AMENDED CLINICAL TRIAL PROTOCOL 06

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**
Amendment number:	**06**
Compound number (INN/Trademark):	**SAR444671 rilzabrutinib/Not applicable**
Brief title:	Rilzabrutinib for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine **RILECSU**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

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EUDAMED:	Not applicable
Other:	Not applicable

Date: 21-Sep-2022 Total number of pages: 140

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 06	All	21 September 2022, version 1 (electronic 9.0)
Amended Clinical Trial protocol 05	All	07 June 2022, version 1 (electronic 8.0)
Amended Clinical Trial protocol 04	All	18 February 2022, version 1 (electronic 7.0)
Amended Clinical Trial protocol 03	Italy only	19 October 2021, version 1 (electronic 5.0)
Amended Clinical Trial protocol 02	Japan only	06 October 2021, version 1 (electronic 4.0)
Amended Clinical Trial protocol 01	Germany only	15 September 2021, version 2 (electronic 2.0)
Original Protocol		14 May 2021, version 1 (electronic 1.0)

Amended protocol 06 (21 September 2022)

This amended protocol 06 (amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reasons for this amendment are:

- To update exclusion criteria as follows:
  - [redacted]
  - To provide a series of examples qualifying the clinically significant diseases, condition, or medical histories that, in the opinion of the Investigator, would interfere with participant safety, trial evaluations, and/or trial procedures as part of exclusion criterion E 04.

Other minor clarifications and corrections deemed necessary by the Sponsor will also be implemented.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page and throughout the protocol	Document formatting revisions were made. The header was updated. The amendment number was updated on the title page.	Administrative change to comply with Sanofi standard format.
[redacted]	[redacted]	[redacted]
Section 1.3 Schedule of activites (SOA)	A check was added at the Follow-up visit for the e-diary completion by participant.	Addition for accuracy.
	Deleted "BHRA" from Sampling for soluble biomarker assays and cellular test and "BHRA will be tested on Day 1 and the follow-up visit" from footnote v.	Changes made due to a new row for BHRA added in this amended protocol.
	Added a row for "BHRA" and a check at D1 and Follow-up visit.	Changes made for clarification.
	Revised footnote d as follows: d. For participants who are considered eligible to enter the OLE phase according to investigator judgement.	Changes made for clarification.
Section 2.2 Background	Updated "Clinical Experience" based on new version of Investigator's Brochure (IB).	To include updated information and maintain consistency with the current IB.
Section 2.3.1 Risk assessment	[redacted]	[redacted]
Section 4.1 Overall design	In the bullet point related to optional OLE phase, replaced "they" by "eligible participants"	Changes made for clarification.
Section 4.2 Scientific rationale for study design	Added references to recent completed or ongoing investigational studies studies with dupilumab (NCT04180488), remibrutinib (NCT03926611), and fenebrutinib (NCT03137069) enrolling omalizumab naïve patients.	To support the rationale of inclusion of omalizumab naïve patients
	Added the following text: "Eligibility for entry into the OLE phase is based on investigator judgement after appropriate review of the participant's course during the double-blind phase, including laboratory values, adverse events, and any other relevant data."	Changes made for clarification.
Section 5.2 Exclusion Criteria	Updated E 04 to provide examples on clinically significant disease, conditions, or medical history: "E 04. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg,	Clarification.

Section # and Name	Description of Change	Brief Rationale
	Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, participants on dialysis), [redacted] neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases, hepatobiliary conditions, which include, but are not limited to, hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, moderate or severe hepatic impairment (Child Pugh B or C) or any other liver disease considered clinically significant by the Investigator. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc)."	
	[redacted]	
	-Corrected platelet count unit from mL to µL.	Correction
	Replaced the word "Sensitivity" by "Hypersensitivity" in E 36.	Changes made for accuracy.
Section 5.4 Screen Failure	[redacted]	
Section 6.1 Study intervention(s) administered	The text related to direct IMP supply to participants was presented in a separate paragraph as follows: "IMP may be supplied from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant. For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9)."	Correction for clarification and to comply with Sanofi template.
Section 1.1 Synopsis Section 4.1 Overall design Section 6.8.1 Rescue medicine	Added information throughout the sections to clarify that rescue therapy should start with an increase in H1-AH whenever possible, followed by a short course of OCS if needed.	Changes were made for clarification.
Section 8.3.7 Adverse event of special interest	Updated bullet point related to ALT as follows: "Increase in ALT: If increase in ALT >3x ULN, report the ALT >3 x ULN together with total bilirubin value including normal ranges and confirm the elevation within 72 hours as indicated in the flow chart appendix 6 (Section 10.6).	Changes were made for clarification.

Section # and Name	Description of Change	Brief Rationale
	Follow the instructions listed in the box at the bottom of the flow chart."	
	Specified the version for CTCAE as v5.0	Accuracy.
Section 9.3.2.2 Sensitvity analysis	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.
[redacted]		
Section 10.1.6 Dissemination of clinical study data	The web-address was changed from "clinicalstudydatarequest.com" to "vivli.org."	Accuracy

In addition,, other minor editiorial changes (eg, grammatical and minor typographical error corrections) were implemented throughout the protocol.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Brief title:

Rilzabrutinib for the treatment of chronic spontaneous urticaria in patients who remain symptomatic despite the use of H1 antihistamine

Rationale:

See study rationale, Section 2.1.

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
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

Overall design:

Study DRI17224 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, followed by an additional 40-week open-label extension (OLE) phase, conducted in symptomatic adult participants with moderate-to-severe chronic spontaneous urticaria (CSU) whose disease cannot be adequately controlled with H1-AH, alone. This study will assess the effect of rilzabrutinib on itch and urticaria frequency and severity assessed by the urticaria activity score (UAS) (composite) scored daily and summed over 7 days, on itch and urticaria scored separately once

[redacted]

Brief summary:

The first phase of this study will be a parallel, 12-week treatment, Phase 2, double-blind, 4 arm study to assess the safety and effectiveness of 3 oral doses of SAR444671 (rilzabrutinib) 400 mg once every evening (QPM), 400 mg twice a day (BID) or 400 mg three times a day (TID) tablets, compared with placebo for decreasing the frequency and severity of itch and urticaria in male and female participants aged 18 years inclusive or older with moderate-to-severe CSU whose disease cannot be adequately controlled with H1-AH, alone.

After completion of the double-blind phase of the study, participants will be given the option of enrolling in the 40-week OLE phase of the study. Participants will receive open-label rilzabrutinib at dose of 400 mg TID (the dose may be modified based on the 12-week safety and efficacy data) (refer to Section 10.8.2 for German-specific requirements). Due to the fact that some participants may be receiving rilzabrutinib for the first time, all participants will be monitored at Week 14,Week 16, Week 20, and Week 24. Afterwards, participants will be monitored at Week 36 and Week 52.

Number of participants:

Approximately 152 participants will be randomized to study intervention (38 participants per intervention group) stratified by region and prior use of omalizumab. Randomized participants are all those from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

For the OLE phase, it is anticipated that 70% of participants (106 in total) will be enrolled.

Intervention groups and duration:

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1:1:1) to one of the following investigational medicinal product (IMP) treatment groups: rilzabrutinib 400 mg QPM, 400 mg BID, 400 mg TID or matching placebo.

Participants should continue their established standard of care background therapy with a long-acting, non-sedating H1-AH, at up to 4-fold the recommended dose.

Refer to Appendix 8 (Section 10.8.1) for Japan-specific requirements for H1-AH use.

Duration of study period (per participant)

Double-blind phase

- Screening period (up to 4 weeks)
- Randomized double-blind IMP treatment period (12 weeks)
- Follow-up period (4 weeks) for participants not entering the OLE phase

Open-label extension phase

- Open Label Extension (40 weeks)
- Follow-up period (4 weeks)

Study interventions

Investigational medicinal products

Rilzabrutinib (SAR444671)

- [redacted]
- Route of administration: oral
- Dose regimen: 400 mg QPM (evening), 400 mg BID (morning and evening), or 400 mg TID (morning, afternoon, and evening)

Placebo

- [redacted]
- Route of administration: oral
- Dose regimen:
  - For placebo control group: 1 tablet placebo TID
  - For rilzabrutinib BID dosing regimen: 1 x 1 tablet placebo (afternoon)
  - For rilzabrutinib QPM dosing regimen: 2 x 1 tablet placebo (morning and afternoon)

[redacted]

If needed, and if unable to increase H1-AH for rescue therapy, participants may be prescribed a short course of OCS as rescue therapy. After any use of OCS, participants will need to seek immediate medical attention to ensure that the initial reaction has been successfully controlled and/or to evaluate for additional therapeutic steps. In order to ensure consistency, when possible, rescue therapy should start with an increase in H1-AH. If use of OCS is needed, it is recommended to use OCS for 5 to 7 days with a starting dose of oral prednisone 40 mg (or clinically comparable OCS) followed by taper per the Investigator's judgment. The use of OCS should be delayed, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of OCS administration as well as the name and dosage regimen of the OCS must be recorded (see Section 6.8.1 for details).

For other information related to H1-AH and OCS including safety precautions, please refer to the National Product labeling.

Background therapy will be supplied by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per country regulation.

Refer to Appendix 8 (Section 10.8.1) for Japan-specific requirements for H1-AH use.

Posttrial access to study medication: No post-trial access is planned for this study.

Statistical considerations:

Sample size calculation

An absolute change of 5 in ISS7 score is considered the minimal clinically important difference (MCID) and an absolute change of 10 in UAS7 is considered the MCID. Based upon a standard deviation (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).

Randomization

Approximately 152 participants will be randomized (1:1:1:1) to 1 of the following IMP treatment groups: rilzabrutinib 400 mg QPM, 400 mg BID, 400 mg TID or placebo. 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 (refer to Section 5.1 for definition of omalizumab-incomplete responders).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.

Primary endpoint

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 summary of primary estimand for the primary endpoint is as below:

- Treatment: rilzabrutinib 400 mg QPM, 400 mg BID, 400 mg TID, and placebo, along with established standard of care background therapy with a long-acting, non-sedating H1-AH.
- Population: omalizumab-naïve

- Variables:
  - Change from baseline in weekly UAS7 at Week 12 (except US and US reference countries).
  - For US and US reference countries only: change from baseline in ISS7 at Week 12.
- Intercurrent event(s) and handling strategy and missing data handling:

  The intercurrent events will be handled as follows:
  - Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy).
  - Taking selected prohibited medications and/or rescue medications 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: 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.

  Of note, details of selection of prohibited medications and/or rescue medications will be specified in the statistical analysis plan (SAP).
- Population-level summary:

  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 subjects, 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.

<u>Main secondary endpoints</u>

The following secondary endpoints will be analyzed using the same approach as for the primary endpoint:

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

- Change from baseline in ISS7 at Week 12 (except US and US reference countries)
- Change from baseline in weekly hives severity score (HSS7) at Week 12

The following responder secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel test adjusted by region:

- Proportion of participants with UAS7 ≤6 at Week 12
- Proportion of participants with UAS7 = 0 at Week 12
- Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after the 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.

Multiplicity considerations

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.

