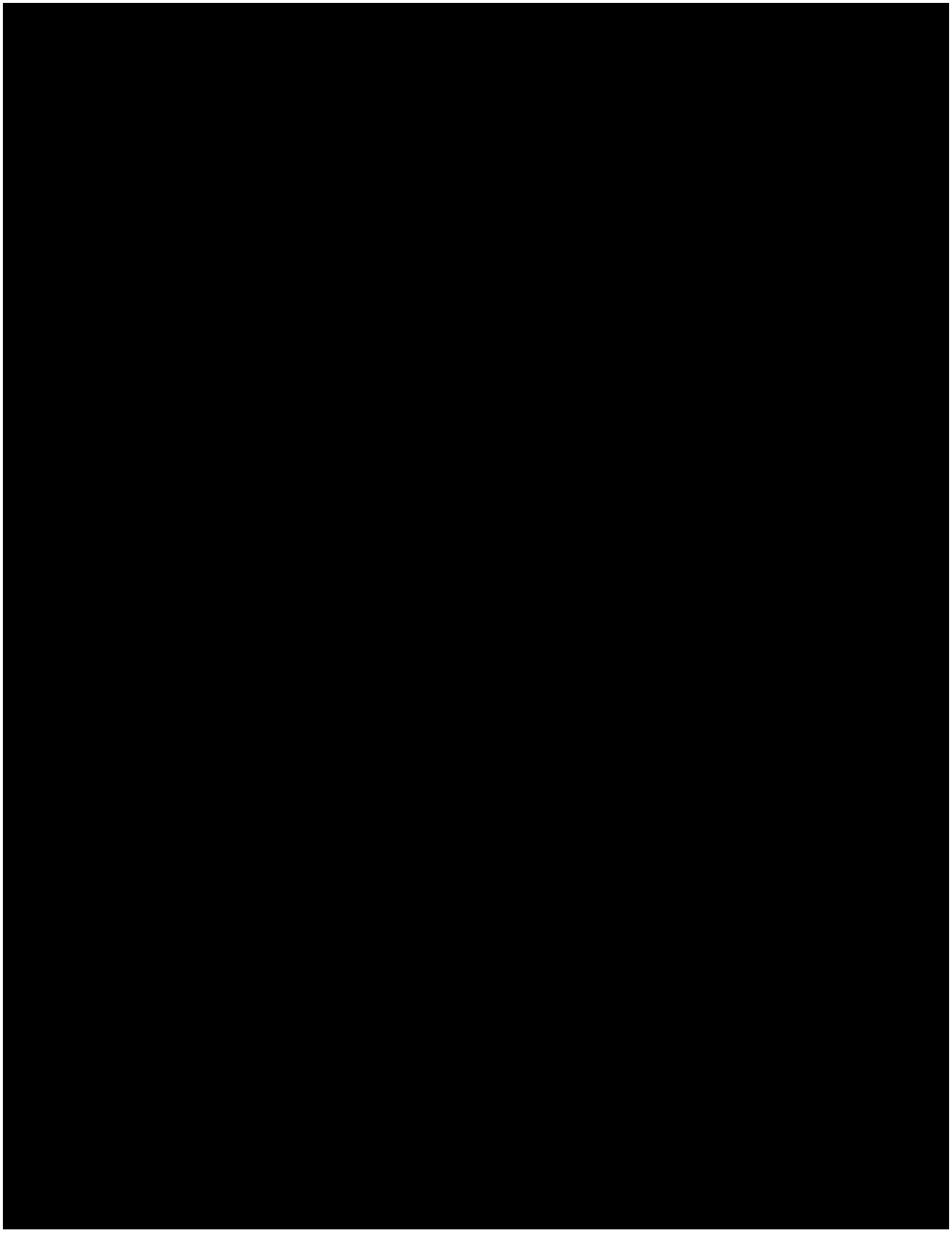
Continuous secondary endpoints will be analyzed using the same approach as the primary endpoint. Unless otherwise specified, the secondary endpoints will be analyzed primarily based on omalizumab-naïve population.

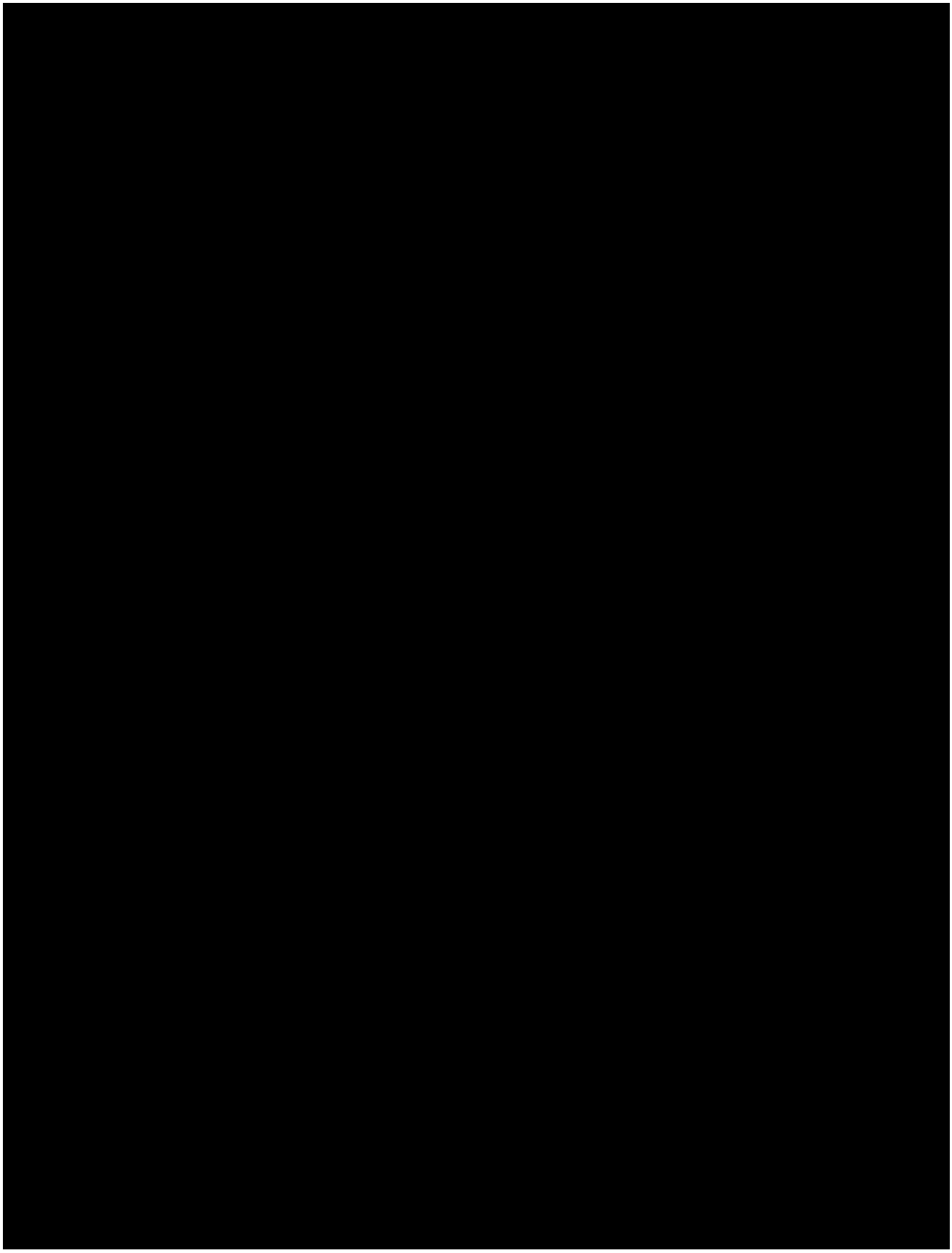
Responder endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted by region. The comparison of the proportions of treatment response between rilzabrutinib and placebo will be derived, and the corresponding odd ratios and the 95% CI will be reported. Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status. Missing data will be considered as non-responders.

3.3.3 Supplementary analysis

The secondary endpoints will also be analyzed based on ITT population. In addition, descriptive statistics for omalizumab-incomplete responders will be provided.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS





[redacted]

3.5 MULTIPLICITY ISSUES

To control the Type I error under circumstance of multiple comparisons for the primary endpoint, the comparison between each dose level of rilzabrutinib and placebo will be conducted in a pairwise manner following a step-down procedure. The hierarchy will be 400 mg TID, 400 mg BID, and 400 mg QPM.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population in the double-blind period and performed on OLE population in the open-label extension period as defined in Section 2 , unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (e.g., exposed but not randomized) will be provided.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance, summarized within the safety population and OLE population separately for different periods.

Duration of IMP exposure

Duration of double-blind IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day in the double-blind period, regardless of unplanned intermittent discontinuations. Duration of IMP exposure will be summarized quantitatively and categorically: >0 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 weeks.

Duration of open-label IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day in the open-label extension period, regardless of unplanned intermittent discontinuations. Duration of IMP exposure will be summarized quantitatively and categorically: >12 to ≤14 weeks, >14 to ≤16 weeks, >16 to ≤20 weeks, >20 to ≤24 days, >24 to ≤36 days, >36 to ≤52 weeks, >52 weeks.

If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Treatment compliance

Treatment compliance will be summarized separately for the double-blind period and open-label extension period.

A given administration will be considered noncompliant if the participant did not receive the planned dose as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant in each period will be defined as the number of tablets that the participant was compliant divided by the total number of tablets that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP in that period.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

Cases of overdose (defined as a single ingestion of a dose equal to or greater than 1200 mg (≥3 times the indicated single dose of 400 mg), provided that it has been taken at once or over 2-hour period) will be listed.