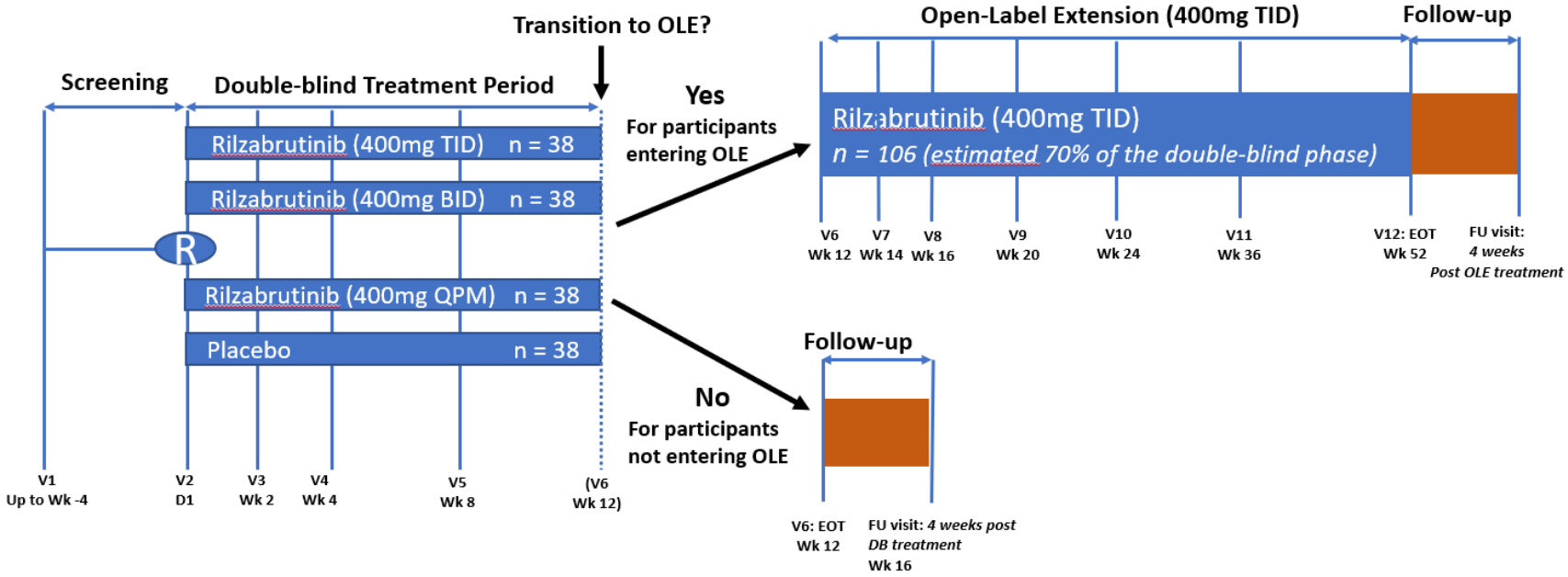
Planned database lock

- A primary database lock will be performed when all randomized patients have completed their 12-week treatment phase. The primary analysis will be conducted to assess the clinical efficacy of rilzabrutinib.
- The database will be updated at the end of the study for all patients to include the OLE and post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock.

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



OLE: open-label extension phase.
Only site visits are displayed in the graphic study design. Phone call contacts are planned at Week 28, Week 32, Week 40, Week 44, and Week 48.
FU vist: follow-up visit 4 weeks after planned EOT:
-for participants who complete the 12-week double-blind treatment phase but who do not enter the OLE phase, Visit 6 (W12) will be their planned EOT, and their FU visit will take place at Week 16 visit;
-for participants who enter and complete the OLE phase (refer to Section 10.8.2 for German-specific requirements regarding rilzabrutinib dosing), Visit 12 (W52) will be their planned EOT, and their FU visit will take place at Week 56 visit -omalizumab-incomplete responders will only be randomized to 400 mg BID, 400 mg TID or placebo.
n: number of participants per arm; R: randomization
D: day; EOT: end of treatment; EOS: end of study; V: visit; Wk: week
BID: twice daily; QPM: every evening; TID: 3 times a day

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before Day 1)	Double-blind phase (12 Weeks)				End of DB/start of OLE	Open-label extension (40 Weeks)								Follow-up (28 days after planned EOT)	Unscheduled visit (if applicable)[a]
		D1	Wk 2	Wk 4	Wk 8	Wk 12	W14	Wk 16	Wk 20	Wk 24	Wk 28 and Wk 32	Wk 36	Wk 40, Wk 44, and Wk 48	Wk 52		
Visit number	1	2	3	4	5	6	7	8	9	10	☎[b]	11	☎[b]	12	FU	100
						EOT of DB[c]								EOT of OLE[c]	EOS[c]	
Viist window (days)			D15 ±3d	D29 ±3d	D5 7 ±3d	D85 ±3d	D99 ±3d	D113 ±3d	D141 ±3d	D169 ±3d	D197 and D225 ±7d	D253 ±7d	D281, D309, and D337 ±7d	D365 ±7d	±7d	
Informed consent	X					(X)[d]										
Inclusion and exclusion criteria	X	X[e]														
Randomization		X														
Inclusion for OLE phase[f]						(X)										
Demographics	X															
Past and current medical conditions[g]	X															

Procedure	Screening (up to 28 days before Day 1)	Double-blind phase (12 Weeks)				End of DB/start of OLE	Open-label extension (40 Weeks)								Follow-up (28 days after planned EOT)	Unscheduled visit (if applicable)[a]
		D1	Wk 2	Wk 4	Wk 8	Wk 12	W14	Wk 16	Wk 20	Wk 24	Wk 28 and Wk 32	Wk 36	Wk 40, Wk 44, and Wk 48	Wk 52		
Complete physical examination including height and weight and vital signs[h]	X															
Abbreviated physical examination including weight and vital signs[h]		X	X	X	X	X	X	X	X	X		X		X	X	X
Treatment																
IMP dispensation		X	X	X	X	(X)[i]				X		X				(X)
NIMP (background therapy[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
e-Diary[k]																
e-diary dispensation and training	X															
e-diary daily completion by participant	←========== →								←======== →				W48 to W52 ←========→		X	(X)

Procedure	Screening (up to 28 days before Day 1)	Double-blind phase (12 Weeks)				End of DB/start of OLE	Open-label extension (40 Weeks)								Follow-up (28 days after planned EOT)	Unscheduled visit (if applicable)[a]
		D1	Wk 2	Wk 4	Wk 8	Wk 12	W14	Wk 16	Wk 20	Wk 24	Wk 28 and Wk 32	Wk 36	Wk 40, Wk 44, and Wk 48	Wk 52		
e-diary review		X	X	X	X	X		X	X	X		X		X	X	(X)
[redacted]																
	X															
	X															
	X															
	X	X		X	X	X		X	X	X	X	X	X	X	X	(x)
	X															
	X	X	X	X	X	X	X	X	X	X		X		X	X	(X)
	X	X	X	X	X	X	X	X	X	X		X		X	X	(X)
	X	X	X	X	X	X	X	X	X	X		X		X	X	(X)
	X					X								X		
	X	←==========→					←==========→								X	X
	X	←==========→					←==========→								X	X

Procedure	Screening (up to 28 days before Day 1)	Double-blind phase (12 Weeks)				End of DB/start of OLE	Open-label extension (40 Weeks)								Follow-up (28 days after planned EOT)	Unscheduled visit (if applicable)[a]
		D1	Wk 2	Wk 4	Wk 8	Wk 12	W14	Wk 16	Wk 20	Wk 24	Wk 28 and Wk 32	Wk 36	Wk 40, Wk 44, and Wk 48	Wk 52		
[redacted]																

Procedure	Screening (up to 28 days before Day 1)	Double-blind phase (12 Weeks)				End of DB/start of OLE	Open-label extension (40 Weeks)								Follow-up (28 days after planned EOT)	Unscheduled visit (if applicable)[a]
		D1	Wk 2	Wk 4	Wk 8	Wk 12	W14	Wk 16	Wk 20	Wk 24	Wk 28 and Wk 32	Wk 36	Wk 40, Wk 44, and Wk 48	Wk 52		
Efficacy Outcome Assessment																
UAS (ISS; [redacted]	←==========→								←=======→				W48 to W52		X	(X)
[redacted]																
Pharmacokinetics/Pharmacodynamics																
[redacted]																

Abbreviations: AAS7: angioedema activity score over 7 days; AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; BHRA: Basophil Histamine Release Assay; BM: biomarker; BTK: Bruton tyrosine kinase; CD: Cluster of differentiation; CPK: creatine phosphokinase; DB: double-blind; DLQI: Dermatology Life Quality Index; e-diary: electronic diary; ED: early discontinuation; EOT: End of Treatment; EOS: End of study; ECG: electrocardiogram; HbA1c: glycated haemoglobin; Hep B: hepatitis B virus; Hep C: hepatitis C virus; H1-AH: H1 antihistamines; HIV: human immunodeficiency virus; HSS: hives severity score; [redacted] IMP: investigational medicinal product; INR: International normalized ratio; ISS: itch severity score; LDH: lactate dehydrogenase; OLE: open-label extension; PBMC: peripheral blood mononuclear cells; [redacted]; [redacted] PK: pharmacokinetic; Planned EOT: Visit 6 (W12), if participant is included in DB only, and Visit 12 (W52), if participant is included in OLE; MRGPRX2: Mas-related G-protein coupled receptor member X2; TB: tuberculosis; UAS7: urticaria activity score over 7 days; UCT: urticaria control test; WOCBP: woman of childbearing potential.

(x) procedure performed if the participant entering the OLE phase or per study procedure in case of early discontinuation (ED)

a Unscheduled visit may be used for early discontinuation or when participant needs a rescue medication for CSU.

b Phone call contact.

c For participants entering the OLE phase, Visit 6 (Week 12) will be their transition visit (start of OLE), Visit 12 (Week 52) will be their EOT visit, and the follow-up visit will take place at Week 56; for participants

not entering the OLE phase, Visit 6 (Week 12) will be their EOT visit and the follow-up visit will take place at Week 16.

d For participants who are considered eligible to enter the OLE phase according to investigator judgement..

e Prior to randomization.

f Refer to Section 10.8.2 for German-specific requirements

g Includes details on treatment history including current therapy.

h Vital signs include temperature, blood pressure, and pulse rate (see Section 8.2.2). Refer to Section 8.2.1 for details of physical examinations.

i The IMP kits for OLE will be dispensed for participants entering the OLE phase. No IMP will be dispensed for participants not entering the OLE phase.

j Participants should remain on their prescreening non-sedating H1-AH dose (list of antihistamines allowed for the study). For participants on stable doses of non-study-approved H1-AH, investigators may switch participants to an equivalent dose of a study-approved H1-AH maintenance medication. Only up to 4-fold the recommended dose is allowed. If participants are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the participant dose to the stipulated range at the screening visit (Visit 1). Participants must remain on this dose of antihistamine for at least 3 consecutive days before screening assessment of UAS7 and ISS7 is initiated. During the OLE phase participants should continue their established standard of care background therapy with a long-acting, non-sedating H1-AH, at up to 4-fold the recommended dose until at least Week 24. After this time, the dose of the established standard of care background H1-AH therapy may be reduced or discontinued at the discretion of the Investigator, but the antihistamine daily dose still may not exceed 4-fold the recommended dose; the dose of rilzabrutinib will remain the same. Background therapy will be supplied by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per country regulation. Refer to Section 10.8.1 for Japan specific requirements on H1-AH use. Any dose change will be checked via the phone call contacts at Week 28, Week 32, Week 40, Week 44, and Week 48.