If applicable, summaries will be provided by trial impact (disruption) due to COVID-19.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Double-blind Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the double-blind treatment-emergent period.
- Open-label Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the open-label treatment-emergent period

The treatment-emergent period covers the follow-up period.

Similarly, the deaths will be analyzed in the pre-treatment, double-blind treatment-emergent and open-label treatment-emergent periods.

The primary AE analyses will be on TEAEs. Pre-treatment AEs will also be described.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severality of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 6.

Table 6 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the [SAR444671 highest dose intervention group (400 mg TID).
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (e.g., treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation
- Any treatment-emergent AESI
- Any TEAE related to IMP

The AE summaries of Table 7 will be generated with number (%) of participants experiencing at least one event.

Table 7 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
	Primary SOC
	PT
	Primary and secondary SOC, HGLT, HLT and PT
Common TEAE (≥2 participants in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment-emergent SAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
Treatment-emergent SAE related to IMP as per Investigator's judgment	Primary SOC, HGLT, HLT and PT
TEAE leading to permanent intervention discontinuation	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
TEAE leading to death[b]	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
Pretreatment AE	Overview[a]
	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any severe AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation
b Death as an outcome of the AE as reported by the Investigator in the AE page

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided if needed:

- Deaths during double-blind treatment-emergent and open-label treatment-emergent periods
- Deaths in non-randomized participants or randomized but not treated participants

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] the [redacted]

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

[redacted]

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count, International normalized ratio (INR) test, prothrombin time, activated partial thromboplastin time (aPTT), fibrinogen (Optical Clot Detection).
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: high-sensitivity C reactive protein (hs-CRP), HbA1c, total protein, creatine kinase
  - Electrolytes: sodium, potassium, chloride, calcium, phosphate
  - Renal function: creatinine, urea nitrogen
  - Liver function: albumin, alanine aminotransferase (AST), aspartate aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total-, direct- and indirect bilirubin
- Urinalysis: Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal)
- Pregnancy test: Serum or highly sensitive urine human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential)
- Other screening tests:
  - Follicle-stimulating hormone (as needed in women of non-childbearing potential only)
  - Serology: if these tests have not been performed within the past 3 months prior to the screening visit (Visit 1)
    - General: HIV antibody, hepatitis B surface antigen (HBsAg), anti-HBc (total and IgM, followed by HBV DNA in case of anti-HBc positivity), and hepatitis C virus antibody (anti-HCV), and HCV RNA
    - Japan-specific: HIV antibody, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HBc (total and IgM), followed by HBV DNA in case of anti-HBc or anti-HBs positivity, and hepatitis C virus antibody (anti-HCV), and HCV RNA
  - Tuberculosis (TB)/QuantiFERON test
- Vital signs: weight (kg), height (cm), BMI (kg/m^2), temperature (degrees Celsius), systolic and diastolic blood pressure (mmHg) according to position (semi-supine, sitting), pulse rate (beats per minute)
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc intervals

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables.

For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

[redacted]

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

Pharmacokinetic (PK) samples will be collected [redacted] At unscheduled (early discontinuation) visit, sample will be optionally taken at random times after last dose (with time of last dose recorded on eCRF).

3.7.1.1.1 Descriptive statistics

PK of rilzabrutinib (PRN1008) and its metabolites [redacted], if available, will be descriptively summarized by scheduled visit and nominal sampling timepoint in the PK population. [redacted] Individual PK data will be listed. The mean concentration of all three metabolites will be plotted against sampling times.

For PRN1008 and [redacted], all concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing. For [redacted] all concentrations below LLOQ will be treated as LLOQ/2, given it is an endogenous compound.

Plasma rilzabrutinib concentration data might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report.

Exploratory PK/PD analyses may be performed as deemed necessary to evaluate exposure-response relationships.

3.7.1.2 Biomarker analyses

Venous blood samples will be collected at Visit 1 (Screening) for total IgG only, and at Visit 2 (Day 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), Visit 6 (Week 12), Visit 7 (Week 14), Visit 8 (Week 16), Visit 9 (Week 20), Visit 10 (Week 24), Visit 11 (Week 36), Visit 12 (Week 52), Follow-up visit and unscheduled visit (if applicable) for measurement of total IgE, IgG and IgM.

Serum and plasma samples will be collected at Visit 2 (Day 1), Visit 4 (Week 4), Visit 6 (Week 12) and Follow-up visit for soluble biomarker assays; at Visit 2 (Week 0) and Follow-up visit for sampling for BHRA assay. Soluble biomarkers will [redacted].

Blood samples will be collected at Visit 2 (Day 1), Visit 4 (Week 4), Visit 6 (Week 12) and Follow-up visit for measurement of immune cell phenotyping. [redacted]

[redacted] are only collected at selected sites where they have the capability to isolate and store peripheral blood mononuclear cells (PBMCs). [redacted]

For those participants who consent to the optional pharmacogenetic/pharmacogenomic sample collection section of the ICF, blood (serum/plasma) for possible future analysis of potential biomarkers of drug response, disease activity, safety, and blood samples for exploratory genetic analysis of DNA or RNA will be collected and stored for possible future use. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Total IgE, IgG, IgM and other selected biomarker parameters will be summarized in the safety population defined as participants who actually received at least 1 dose of the IMP. Baseline values will be the last value collected prior to the first IMP. Descriptive statistics (including number, mean and SD, geometric mean and CV, median, Q1, Q3, min, max) of biomarkers at baseline and other sampling visits will be summarized. Summary plots (median with interquartile range) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for the total IgE, IgG and IgM and other selected biomarker parameters by intervention group and visit.

In addition, for participants who take selected prohibited medications and/or rescue medications defined in Table 5, the data after the medications will be censored and then last observation carried forward (LOCF) method will be implemented for missing data imputation in the analysis. BHRA assay status will be summarized using number and percentage by intervention and visit and shift table according to baseline status.

[redacted]

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Age group (< median, ≥ median; <65, ≥65 years).
- Gender (Male, Female).

[redacted]

- Region (see Section 5.3, the small regions may be combined with other regions).
- Race (White, all the Others).
- Ethnicity (Hispanic, non-Hispanic).
- Angioedema at baseline (Yes, No).
- Baseline UAS7 score (<28, ≥28).
- Baseline ISS7 score (<13, ≥13).
- Duration of disease (<2, 2-10, >10 years).
- H1-AH baseline dose (1-fold, 2-4-fold).
- Baseline serum Total IgE (<300 UI/mL, ≥300 UI/mL).
- Baseline BHRA status (BHRA-/BHRA+)

To assess the consistency of the treatment effects across the subgroup levels, subgroup analyses will be conducted for the primary endpoint at Week 12. The analysis will be performed based on imputed datasets from the primary analysis.

To test the interaction between intervention and subgroup factor, an ANCOVA model incorporating subgroup-by-treatment interaction will be built for each subgroup factor. Statistical inference obtained from all imputed data will be combined using Rubin's rule. A p-value for the test of interaction will be provided based on the combined inference.

In each subgroup, the primary endpoint will be analyzed using the primary approach for the primary endpoint, but on the specific subgroup analysis population. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means for each subgroup will be provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) will be provided for each subgroup. Forest plots will be provided.

3.8 INTERIM ANALYSES

No interim analysis is planned.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 9 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
02 (Germany only)	15-Sep-2021	[redacted]	[redacted]
04	18-Feb-2022	Removed "and who are naïve to omalizumab" from protocol title, brief tiltle and overall design.	Changes to align with the inclusion of omalizumab-incomplete responders to the study.
		Add prior use of omalizumab as a stratification factor	Addition of stratification by omalizumab-treatment status at randomization to maintain balance between omalizumab-naïve and omalizumab-incomplete responders between arms.
		The population for primary estimand was changed from "Intent-to-treat" to "Omalizumab-naïve". ITT population will be used as supplementary analysis.	Change to clarify that the primary analysis population remains as omalizumab-naïve participants only.
05	7-Jun-2022	Added “Open-label extension (OLE) population and its related description” to population for analyses	Changes were made for accuracy.
06	21-Sep-2022	Deleted the following: “Tipping point analyses and other sensitivity analyses will be performed to confirm robustness of the results with respect to the missing data handling.”	Deleted because not applicable to the study.

4 SAMPLE SIZE DETERMINATION

Approximately 152 participants will be randomized to the intervention group in a ratio of 1:1:1:1, ie, 38 per intervention group.

An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 score is considered the MCID. Based upon a SD of 7, a change of 5 in the ISS7 would correspond to an effect size of approximately 0.71. Based upon a SD of 14, a change of 10 in the UAS7 would correspond to an effect size of approximately 0.71. Based on this assumption, plus the assumption of a 15% dropout rate before Week 12, it is estimated that 38 patients per group will provide approximate 80% power to detect an effect size of 0.71 or higher between the rilzabrutinib arm and placebo using a 2-sided t-test with alpha = 0.05. This sample size estimate applies to both ISS7 (primary endpoint for US and US reference countries) and UAS7 (primary endpoint for all countries except US and US reference countries).

The sample size calculations were performed using EAST 6.5.