k [redacted]

l Hepatitis B and C testing includes: HBsAg, anti-HBc (total and IgM, followed by HBV DNA in case of anti-HBc positivity), anti-HCV, and HCV RNA if these tests have not been performed within the past 3 months prior to the screening visit (for Japan-specific requirements see Section 10.8.1).

m QuantiFERON-TB Test should be collected for all participants at the screening visit (Visit 1). If the result is confirmed positive, the participant should be referred to an Infectious Disease specialist. Please refer to the central laboratory manual for additional details. Sites may repeat locally an indeterminate TB test that must be negative to allow entry into the study

n COVID-19 molecular test (if COVID-19 testing is required per local guidelines, to be determined for each site). If COVID-19 vaccine will be started before the first dose of the study administration, the first dose of the study medication should be received after at least 14 days of the first dose of the vaccine. Initiation of COVID-19 vaccine is allowed during the treatment period (refer to Section 10.8.2 for German-specific requirements).

o Only for women of childbearing potential (WOCBP): serum pregnancy test (β-HCG test) at Screening/V1 and urine pregnancy tests at every visit except at Screening and Week 2. A negative result must be obtained at V1 and at V2 prior to randomization. In case of positive urine test, the study intervention will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases. For the OLE phase, women will perform home pregnancy tests every 4 weeks, unless attending a visit at site (see Section 8.3.5).

p To confirm postmenopausal status for women who are not surgically sterile and of reproductive potential.

q Serum chemistry includes AST; ALT; total, direct, and indirect bilirubin; ALP; LDH; albumin; creatinine; urea; total protein; sodium, chloride, calcium, phosphate, potassium; high-sensitivity C-reactive protein (hs-CRP); HbA1c and CPK. CPK and HbA1c will be tested at Screening and on Week 12. Urinalysis includes pH, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes.

r Hemotology includes hemoglobin, hematocrit, erythrocyte count (red blood cell [RBC] count), thrombocyte count (platelets), leukocyte count (white blood cell [WBC] count) with differential and absolute counts (including neutrophils, eosinophils, basophils, lymphocytes, monocytes).

s Coagulation includes international normalized ratio (INR) test, prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen (Optical Clot Detection).

t ECG will be performed and read locally

u A phone call assessment for AEs and medications once a month unless that subject has a clinic visit. Recall for OCS use over the past month or unscheduled visits for CSU such as clinic visit, ER, hospital.

v [redacted]

w [redacted]

x [redacted]

y PK samples will be collected predose on Day 1, Week 4, Week 12, Week 16 (for participants who enter the OLE phase), Week 20 (for participants who enter the OLE phase), Week 24 (for participants who enter the OLE phase), and Week 52 (for participants who enter the OLE phase), and two hours (±15 min) post-dose on Day 1, Week 4, and Week16 (for participants who enter the OLE phase). On unscheduled (early discontinuation) visit, sample will be optionally taken at random times after last dose (with time of last dose recorded on eCRF).

z [redacted]

aa [redacted].

2 INTRODUCTION

Rilzabrutinib (SAR444671, formerly PRN1008) is a novel investigational drug that inhibits Bruton's tyrosine kinase (BTK), a Tec family tyrosine kinase expressed in B-cells and myeloid-lineage cells (1, 2).

By blocking B cell receptor (BCR), which inhibits plasma cell differentiation and antibody production, as well as IgE mediated Fc-epsilon receptor 1 (FcεRI) activation and degranulation of mast cells and basophils, rilzabrutinib is expected to decrease CSU disease activity.

2.1 STUDY RATIONALE

Chronic spontaneous urticaria (CSU), formerly known as chronic idiopathic urticaria (CIU) is a common condition characterized by the spontaneous appearance of pruritic hives and wheals with or without angioedema for more than 6 weeks without a clear inciting factor. Although the molecular mechanisms are still being elucidated, CSU is thought to be driven by pathogenic activation of mast cells and basophils leading to local release of degranulation products. Of these degranulation products, histamine is felt to play a central role in CSU pathogenesis, driving the pruritus and local vascular permeability (leading to urticaria/angioedema) characteristic of this disease. Of note, emerging data suggest that mast cell and basophil activation in CSU is mediated by activation of the high-affinity IgE receptor, FcεRI, either from development of IgE to autoantigens such as IL-24 or thyroid peroxidase (autoimmune Type I phenotype) or development of activating IgG autoantibodies to IgE or FcεRI (autoimmune Type IIb phenotype) (3, 4, 5). Current approved treatments for CSU are targeted against either mast cell degranulation products or the IgE receptor. H1-antihistamines (H1-AH) are first-line therapy in most practice settings. Approximately 50% of patients achieve symptomatic control with H1-AH, alone. Omalizumab, an anti-IgE monocloncal antibody which reduces both serum IgE and cell-surface FcεRI, has emerged as an effective treatment for CSU with inadequate response to H1-AH. However, it has been reported that nearly 50% of patients who receive omalizumab have an inadequate response to this therapy (6). In particular, patients with Type IIb autoimmunity are less likely to respond to treatment with H1-AH or omalizumab (7). As such, there is a need for additional treatments for CSU.

Emerging evidence suggests that BTK plays a role in signal amplification after FcεRI cross-linking, leading to enhanced activation of mast cells and basophils (8). Consistent with this observation, BTK antagonists have demonstrated an inhibitory effect on basophil activation by allergens or anti-IgE antibodies (9). Given its importance in both the generation of antibodies and signaling through FcεRI, BTK has [redacted] potential as a target in CSU therapy, [redacted] multiple clinical studies investigating the effect of BTK inhibitors on patients with CSU who are refractory to treatment with H1-AH, and are omalizumab-naïve (10, 11).

Notably, results from the BTK inhibitor fenebrutinib study suggest a differential response based on the basophil histamine release assay (BHRA) status of the patients, wherein BHRA-positive patients may be more sensitive to BTK inhibition, especially at lower doses, compared to BHRA-

negative patients (10). Separately, studies suggest that CSU patients who are BHRA-positive are more likely to have a poorer response to omalizumab compared to those who are BHRA-negative. As omalizumab-incomplete responders may be enriched for BHRA-positive CSU patients, who are in turn more likely to have Type IIb autoimmunity and be less responsive to available treatments, they may be best poised to benefit from BTK inhibition. Omalizumab-incomplete responders who are BHRA-negative may also stand to benefit from BTK inhibition, although this benefit may be seen at higher doses compared to BHRA-positive patients (12). We thus propose a study to evaluate the efficacy of rilzabrutinib in omalizumab-naïve and omalizumab- incomplete responders.

Rilzabrutinib (SAR444671) is a novel investigational drug that inhibits BTK. It has high affinity for BTK and is able to achieve prolonged target occupancy due to its slow off-rate. This results in a long duration of action while minimizing nonspecific and off-target binding. In a Phase 1 healthy volunteer study, rilzabrutinib was shown to be safe and well-tolerated, while achieving near complete BTK occupancy at higher doses. The clinical efficacy of rilzabrutinib was demonstrated in an open-label, Phase 1/2 study in immune thrombocytopenic purpura (ITP) (PRN1008-010). In this trial, 50% of participants achieved the primary response endpoint after treatment with rilzabrutinib for at least 12 weeks. Furthermore, there were no treatment-emergent serious adverse events (TESAEs) observed. Collectively, these and other studies have shown rilzabrutinib to be a safe and effective inhibitor of BTK.

The goal of this DRI17224 Phase 2 study is to assess the efficacy and safety of rilzabrutinib in a dose-ranging study.

2.2 BACKGROUND

Chronic spontaneous urticaria is fairly common, with a prevalence between 0.5% and 1% (13). It more commonly affects females, and the peak incidence is between 20 and 40 years of age. CSU can have significant detrimental impacts on quality of life, productivity and psychological health (14).

Bruton's tyrosine kinase is a Tec family tyrosine kinase expressed in B-cells and myeloid-lineage cells (1, 2). It plays important roles in signal transduction for a variety of inflammatory receptors, most notably the BCR, Fc-gamma receptor (FcγR) and FcεRI (8, 15). In BCR signaling, BTK is an essential component of the proximal signal transduction pathway, and it plays a role in activating several key mediators of B-cell survival and activation. The importance of BTK in BCR is exemplified in X-linked agammaglobulinemia, where loss-of-function mutations in BTK lead to defective BCR signaling, impaired B-cell development and resultant agammaglobulinemia (16). The role of BTK in FcεRI is still being elucidated.

Rilzabrutinib (SAR444671)

[redacted]

[redacted]

Clinical experience

[redacted]

[redacted]

[redacted]

2.3.1 Risk assessment

[redacted]

[redacted]

Potential risks reported with other BTK inhibitors

There are AEs that have been reported during the administration of other drugs from the same therapeutic class (BTK inhibitors) as rilzabrutinib, but primarily for oncologic indications, including B-cell malignancies (18).

These AEs include:

- Cytopenia
- Bleeding
- Atrial fibrillation

Rilzabrutinib has characteristics that may solve many of the selectivity- and reversibility-related concerns accompanying currently available BTK inhibitors (19). Rilzabrutinib binds in a covalent manner, increasing selectivity by forming a chemical bond to a specific cysteine residue present in BTK. [redacted]

2.3.2 Benefit assessment

To date, there is no information to confirm whether there may be direct health benefit for participants from receipt of study intervention. There is nevertheless a potential benefit that the drug will improve the signs, symptoms and quality of life of patients with CSU. In any case, participants may benefit from having regular clinical and laboratory evaluations throughout the study.

2.3.3 Overall benefit: risk conclusion

Rilzabrutinib is being developed for systemic oral treatment for immune-mediated diseases. Safety data from the ongoing clinical program with rilzabrutinib favors the benefit over the risk. Rilzabrutinib was well tolerated in both healthy participants and participants with PV or ITP.

[redacted]

The design of the present study (DRI17224), including selection criteria of the study population, risk mitigation strategy, and monitoring of safety variables, should maintain the[redacted] regarding the[redacted] efficacy/safety ratio for rilzabrutinib in the treatment of patients with CSU.

3 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
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

Objectives	Endpoints
Tertiary	
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

The assessments used in this study are standard endpoints in evaluation of disease activity and response to therapy in CSU. Clinically, CSU is characterized by the spontaneous and recurrent appearance of pruritic hives. The proposed primary endpoints are the UAS7 at Week 12 in EU and EU reference countries and the ISS7 in the US. Regardless of where a participant is from, all assessments will be same. The UAS7 score is a composite score containing both the HSS7 and the ISS7. This allows a global assessment of the two key components of urticaria: hives and itch. The UAS7 score has been well-established as a prospective measure of CSU activity and has been used in a number of clinical studies as a primary outcome measure (20, 21, 22). As an independent score, ISS7 has also been well established and widely accepted as a primary outcome measure for CSU activity (23).