The randomization will be stratified by region and prior use of omalizumab (yes or no). Note: prior use of omalizumab = yes represents omalizumab-incomplete responders, and prior use of omalizumab = no represents omalizumab-naïve patients. Omalizumab-incomplete responders will only be randomized to the 400 mg BID, 400 mg TID and placebo arms, and they will be capped at up to 15% of the patients in that arm.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

[redacted]

AE:	adverse event
AESIs:	adverse events of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
ATC:	anatomic category
BMI:	body mass index
CI:	confidence interval
CLcr:	Creatinine clearance

[redacted]

ECG:	electrocardiogram
eCRF:	electronic case report form
HGLT:	high level group term
HLT:	high level term
HSS7:	weekly hives severity score
ISS7:	weekly itch severity score
ITT:	intent-to-treat
LLT:	lower-level term
LS:	least squares
MedDRA:	medical dictionary for regulatory activities
PCSA:	potentially clinically significant abnormality

[redacted]

PK:	pharmacokinetic
PT:	preferred term
SAP:	statistical analysis plan
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment-emergent adverse event, treatment-emergent adverse event
UAS7:	weekly urticaria activity score

[redacted]

WHO-DD:	World Health Organization-drug dictionary
WOCF:	worst-observation carried forward

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided for the double-blind period:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the double-blind study intervention period as per protocol
- Participants who did not complete the double-blind study intervention period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the double-blind period as per protocol
- Participants who did not complete the double-blind period as per protocol and main reason for study discontinuation
- Vital status at last contact in double-blind period

The number (%) of participants in the following categories will be provided for the open-label extension period:

- Enrolled in open-label period
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the open-label study intervention period as per protocol
- Participants who did not complete the open-label study intervention period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the open-label period as per protocol
- Participants who did not complete the open-label period as per protocol and main reason for study discontinuation
- Vital status at last contact in open-label period

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

If needed, number (%) of participants with any reasons for exclusion from the population without trial impact (disruption) due to COVID-19 in the randomized population will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population in double-blind and open-label extention periods as well as displayed separately as related versus not related to COVID-19 if applicable. In addition, deviations potentially impacting the primary endpoint analysis may be summarized.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population in the double-blinded period and open-label extension period separately.

Demographic and baseline characteristics

- Age in years as quantitative variable and in categories (≥18 to <40, ≥40 to <65, ≥65)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiple, Unknown, Not reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Region (**Asia**: South Korea, Taiwan, Japan; **Western Countries**: Spain, Italy, Germany, Canada, Greece, Netherlands; **Eastern Europe**: Poland; **Latin America**: Argentina, Chile)
- Weight in kg (quantitative and qualitative variable: <60, ≥60 kg)
- BMI in kg/m^2 (quantitative and qualitative variable: <25, ≥25 - <30, ≥30 kg/m^2)

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Comorbidity will be summarized separately. The following comorbid diseases will be summarized from electronic case report form (eCRF) pages which were filled in by investigators based on participant reporting. Angioedema history will be further summarized under disease characteristics at baseline.

- Angioedema (Yes, Ongoing condition)
- Atopic Dermatitis (Yes, Ongoing condition)
- Allergic Rhinitis (Yes, Ongoing condition)
- Allergic Conjunctivitis (Yes, Ongoing condition)
- Asthma (Yes, Ongoing condition)
- Food Allergy (Yes, Ongoing condition)
- Chronic Rhinosinusitis (Yes, Ongoing condition)
- Nasal Polyps (Yes, Ongoing condition)
- Eosinophilic Esophagitis (Yes, Ongoing condition)

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by intervention group:

- Age at onset of CSU (years)
- Time since first diagnosis of CSU (years) to be derived as:

  (Year of randomization – Year of first diagnosis of CSU) + (month of randomization-month of first diagnosis of CSU)/12
- Presence of angioedema at baseline
  - Number of episodes in past 6 months
  - Time since last episode (months)
- Baseline ISS7 score (quantitative and qualitative variable: <13, ≥13)
- Baseline UAS7 score (quantitative and qualitative variable: <28, ≥28)
- Baseline weekly hives severity score (HSS7)
- Baseline angioedema activity score over 7 days (AAS7) for participants with angioedema
- Baseline urticaria control test (UCT)
- Baseline Dermatology Life Quality Index (DLQI)
- Baseline Patient Global Impression of Severity (PGIS)
- Baseline IgE (quantitative and qualitative variable: <300 UI/mL vs ≥300 UI/mL)
- Baseline IgG (quantitative and qualitative variable: <210 UI/mL vs ≥210 UI/mL)
- Baseline IgM (quantitative and qualitative variable: <300 UI/mL vs ≥300 UI/mL)

- Baseline BHRA status (BHRA-/BHRA+)
- Baseline H1-AH dose (1-fold, 2-3-fold, 4-fold)
- Prior use of omalizumab (Yes, No)

[redacted]

Procedures will be summarized by intervention group by primary SOC (sorted by internationally agreed order) and PT (sorted in alphabetical order), sorting is based on the overall incidence across intervention groups.