4 STUDY DESIGN

4.1 OVERALL 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 an 40-week 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. Participants will be randomized 1:1:1:1 to one of 3 doses of rilzabrutinib or placebo. The randomization will be stratified by region and prior use of omalizumab.

[redacted]

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): 152 participants will be randomized 1:1:1:1 to 1 of the following treatments:
  - Rizlabrutinib 400 mg TID
  - Rilzabrutinib 400 mg BID with matched placebo
  - Rilzabrutinib 400 mg QPM with matched placebo
  - Matched placebo
- Optional OLE phase (40 weeks): For participants who complete the 12-week double-blind phase, eligible participants 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 (the dose may be modified based on the 12-week safety and efficacy data) (refer to Section 10.8.2 for German-specific requirements).
- Follow-up period (4 weeks)

During the double-blind IMP treatment phase of this study, participants should continue their established standard of care background therapy with an approved long-acting H1-AH, at up to 4-fold the recommended dose. If a participant is on an H1-AH dose higher than 4-fold the recommended dose at the screening visit, the Investigator may adjust the participants dose to within the stipulated dose range at the screening visit. [redacted] Participants should continue their

screening dose of H1-AH throughout the double-blind phase of the study, unless they experience a disease flare. [redacted]

In the case that participants may be considered for rescue therapy, participants on 1-, 2- or 3-fold the recommended H1-AH may receive additional doses of their study-approved H1-AH as rescue medication, as long as their daily dose does not exceed 4-fold the recommended daily dose of the H1-AH. At the investigator's discretion, participants may be prescribed a short course of oral corticosteroids (OCS) as rescue therapy during the treatment, OLE and follow up periods. Rescue therapy should start with an increase in H1-AH whenever possible, followed by a short course of OCS if needed. For analysis of urticaria activity (including itch and hives individually), [redacted] use will be set to missing and the worse post-baseline values before OCS therapy will be used.

Refer to Appendix 8 (Section 10.8.1) for Japan-specific requirements and (Section 10.8.2) for German-specific requirements.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, placebo-controlled study design will be employed to assess the efficacy and safety of multiple doses of the IMP in participants with moderate to severe CSU uncontrolled on background standard of care oral H1-AH, who are either naïve to omalizumab or are incomplete responders to omalizumab. Rilzabrutinib is [redacted] for CSU patients [redacted] Therefore, rilzabrutinib is evaluated in this study as a first-line treatment primarily in omalizumab naïve patients, similar to recent investigational studies with dupilumab (NCT04180488), remibrutinib (NCT03926611) and fenebrutinib (NCT03137069). Evaluation of omalizumab incomplete responders is also important for this population with no approved treatment options after failure of response to omalizumab.This study design approach is considered to be the most appropriate to provide an unbiased and definitive determination of IMP clinical efficacy of three active doses in CSU as well as capture safety assessments and tolerability of up to 1 year of treatment.

Approximately 50% of CSU patients do not achieve clinical control of their disease with oral H1-AH (13). Thus, alternative safe and effective oral agents are needed for this population. BTK is an enzyme that is involved in the signal transduction downstream of the high affinity FcεRI and B-cell receptor. BTK is essential for FcεRI-mediated activation of mast cell activation and maturation and function of B cells (29). BTK inhibition with a non-selective inhibitor, ibrutinib, was able to block IgE and mast cell-mediated responses in humans (30). Clinical efficacy has recently been demonstrated in CSU with BTK inhibitors fenebrutinib (10) and remibrutinib (11), validating BTK as a relevant clinical target for CSU. This study will extend the treatment period to 12 weeks to allow for a potential larger population response. It is anticipated that a significant proportion of CSU participants may experience a clinical benefit within 4 weeks of treatment

(rapid-responders) whereas a smaller subgroup may require a longer treatment to achieve clinical benefit (slow-responders).

After successful completion of the 12 week blinded phase of the study, eligible participants may enroll into the OLE phase of the study. Eligibility for entry into the OLE phase is based on investigator judgement after appropriate review of the participant's course during the double-blind phase, including laboratory values, adverse events, and any other relevant data. They will receive 400 mg TID dose [redacted] If a significant AE signal emerges at this dose, or at the conclusion of the blinded phase of the study demonstrates the optimal dose is lower, participants in the OLE will have their dose lowered. This phase of the study will provide long-term safety data as well as durability of response information.

4.3 JUSTIFICATION FOR DOSE

[redacted]

4.4 END OF STUDY DEFINITION

The end of the study in the 12-week double-blind phase of the study is defined as the date of the last follow-up visit of the last participant in the double-blind phase of study.

The end of the study in the 40-week open-label phase of the study is defined as the date of the last follow-up visit of the last participant in the open-label phase of study.

A participant is considered to have completed the 12-week double-blind phase of study if he/she has completed the 12-week phase of the study, including the last follow-up visit.

A participant is considered to have completed the 40-week open-label phase of study if he/she has completed the 40-week phase of the study including the last follow-up visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

Participants who have a diagnosis of CSU refractory to H1-AH at the time of randomization, as defined by all of the following:

I 02. Diagnosis of CSU ≥3 months prior to screening visit (Visit 1).

I 03. The presence of itch and hives for ≥6 consecutive weeks at any time prior to screening visit (Visit 1) despite the use of H1-AH during this time period.

I 04. Participants using a study defined H1-AH for CSU treatment (see Appendix 10, Section 10.10.2 for the list of antihistamines allowed for the study). For participants on stable doses of non-study-approved H1-AH, investigators may switch participants to an equivalent dose of a study-approved H1-AH maintenance medication. Note: participants should remain on their prescreening non-sedating H1-AH dose. Only up to 4-fold the recommended dose is allowed. If participants are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the participant dose to the stipulated range at the screening visit (Visit 1). Participants must remain on this dose of antihistamine for at least 3 consecutive days before screening assessment of UAS7 and ISS7 is initiated. (Refer to Section 10.8.1 for Japan-specific requirements).

I 05. Participants who are omalizumab naïve OR omalizumab-incomplete responders (as determined by the Site Investigator and defined as inadequate control of CSU symptoms despite treatment with omalizumab 300 mg every 4 weeks for at least 3 months (minimum 3 injections). Note: Documentation of incomplete response must be documented in the patient's medical records).

I 06. During the 7 days before randomization:

- UAS7 ≥16
- ISS7 ≥8

- Note: to be eligible for the study, participants must have no missing electronic diary (e-diary) (UAS7 and ISS7) in the 7 days before randomization.

I 07. Participants must be willing and able to complete a daily symptom e-diary for the duration of the study.

Weight

I 08. Inclusion criterion I 08 deleted in Amended protocol 04.

[redacted]

I 09. All (male or female)

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 13 weeks after the last administration of study intervention:

- Refrain from donating or cryopreserving sperm.

PLUS, either**:**

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below
  - A male condom and an additional highly effective contraceptive method as described in Appendix 4 Contraceptive and barrier guidance (Section 10.4) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
  - A male condom when engaging in any activity that allows for passage of ejaculate to another person.

b) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 Contraception and barrier guidance (Section 10.4)

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 (Section 10.4) during the study intervention period (to be effective before starting the intervention) and for at least 4 weeks after the last administration of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
  - A WOCBP must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 8.2.5 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed Consent

I 10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of this protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative (LAR). (refer to Section 10.8.2 for German-specific requirements).

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Clearly defined underlying etiology for CUs other than CSU (main manifestation being physical urticaria). This includes but not limited to the following urticarias:

- Inducible urticaria: acute urticaria, solar, cholinergic, heat, cold, aquagenic, vibratory angioedema, symptomatic dermographism, delayed pressure, or contact.
- Diseases with possible symptoms of urticaria or angioedema: systemic lupus erythematosus, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.

E 02. Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.

E 03. Participants with active atopic dermatitis (AD).

E 04. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to participants with short life expectancy, participants with uncontrolled diabetes (hemoglobin A1c ≥9%), participants with cardiovascular conditions (eg, Class III or IV cardiac failure according to

the New York Heart Association classification), severe renal conditions (eg, participants on dialysis), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases, hepatobiliary conditions, which include, but are not limited to, hepatitis virus infections, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis, moderate or severe hepatic impairment (Child Pugh B or C) or any other liver disease considered clinically significant by the Investigator. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc).

E 05. Known or suspected immunodeficiency, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator.

E 06. History of serious infections requiring intravenous (IV) therapy with the potential for recurrence (as judged by the Site Investigator) with less than 4 weeks interval between resolution of serious infection and first dose of study drug, or currently active moderate to severe infection at Screening (Grade 2 or higher), including active coronavirus disease 2019 (COVID-19) (refer to Section 10.8.3 for Italy-specific requirements).

E 07. Live vaccine except Bacille Calmette Guerin-vaccination within 28 days prior to Day 1 or plan to receive one during the trial; Bacille Calmette Guerin-vaccination within 12 months prior to Screening.

E 08. COVID-19 vaccine within 14 days prior to Study Day 1 (refer to Section 10.8.2 for German-specific requirements).

E 09. Active malignancy or history of malignancy within 5 years before Day 1, except completely treated in situ carcinoma of the cervix, completely treated and resolved non metastatic squamous or basal cell carcinoma of the skin.

E 10. Participant with any other medical or psychological condition including relevant laboratory or electrocardiogram (ECG) abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, CRF, etc).

E 11. History of drug abuse within the previous 12 months

E 12. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day.

E 13. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.

E 14. Conditions that may predispose the participant to excessive bleeding:

- A bleeding disorder or known platelet dysfunction at any time prior to the Screening Visit
- The participant has had major surgery within 4 weeks prior to the Screening Visit, which could affect the participant's safety or affect immune response (as judged by the Investigator) or has planned any elective major surgery during the study.
- A history of significant bleeding event within 6 months prior to screening, according to the Investigator's judgment such as, but not limited to cerebral or gastrointestinal bleeding.

E 15. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

E 16. [redacted]

E 17. Planned major surgical procedure during the patient' participation in this study.

E 18. Prior utilization of IV steroids for treatment of laryngeal angioedema.

E 19. Any participant with an **uncontrolled** disease state as judged by the Investigator, such as asthma, psoriasis, or inflammatory bowel disease, etc. that are typically treated with oral or parenteral corticosteroids.

[redacted]

[redacted]

[redacted]

Diagnostic assessments

E 30. Positive for human immunodeficiency virus (HIV) antibody test.

E 31. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) with positive DNA test result at screening or within 3 months prior to the screening visit (for Japan-specific requirements see Section 10.8.1).

E 32. Positive hepatitis C antibody test result at screening or within 3 months prior to the screening visit. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

E 33. Exclusion related to Tuberculosis infection (TBI):

- Active TBI or a history of incompletely treated TBI regardless of screening Quantiferon result
- Quantiferon positive patients (no active disease) are excluded from the study unless the following conditions are met
  - Patients with a history of prior documented completed chemoprophylaxis for latent TBI (eg, acceptable treatments would be 9 months of isoniazid 300 mg oral daily or equivalent proven regimen per local guidelines) or treatment of active TBI who has obtained consultation with a specialist to rule out active TBI or treat active TBI.
  - Consultation with and prior approval from sponsor are required in either of the aforementioned scenarios.

  Otherwise a documented negative screening for TB via a negative Quantiferon result within 3 months prior to screening (and if required per local standard of care, a chest X-ray), is sufficient and no further screening with Quantiferon test is required; if clinically indicated the test may be repeated based on clinical judgment, borderline results, or clinical suspicion of TB infection.
- Clinically significant abnormality consistent with prior/active TBI infection based upon chest radiograph with at least posterior-anterior view (radiograph must be taken within 12 weeks prior to screening visit or during the screening period). Additional lateral view is recommended but not required.
- Suspected extrapulmonary TBI regardless of screening Quantiferon result.
- Patients at high risk of contacting TB, such as close contact with individuals with active or latent TBI.

E 35. Electrocardiogram findings of QT corrected for heart rate (QTc) >450 msec (males) or >470 msec (females), poorly controlled atrial fibrillation (ie, symptomatic participants or a

ventricular rate above 100 beats/min on ECG), or other clinically significant cardiovascular abnormalities.

Other exclusions

E 36. Hypersensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 37. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures

E 38. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6)

E 39. Any specific situation during study implementation/course that may raise ethics considerations.

E 40. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

[redacted]

5.3.2 Caffeine, tobacco, and activity

[redacted]

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

If a participant fails to complete 2 or fewer days of their UAS7 evaluation at screening, or if their e-diary device fails, that participant may be rescreened once. However, if a participant does not meet the minimum UAS7 or ISS7 score in screening, that participant would not be eligible for re-screening.

In cases where original screen failure was due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the participant may be rescreened one time for this study after notification of the Sponsor. Rescreened participants will be assigned a new participant number for the re-screening event. There is no requirement for a waiting period between the screen-failure and the re-screening. A new consent form must be signed and Visit 1 procedures must be repeated for re-screened participants.

Re-testing: Laboratory Inclusion/Exclusion Criteria

If a participant does not meet certain laboratory inclusion/exclusion criteria at Screening due to the following laboratory results, the Investigator may repeat one or more of these tests once during the screening period (refer to Section 10.8.3 for Italy-specific requirements).

[redacted]

If the participant meets the laboratory eligibility criteria on the second assessment, he or she will be permitted to enter the study. It will not be considered a retesting if blood samples have to be redrawn because of sample handling problems, breakage, sample integrity, or laboratory error.

If a hematology/chemistry laboratory value falls outside the normal range and is judged by the Investigator to be clinically significant and is NOT one of explicit exclusionary laboratory testing, it may be repeated once and if the repeat value is no longer considered clinically significant then that specific laboratory testing result should not disqualify a participant from the study.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9).

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

[redacted]

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Overview of study interventions administered

Intervention label	Rilzabrutinib	Placebo
Intervention name	Rilzabrutinib	Placebo
Type	Drug	Drug
Dose formulation[a]	Tablets [redacted]	Placebo to match rilzabrutinib tablets (modified-capsule shaped tablets/caplets)
Unit dose strength(s)	400 mg	0 mg
Dosage level(s)	400 mg (1 tablet) BID, QPM, or TID	1 tablet BID, QPM, or TID
Route of administration	Oral	Oral
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Packaging and labeling	During the double-blind phase, IMP will be provided in wallets of 1 blister pack, and each wallet will be labeled as required per country requirement; during the open-label phase, IMP will be supplied in white plastic bottles, and each bottle will be labeled as required per country requirement.	During the double-blind phase, IMP will be provided in wallets of 1 blister pack, and each wallet will be labeled as required per country requirement.
[Current/Former name(s) or alias(es)]	Rilzabrutinib (SAR444671)/PRN1008	Placebo

a [redacted]

Table 4 - Arms and associated interventions

Arm name	[redacted]		Placebo
Associated interventions (intervention label[s])	Rilzabrutinib or Placebo	Rilzabrutinib or Placebo	Rilzabrutinib or Placebo	Rilzabrutinib or Placebo

Noninvestigational medicinal products

Participants should continue their established standard of care background therapy with a long-acting, non-sedating H1-AH [redacted] during the study. [redacted] Only up to 4-fold the recommended dose is allowed. If participants are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the participant dose to the stipulated range at the screening visit (Visit 1). Participants must remain on this dose of antihistamine for at least 3 consecutive days before screening assessment of UAS7 and ISS7 is initiated. Participants should continue to take the same daily dose throughout the study unless they experience a flare for which rescue therapy may be initiated (refer to Section 6.8.1 for rescue therapy). [redacted]

[redacted]

For other information related to H1-AH including safety precautions please refer to the National Product labeling.

Refer to Appendix 8 (Section 10.8.1) for Japan-specific requirements.

IMP will be supplied to the participant at the site by the investigator.

IMP may be supplied from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9).

Background therapy will be supplied by Sponsor's local affiliate as locally required or by sites. Reimbursement will be provided when deemed necessary and as per country regulation.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall SAR444671 (rilzabrutinib) and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-participant [DTP] shipment, for which a courier company has been approved by the Sponsor), allow IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.(refer to Section 10.8.2 for German-specific requirements for DTP services).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A randomized intervention kit number list is generated centrally by Sanofi. The IMPs (rilzabrutinib or matching placebo) are packaged in accordance with this list.

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the telephone number and call-in directions for the interactive voice response system (IVRS) and/or the log in information and directions for the interactive web response system (IWRS) will be provided to each site.

Randomization will take place at Day 1 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 (refer to Section 5.1 for definition of omalizumab-incomplete responders). 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 Investigator or designee will obtain the treatment kit numbers at randomization (Day 1, Baseline) and subsequent scheduled dosing visits via IRT that will be available 24 hours/day.

Although the kit numbers will vary for the individual participant, the treatment group assignment and randomization will not change throughout the study.

Treatment kits will be dispensed at the study visits summarized in SoA. Returned study treatment kits should not be re-dispensed to the participants.

A randomized participant is a participant from screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not.

A participant cannot be randomized more than once in the study.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

Methods of blinding

Rilzabrutinib 400 mg tablets and matching placebo will be provided in identically and visually indistinguishable tablets.

The Investigator, other staff members, as well as the participant will remain blinded and will not know the participant's intervention assignment during the study.

At the facilities where the systemic drug concentration and selected biomarkers are determined, the samples will be analyzed prior to database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team. In addition, one programmer may be unblinded to prepare the dataset for population PK analysis, if needed, and there will be strict procedures to maintain blind beyond the programmer.

Procedure to maintain blinding if interim analyses are performed will be detailed in SAP.

Blind break

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable. If the code is broken upon Investigator's request, the participant must withdraw from IMP administration.

6.4 STUDY INTERVENTION COMPLIANCE

The following describes methods used by the Investigator or his/her delegate to ensure that the IMP was administered.

- IMP accountability:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
  - The Investigator counts the number of tablets remaining in the returned packs (tablets packed in wallets during the double-blind phase and in bottles during the OLE phase), and fills in the Intervention Log Form.
  - The Investigator records the dosing information on the appropriate page(s) of the electronic case report form (eCRF).
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and reported in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of rilzabrutininb 400 mg tablets and matching placebo dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy unused IMP, used, or partially used kits unless the Sponsor provides written authorization.

6.5 DOSE MODIFICATION

Rilzabrutinib dose modification will not be allowed [redacted]

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Continued access to study intervention after the end of study is not planned for this study.

6.7 TREATMENT OF OVERDOSE

[redacted]

No specific information is available on the treatment of overdose of rilzabrutinib.

In the event of an overdose, the participants should be followed, TEAE reported, and clinically appropriate supportive treatment provided.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until rilzabrutinib can no longer be detected systemically (at least 1 day).
4. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document appropriately in the eCRF.

For more details concerning overdose refer to the IB.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy

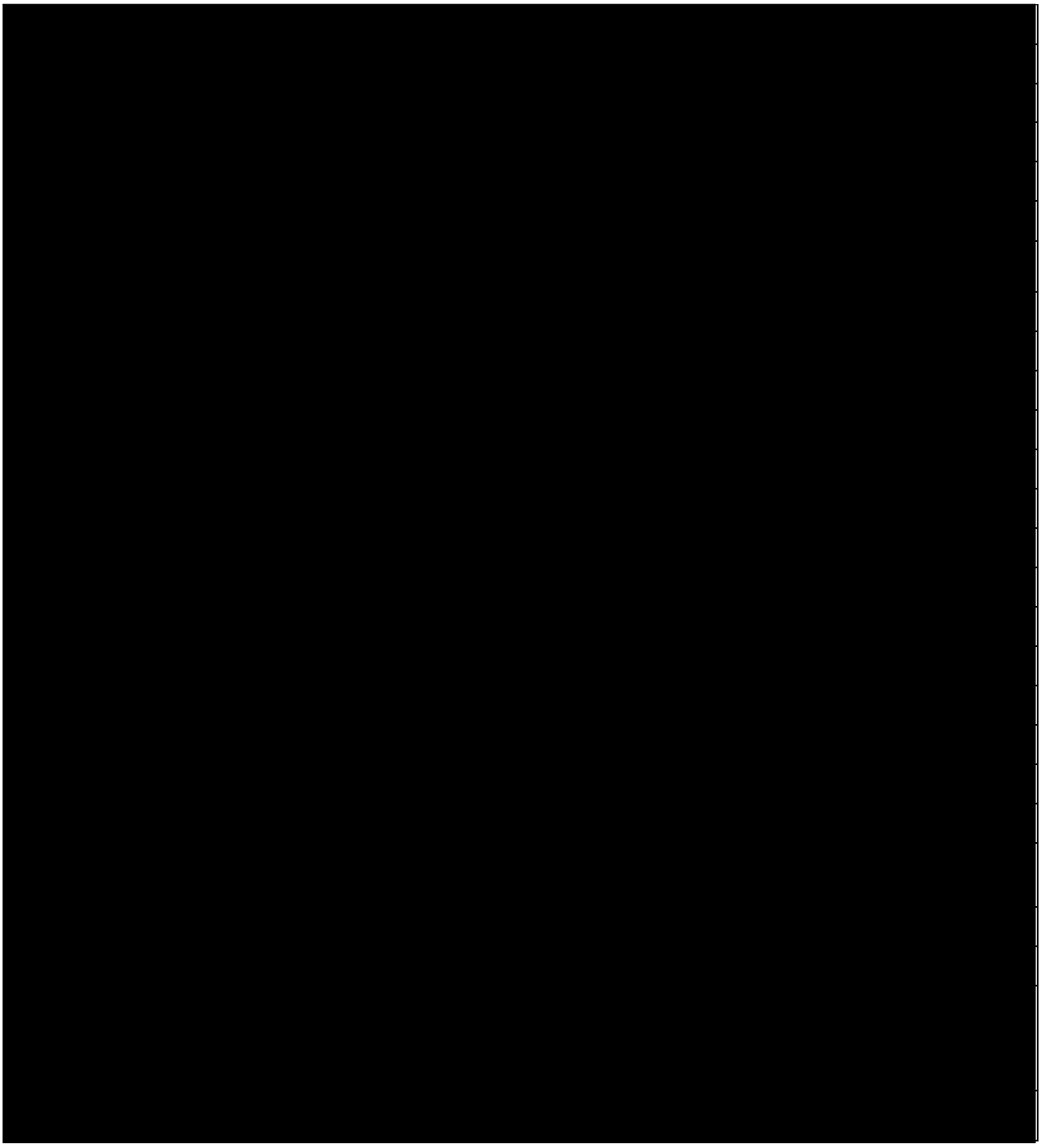
[redacted]. New or chronic prescription medications may be used if needed at the discretion of the Investigator. The Medical Monitor should be contacted if there are any questions regarding new or chronic medications. Refer to Section 5.2 for details on prohibited prior therapy and prohibited concomitant therapy.