Rescue medications

The following rescue medications may be used:

- Additional doses of H1-AH up to 4-fold the recommended dose (2-fold in Japan)
- Short course of OCS

The use of OCS should be delayed, if possible, for at least 8 weeks following the initiation of IMP. The following specific medications will be summarized:

- Rescue medications taken during the study will be summarized separately overall and by type (additional doses of H1-AH medications, OCS therapy).
- The total number of days rescue medication was taken by type will be summarized.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Demographic formulas

Age of onset of CSU is calculated as:

Year of CSU diagnosis – Year of birth

BMI is calculated as:

Weight in kg / (height^2 in meters)

For adults, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 - age) × weight (kg) × (1 - 0.15 × sex (0-M, 1-F)) / (0.814 × creatinine (μmol/L))

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement.

Data handling conventions for other efficacy endpoints

[redacted]

[redacted]

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy, safety, PK and biomarker variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

The reference date for the derivation of relative days of measurements will be the date of first IMP administration if the participant is treated with study intervention, or the randomization date if the participant is not treated.

Daily e-diary weekly scores

For the daily efficacy endpoints (ISS, UAS, HSS, and [redacted] the time period used to calculate the weekly score at each designated study day is summarized in Table 10 and Table 11.

Table 10 - Analyses window definition for double-blind period

Time	Targeted study day	Day range for calculating weekly score
Baseline (Week 0)	1	-7- -1
Week 1	8	1-8
Week 2	15	9-15
Week 3	22	16-22
Week 4	29	23-29
Week 5	36	30-36

Time	Targeted study day	Day range for calculating weekly score
Week 6	43	37-43
Week 7	50	44-50
Week 8	57	51-57
Week 9	64	58-64
Week 10	71	65-71
Week 11	78	72-78
Week 12	85	79-85 [a]
End of Study	113	107-113

Study days are calculated considering Day 1 as the day of first double-blind IMP administration (or the day of randomization for participant not exposed).
[a] If the participant's double-blind EOT visit falls in this window, the score collected on and after this day will be removed from the calculation of Week 12 score given the transition to OLE at EOT visit.

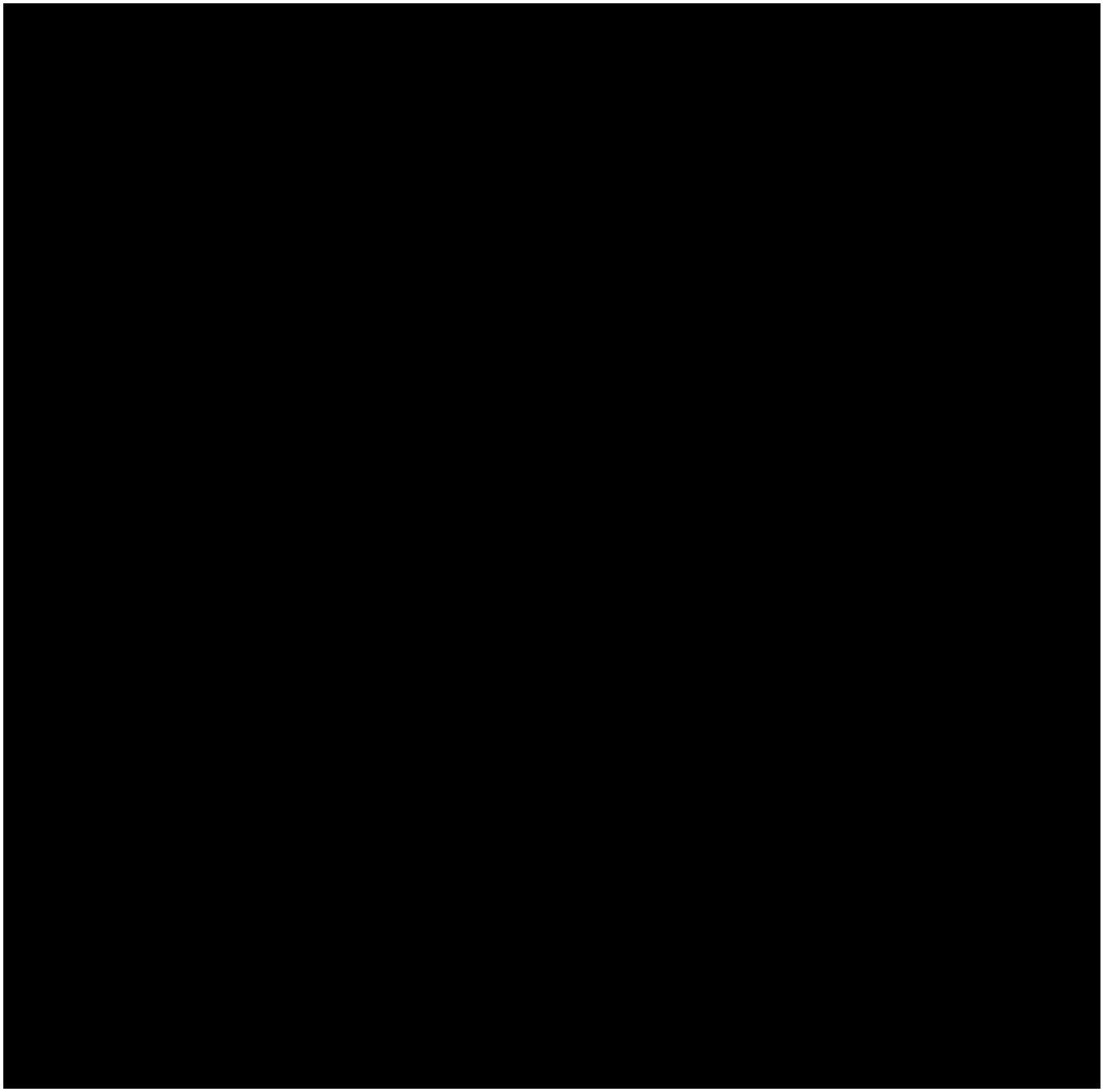
Table 11 - Analyses window definition for open-label period