[redacted]

[redacted]

Note: participants should continue their established standard of care background therapy with a long acting, non-sedating H1-AH (defined as noninvestigational medicinal product [NIMP], see Section 6.1). [redacted]

[redacted]



6.8.1 Rescue medicine

As rescue medication, up to 4-fold of the approved dose of the participants usual H1-AH can be given on days where pruritus and wheal development are severe. The total daily H1-AH dose is not to exceed 4-fold the recommended dose during the screening, treatment and follow-up period.

[redacted]

If needed, or if unable to increase H1-AH as an initial step for rescue therapy, participants may be prescribed a short course of OCS. After any use of OCS, participants will need to seek immediate medical attention to ensure that the initial reaction has been successfully controlled and/or to evaluate for additional therapeutic steps. In order to ensure consistency, when possible, it is recommended to use OCS for 5 to 7 days with a starting dose of oral prednisone 40 mg (or clinically comparable OCS) followed by taper per the Investigator's judgment. The use of OCS should be delayed, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of OCS administration as well as the name and dosage regimen of the OCS must be recorded.

For other information related to H1-AH and OCS including safety precautions please refer to the National Product labeling.

Unless permanently discontinued from the study, all participants will complete the scheduled study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for CSU.

- Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.
- Participants who receive rescue therapy with OCS during the study treatment will be considered "treatment failure" for the analysis of all efficacy endpoints.

Refer to Appendix 8 (Section 10.8.1) for Japan-specific requirements.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for efficacy and safety. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The Investigator/Sponsor must permanently discontinue dosing with rilzabrutinib in a participant if any of the following participant-level stopping rules are met:

- Pregnancy will lead to permanent intervention discontinuation in all cases.
- Change in compliance with inclusion/exclusion criteria that is clinically relevant and affects participant's safety.
- Intake of non-permitted concomitant medications that might affect participant's safety or study assessments/objectives.
- An allergic reaction, including an anaphylactic reaction, in association with IMP administration.
- Occurrence of AEs, that, in the opinion of Investigator/Sponsor, may jeopardize

[redacted]

Any clinically significant abnormal laboratory value will be immediately rechecked for confirmation after 24 hours, before making a decision of permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

[redacted]

7.1.3 Temporary discontinuation

Temporary intervention discontinuation decided by the Investigator corresponds to [redacted] not administered to the participant.

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (see Appendix 9, Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria met

[redacted]

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Patient-reported outcomes (PRO) questionnaires should be completed by the participants before the consultation and/or clinical tests, in a quiet place. The questionnaires should be completed by the participants themselves, independently from their physician, the study nurse, or any other medical personnel and without any help from friends or relatives.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to Investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 470 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

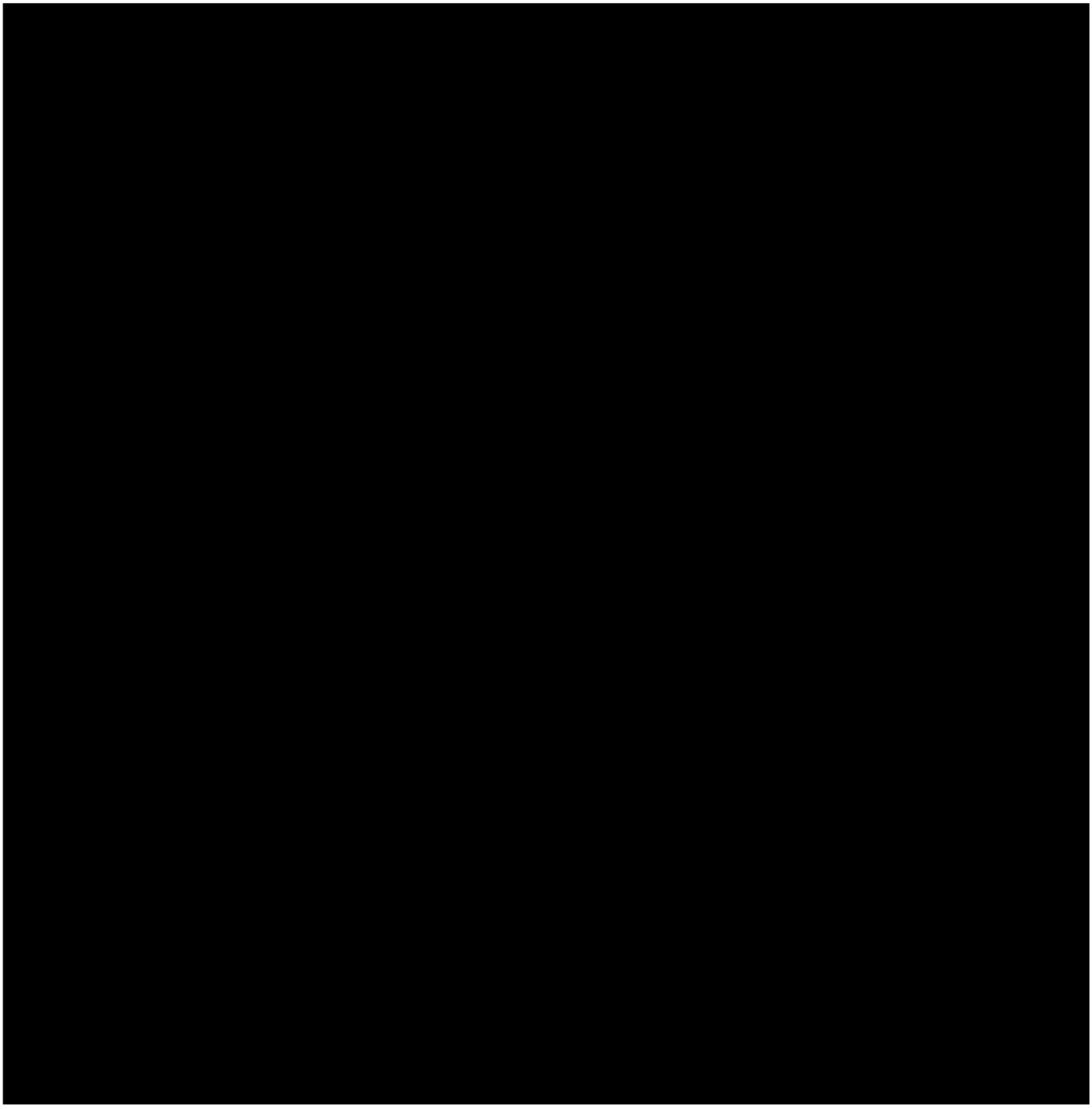
Efficacy data will be collected via electronic devices.

The e-diary is used for daily recording of PRO such as the UAS7 [redacted] questionnaires, and use of H1-AH medication. This device will be dispensed at screening visit (Visit 1), including instructions for use and participant(s) will be instructed on the use of the device.

Recorded information will be downloaded from this device daily, the e-diary will be downloaded and returned to the site at the end of the study participation.

On regular basis, the site staff should review on vendo´s website the information downloaded from participants´ ediary. They should particularly check status of the disease reviewing UAS7

[redacted]



8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological, and skin systems. Height and weight will also be measured and recorded.
- An abbreviated physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

For Japan-specific requirements see Section 10.8.1.

8.2.2 Vital signs

Vital signs will be measured in a semi-supine or sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.2 for exclusion criterion related to clinically significant cardiovascular abnormalities.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3.)

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at study visits according to the SOA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion criteria
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study

8.2.6 Suicidal ideation and behavior risk monitoring

Not applicable.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of adverse event of special interest (AESI) is provided in Section 8.3.7.

The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3) (refer to Section 10.8.2 for German-specific requirements). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the IB.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until for at least 4 weeks after the last administration of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

See Section 10.3.1 for disease-related events not meeting the AE definition.

8.3.7 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to

characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and [redacted]
  - An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the maximum allowed daily dose, within the intended therapeutic interval. For H1-AH only, an overdose is defined as any dose that exceeds the maximum allowed daily dose in this protocol (see Section 6.1 and Section 6.8.1).
- Increase in ALT: If increase in ALT >3x ULN, report the ALT >3 x ULN together with total bilirubin value including normal ranges and confirm the elevation within 72 hours as indicated in the flow chart appendix 6 (Section 10.6). Follow the instructions listed in the box at the bottom of the flow chart.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Plasma samples will be obtained for PK characterization of rilzabrutinib as outlined in the SoA (see Section 1.3). Selected residual plasma samples may be utilized to assess PK of relevant metabolites of rilzabrutinib. Concentrations at each time point will be reported.

- Whole blood samples of approximately 4.0 mL will be collected and processed into plasma for measurement of plasma concentrations of rilzabrutinib (and relevant metabolites, as applicable) as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of rilzabrutinib (and relevant metabolites, as applicable). Each plasma sample will be divided into 2 aliquots (1 each for primary and a back up).
- Population PK analysis may be conducted to obtain PK parameters of rilzabrutinib. If performed, the results will be summarized in a separate report.
- Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5 GENETICS AND/OR GENOMICS

Optional peripheral whole blood samples will be collected for RNA isolation for future research (see Section 8.9).

See Appendix 5 (Section 10.5) for information regarding genetic/genomic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.6 BIOMARKERS

Collection of biological samples for other biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3):

- Serum and plasma samples for soluble biomarkers and cellular tests
- Blood sample for immune cell phenotyping
- [redacted]
- Serum sample for future use (optional): Other optional samples may be used for research to develop methods or assays related to the disease process, pathways associated with disease state, and/or mechanism of action of rilzabrutinib. These tests will be performed only in participants who provide consent for future use of biological samples (Section 8.9).

8.7 IMMUNOGENICITY ASSESSMENTS

Antibodies to rilzabrutinib will not be evaluated in this study.

8.8 HEALTH ECONOMICS

Health economics will not be evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a

subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

In this study, 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: there is no treatment difference between rilzabrutinib and placebo.
- Alternative hypothesis H1: there is a treatment difference between rilzabrutinib and placebo.

The statistical hypotheses to be tested on secondary efficacy endpoints can be specified similarly as those on the primary endpoint.

9.1 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 (refer to Section 5.1 for definition of omalizumab-incomplete responders). 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.

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - 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.
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.

ICF: informed consent form, IMP: investigational medicinal product, IRT: interactive response technology

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.

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

9.3 STATISTICAL ANALYSES

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.3.1 General considerations

Common definitions of baseline

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 enrolled/randomized but not treated, the baseline value is defined as the last available value before enrollment/randomization.

General methods

- Descriptive analyses will include summarization of quantitative variables (using n, mean, SD, inter quartile range, median, minimum, and maximum) and qualitative data (by reporting absolute and relative frequencies).
- 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.

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-blinded 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.
  - 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.

[redacted]

[redacted]

9.3.2 Primary 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.

9.3.2.1 Primary estimand

The summary of primary estimand for the primary endpoint is as below:

Treatment:

Rilzabrutinib 400 mg QPM, 400 mg BID, 400 mg TID, and placebo, along with established standard of care background therapy with a long-acting, non-sedating H1-AH.

Population:

Omalizumab-naïve

Variables:

- Change from baseline in UAS7 at Week 12 (except US and US reference countries).
- For US and US reference countries only: change from baseline in ISS7 at Week 12.

Intercurrent events and handling strategy and missing data handling:

The intercurrent events will be handled as follows

- Discontinuing the study intervention: all data collected after discontinuation will be used in the analysis (treatment policy strategy).
- Taking selected prohibited medications and/or rescue medications 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: 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.

Of note, details of selection of prohibited medications and/or rescue medications will be specified in the SAP.

Population-level summary:

Analysis of covariance 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 subjects, mean, standard error, and 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.

9.3.2.2 Sensitivity analysis

Details of the sensitivity analyses will be provided in the SAP.

9.3.2.3 Supplementary analysis

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

As-observed analysis (including all data after taking the prohibited and/or rescue medications) and other supplementary analyses will be performed to provide additional insights into the understanding of the treatment effect. Details of the supplementary analyses will be provided in the SAP.

In addition to the comparison between each dose level of rilzabrutinib and placebo in a pairwise manner, a pooled analysis of the BID and TID doses may be performed as appropriate.

9.3.2.4 Subgroup analysis

To assess the consistency in treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint with respect to age group, gender, region, and other factors that will be specified in the SAP.

9.3.2.5 Multiplicity

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.

9.3.3 Secondary endpoint(s)

The following secondary endpoints will be analyzed using the same approach as for the primary endpoint:

- 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 following responder secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel test adjusted by region:

- Proportion of participants with UAS7 ≤6 at Week 12
- Proportion of participants with UAS7 = 0 at Week 12

Participants who receive selected prohibited medications and/or rescue medications will be considered as non-responders for time points after the 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.

No multiplicity adjustment for the secondary efficacy endpoints will be made. A pooled analysis of the BID and TID doses may be performed as appropriate. The details will be described in the study SAP.

9.3.4 Tertiary endpoints

The details about the analysis of tertiary endpoints will be described in the study SAP.

9.3.5 Safety analysis

All safety analysis will be based on the safety population according to the intervention group to which the participants are exposed.

The safety analysis will be conducted separately for double-blind period and open-label period.

9.3.5.1 Adverse events

General common rules for adverse events

Treatment emergent period, for double-blind and open-label separately, includes both on-treatment period and post-treatment period as defined in Section 9.3.1.

The AEs will be analyzed in the following 3 categories according to the observation period defined in Section 9.3.1:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- Double-blind TEAEs: AEs that developed, worsened, or became serious during the double-blind treatment-emergent period.
- Open-label TEAEs: AEs that developed, worsened, or became serious during the open-label treatment-emergent period.

Similarly, the deaths will be analyzed in the pre-treatment and treatment-emergent periods.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a preferred term [PT]or a prespecified grouping), all treatment emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

Adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and PT sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

For death, the following summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- Treatment-emergent AE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

9.3.5.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables and vital signs, descriptive statistics for results and changes from baseline will be provided for each planned visit/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.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

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, 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

9.3.6 Other analysis

Pharmacokinetic, pharmacodynamics (PD), and biomarker exploratory analyses will be described in the SAP finalized before database lock.

Data collected regarding the impact of the COVID-19 or other pandemics, on the participants will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other pandemics requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9, Section 10.9, as applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, IDFU and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study). (refer to Section 10.8.2 for German-specific requirements).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. (refer to Section 10.8.2 for German-specific requirements).

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable. (refer to Section 10.8.2 for German-specific requirements).

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9, refer to Section 10.8.2 for German-specific requirements).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Not applicable.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in partcipants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property.

For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the

Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in trainings materials or study manuals.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central or local laboratory.
- For tests to be performed by the central laboratory: local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded into the CRF.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Coagulation	International normalized ratio (INR) test, prothrombin time, activated partial thromboplastin time (aPTT), and fibrinogen (Optical Clot Detection).
Clinical (serum) chemistry[a]	
	Urea
	Albumin
	Total protein
	Creatinine
	high-sensitivity C reactive protein (hs-CRP)
	Creatine kinase (CPK)
	HbA1c
	Potassium
	Sodium
	Chloride
	Phosphate
	Calcium
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Alkaline phosphatase
	Total, direct, and indirect bilirubin
	Lactate dehydrogenase
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b]

Laboratory tests	Parameters
[redacted]	[redacted]

NOTES :

a D[redacted]

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are

of participant/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by participants/LARs will be collected during interview with the participants/LARs and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Note: examples of such events include invasive or malignant cancers, 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 drug dependency or drug abuse.

10.3.3 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours (refer to Section 10.8.2 for German-specific requirements).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in Investigator site file.

SAE reporting to the Sponsor via paper data collection tool (In case of failure of electronic reporting of SAE via the electronic data capture system)

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator site file.

10.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important**

that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female

   A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

10.4.2 Contraception guidance

- Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova up to [redacted]
- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Male participants with partners of reproductive potential who become pregnant:

- The Investigator will attempt to collect pregnancy information on any female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Follow-up will be no more than [redacted] following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant:

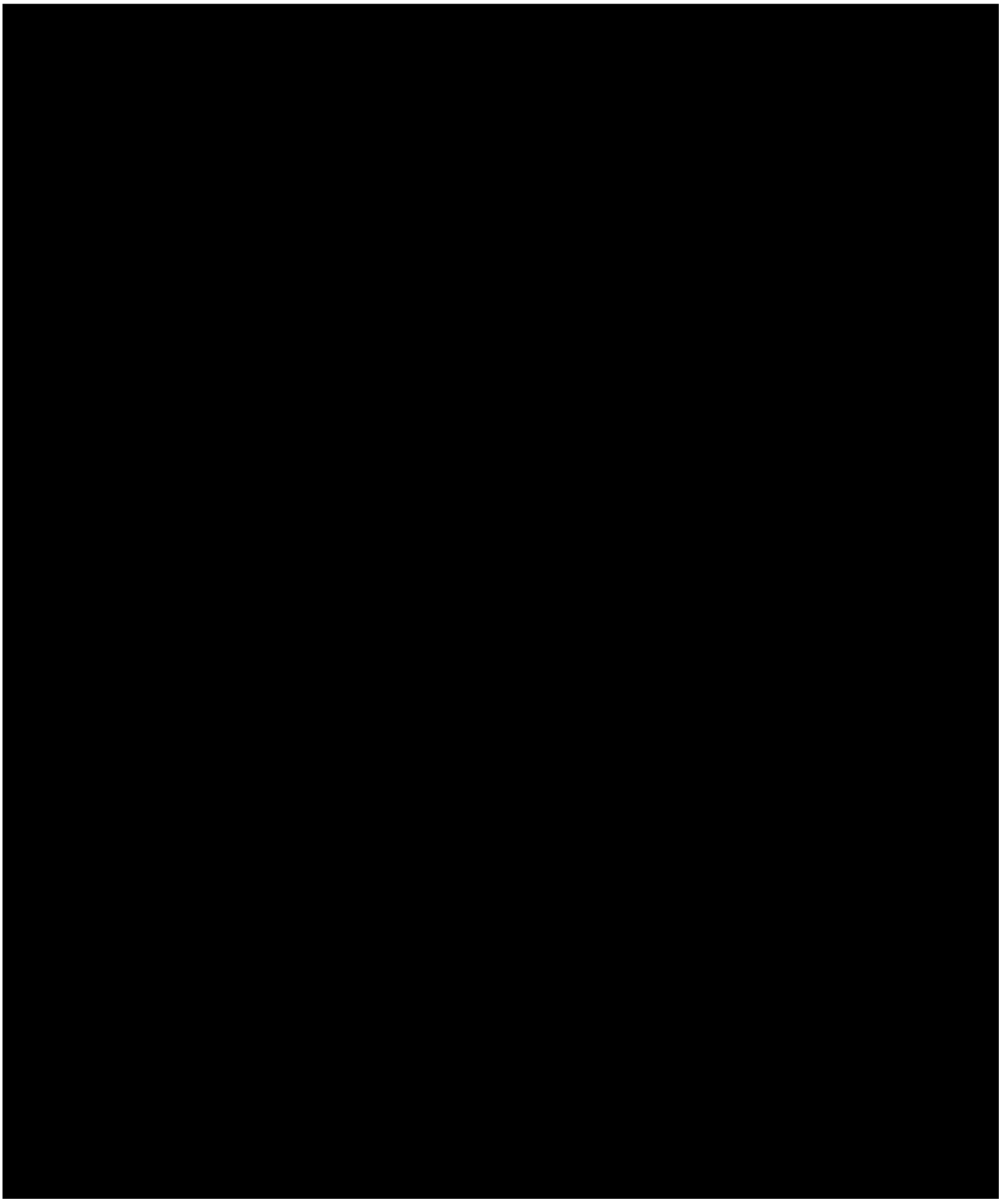
- The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Follow-up will not be required for more than [redacted] beyond the estimated delivery date.
- Additional follow-up information may be requested about the baby until at least 1 year after the birth of the baby, due to potential risk of abnormalities not present at birth.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 10.3.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.