Time	Targeted study day	Day range for calculating weekly score
Week 13	7	1-7
Week 14	14	8-14
Week 15	21	15-21
Week 16	28	22-28
…		
Week X	7*X	7*(X-13) +1 - 7*(X-12)
Week 52	280	274-280
End of Study	308	302-308

For participants whose last double-blind IMP and first open-label IMP are on the day of double-blind EOT visit, study days are calculated from the day after last double-blind IMP administration, i.e., last double-blind IMP administration +1 day being Day 1.
For participants whose first open-label IMP is after the day of double-blind EOT visit, study days are calculated from the day of first open-label IMP administration, i.e., first open-label IMP administration being Day 1.

Other Efficacy assessments

For other efficacy assessment, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 12 and Table 13.



Safety assessments

Selected safety variables will be summarized by the analysis window defined in Table 14 and Table 15 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. For procedures planned on Visit 2, if it is done on the same date as the first IMP but the performance time is missing, it will belong to Visit 2 time window.

Table 14 - Time window for safety endpoints for double-blind period

		Time windows for					
Visit	**Target Day**	**Vital signs**	**Hematology, chemistry [a], urinalysis**	**Hepatitis, HIV serology, QuantiFERON**	**Pregnancy test**	**Physical exam**	**ECG**
Visit 1 (Week -4 to Day -1)	<1	<1	<1	<1	<1	<1	<1
Visit 2 (Day 1)	1	1^{-}	1^{-}		1^{-}	1^{-}	
Visit 3 (Week 2)	15	1^{+}-22	1^{+}-22		1^{+}-22	1^{+}-22	
Visit 4 (Week 4)	29	23-43	23-43		23-43	23-43	
Visit 5 (Week 8)	57	44-71	44-71		44-71	44-71	
Visit 6 (Week 12)	85	72-99	72-99		72-99	72-99	>1
End of Study	113	>99	>99		>99	>99	

Study days are calculated considering Day 1 as the day of first double-blind IMP administration (or the day of randomization for participant not exposed).

1^{-}: up to 1st dose date/time; 1^{+}: after 1st dose date/time;

a CPK and HbA1c will be tested at Screening and on Week 12

Table 15 - Time window for safety endpoints for open-label period

		Time windows for					
Visit	**Target Day**	**Vital signs**	**Hematology, chemistry, urinalysis**	**Hepatitis, HIV serology**	**Pregnancy test**	**Physical exam**	**ECG**
Visit 7 (Week 14)	14	1-21	1-21		1-21	1-21	
Visit 8 (Week 16)	28	22-42	22-42		22-42	22-42	
Visit 9 (Week 20)	56	43-70	43-70		43-70	43-70	
Visit 10 (Week 24)	84	71-126	71-126		71-126	71-126	
Visit 11 (Week 36)	168	127-224	127-224		127-224	127-224	
Visit 12 (Week 52)	280	225-294	225-294		225-294	225-294	>1
End of Study	308	>294	>294		>294	>294	

For participants whose last double-blind IMP and first open-label IMP are on the day of double-blind EOT visit, study days are calculated from the day after last double-blind IMP administration, i.e., last double-blind IMP administration +1 day being Day 1.

For participants whose first open-label IMP is after the day of double-blind EOT visit, study days are calculated from the day of first open-label IMP administration, i.e., first open-label IMP administration being Day 1.

[redacted]

[redacted]

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits. Unscheduled visit measurements for efficacy data will be included in the by-visit summaries if they are re-allocated to scheduled visits.

Missing data handling for safety analysis

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

Handling of computation of study intervention duration if investigational medicinal product end of study intervention date is missing:

For the calculation of the study intervention duration, the date of the last dose of IMP is equal to the date of last administration reported in the eCRF. If this date is missing, the exposure duration should be left as missing.

The last dose administration should be clearly identified in the eCRF and should not be approximated by the last returned package date.

Handling of adverse events with missing or partial date/time of onset:

Adverse event of missing or partial onset date/time will be classified as treatment-emergent when the partial adverse event onset date/time information does not indicate that the adverse event started prior to study intervention or after the treatment-emergent adverse event period. The handling rules are for categorization purpose only and will not be used in listings.

Missing or partial start date/time of AE will be imputed using the following rules:

- If it has missing minute or missing hour/minute or missing day/hour/minute, and if the remaining non-missing date/time parts are the same as the counterparts in date/time of the first dose of IMP, then impute missing parts with the same parts from date/time of the first dose of IMP. If the date/time is later than the AE end date/time, then use AE end date/time instead. Otherwise impute with 00 for hour/minute or 01 for day. If the date is before informed consent, use the informed consent date instead.
- If only year is not missing, and if it's less than the first dose year, then use informed consent day/month, or if it's equal to first dose year, then use the first dose day/month, or if it's after the first dose year, then use January 01. If the date is after AE end date, use AE end date instead.
- After the above process, if the AE with imputed date/time is not the first record of an AE, and the imputed date/time is earlier than the start date/time of the previous record, then use the start date/time of previous record instead.
- If AE start year is missing, no imputation can be done.

Missing or partial date/time of end date/time of adverse event and adverse event resolution will not be handled.

Handling of adverse events when date and time of first investigational medicinal product administration is missing:

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events:

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of medication missing/partial dates:

To determine whether a medication is prior medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible.

Missing or partial medication start date will be imputed using the following rules:

- If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month.
- If start month is missing, and start year is not missing: Impute the day and month using 01 January.
- If start year is missing, no imputation can be done. Medication will be assumed to start prior to IMP intake.

Missing or partial medication end date will be imputed using the following rules:

- If end day is missing, and end month and year are not missing: Impute end date using the last day of the month.
- If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month.
- If end year is missing, no imputation can be done.

Handling of potentially clinically significant abnormalities:

If a participant has a missing baseline, he/she will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing, eg, for eosinophils the PCSA is $> 0.5 \times 10^9$/L or > ULN if ULN $\geq 0.5 \times 10^9$/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

5.5 APPENDIX 5 SAMPLE SAS CODE

The multiple imputation and analysis model for the primary analysis approach will be built with the following sample SAS code.

1. 40 datasets with a monotone missing pattern will be obtained, induced by Markov Chain Monte Carlo (MCMC) method on participants who have not taken selected prohibited medications and/or rescue medications or have not discontinued study intervention due to lack of efficacy prior to Week 12.

```
proc mi data=dat_etd seed=17224 nimpute=40 out=dat_mc;
    mcmc impute=monotone;
    var region trt01p iss7bl chg1iss …  chg12iss;
run;
```

2. For each of the imputed dataset with monotone missing pattern in step 1, the remaining missing data will be imputed using the regression method for the monotone pattern with adjustment for covariates including intervention groups, region and baseline value of the response variable.

```
proc mi data=dat_mc nimpute=1 seed=17224 out=dat_mi;
    by _imputation_;
    class region trt01p;
    monotone method=reg;
    var region trt01p iss7bl chg1iss … chg12iss;
run;
```

3. Each of the 40 imputed datasets will be merged with the one dataset imputed by WOCF approach, and then be analyzed using the main statistical model. These 40 imputed datasets will be saved.

```
%macro w1;
      %do i=1%to 40;
          data wocf&i.;
              set wocf;
              _imputation_=&i.;
          run;
      %end;
      data wocf_all;
          set %do j=1 %to 40; wocf&j. %end;;
      run;
%mend w1;

%w1;

data dat_imp;
    set dat_mi  wocf_all;
Run;

proc sort data=dat_imp;
    by _imputation_;
run;
```

```
proc glm data= dat_imp;
    by _imputation_;
    class region angiobl trt01p;
    model chg12iss = iss7bl region trt01p;
    lsmeans trt01p / stderr;
    estimate 'Diff Rilzabrutinib vs Placebo' trt01p -1 1;
    ods output LSMeans=implsmeans Estimates=implsmeandiff;
run;
```

4. Applying Rubin's rule to combine analysis results (point estimates and standard errors) from 40 imputations using PROC MIANALYZE for the LS means and difference in LS means between rilzabrutinib and placebo. Sample code:

```
proc sort data=implsMeans; by trt01pn _imputation_;run;

proc mianalyze data= implsmeans;
    by trt01pn;
    modeleffects lsmean;
    stderr stderr;
    ods output ParameterEstimates=lsmeans;
run;

proc mianalyze data=implsmeandiff;
    modeleffects estimate;
    stderr stderr;
    ods output ParameterEstimates=lsmeandiff;
run;
```

6 REFERENCES

1. Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and inference via Multiple Imputation. J Biopharm Stat. 2013;23:1352-71.

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