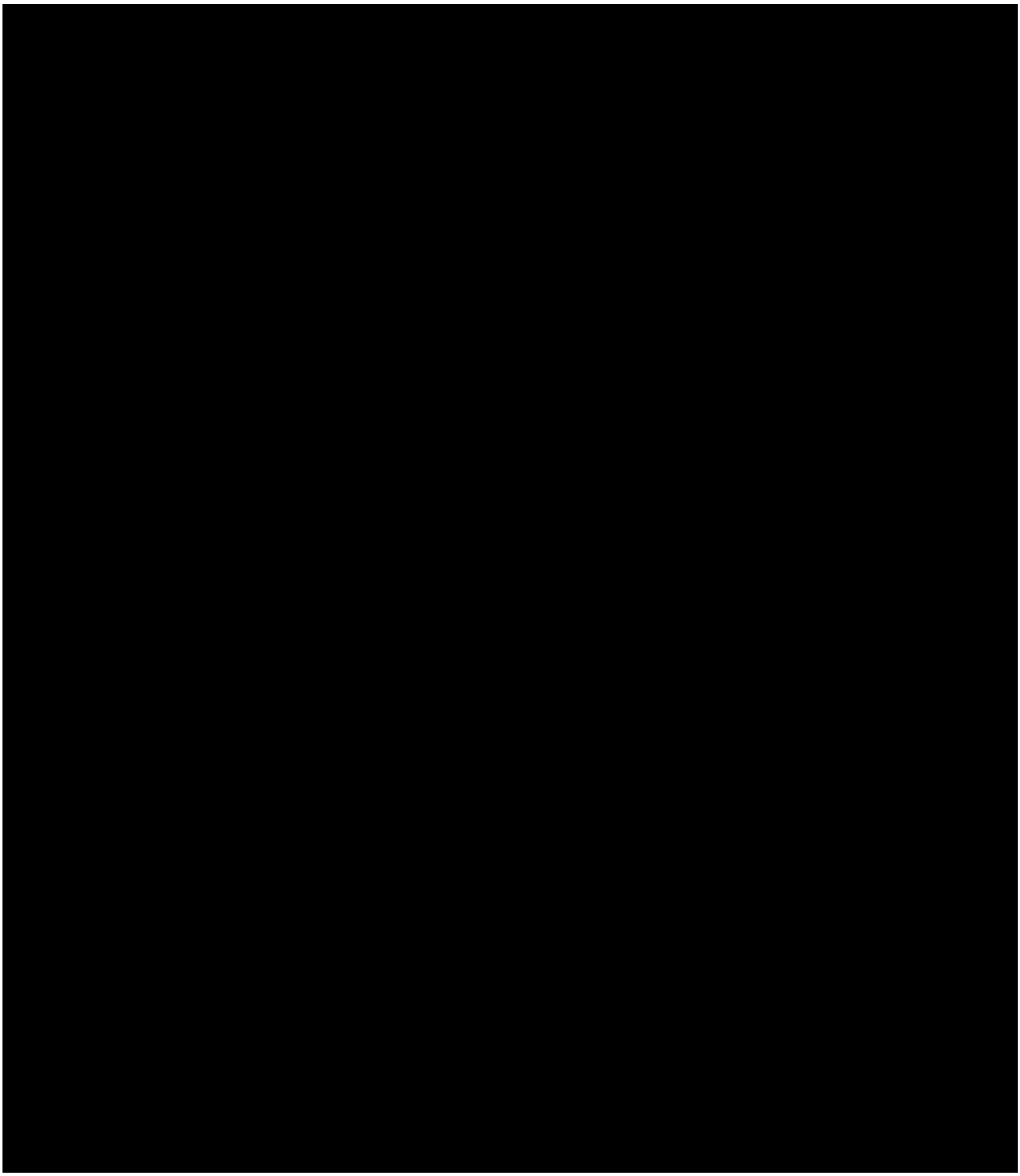
10.5 APPENDIX 5: GENETICS

Use/Analysis of RNA/DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, whole blood samples will be collected for RNA/DNA analysis from consenting participants.
- RNA/DNA samples will be used for genetic/genomic research related to rilzabrutinib or CSU and related diseases. They may also be used to develop tests/assays including diagnostic tests related to rilzabrutinib and/or drugs of the same class and CSU. Genetic/genomic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- RNA samples will be analyzed for RNA sequencing and qRT-PCR validation of biomarkers. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to rilzabrutinib or drugs of this class to understand study disease or related conditions.
- The results of genetic/genomic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the RNA/DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on rilzabrutinib continues but no longer than 15 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS





[redacted]

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Japan-specific requirements

[redacted]

[redacted]

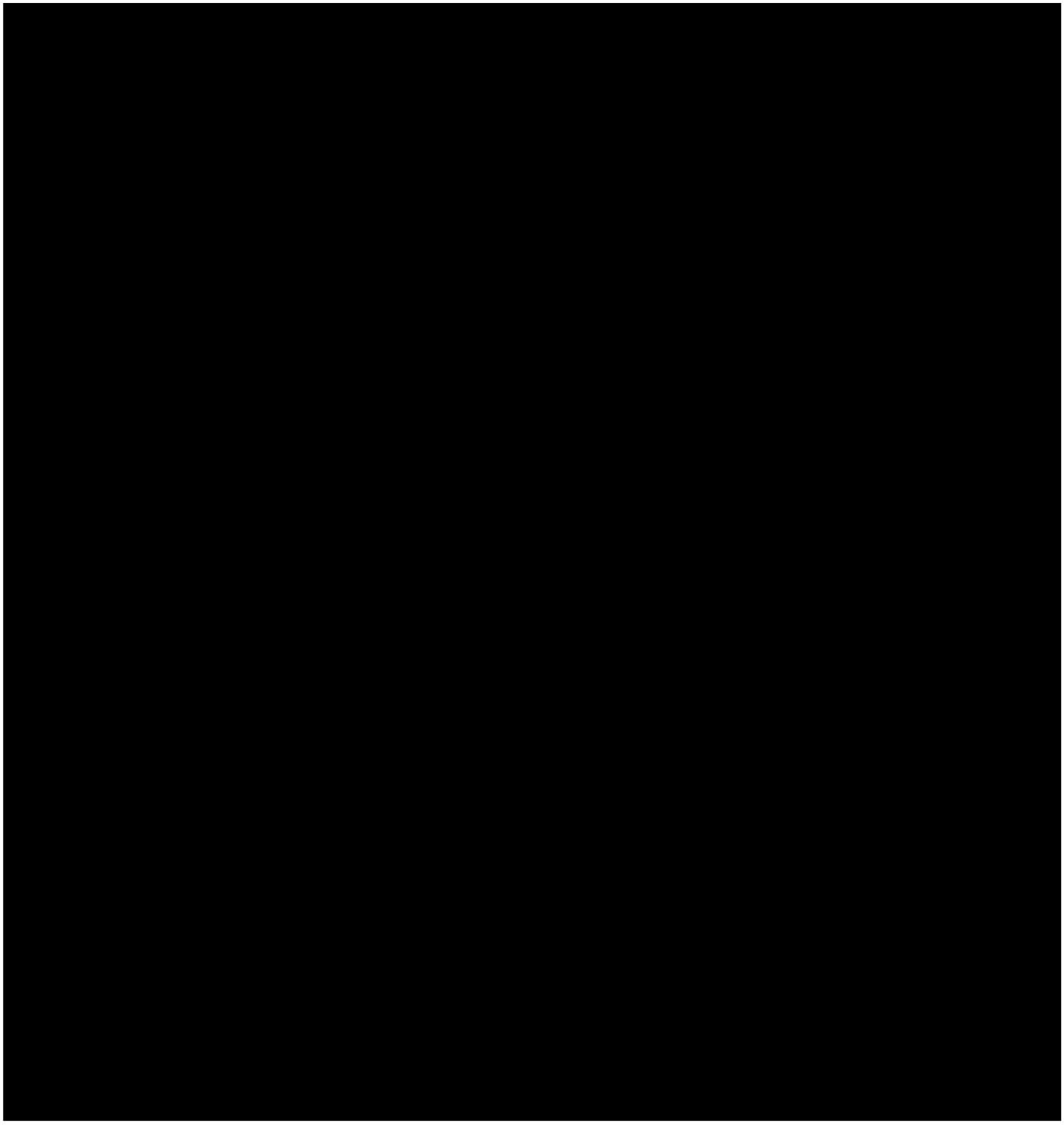
[redacted]

[redacted] (Section 10.2)

Laboratory tests	Parameters
Other screening tests	• Serology (if these tests have not been performed within the past 3 months prior to the screening visit [Visit 1]) - 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], - Hepatitis C virus antibody [anti-HCV], and HCV RNA

[redacted]

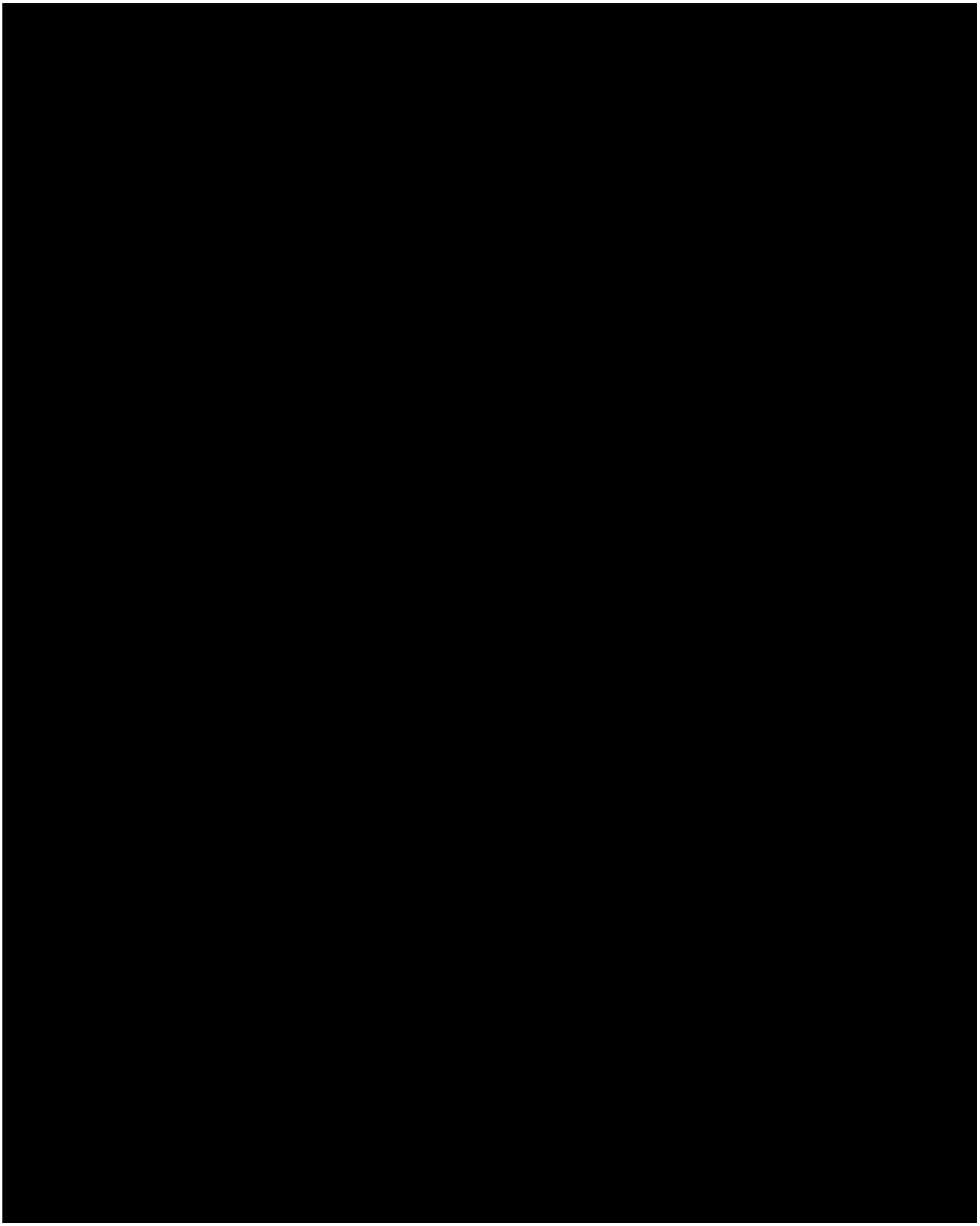
[redacted]



[redacted]

Section 5.4 Screen Failures (Section 5.4)

[redacted]



[redacted]

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained, refer to Section 10.8.2 for German-specific requirements).

Study intervention

The following contingencies may be implemented to make clinical supplies available to the participant for the duration of the emergency.

- The DTP supply of rilzabrutinib from the PI/site/Sponsor where allowed by local regulations and agreed upon by the participant.

Study assessments and procedures

Temporary IMP discontinuation may apply in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer feasible.

In the case of an exceptional temporary treatment discontinuation, the discontinuation should be approved by the Sponsor. The Sponsor should also be notified to determine if treatment should be resumed. If deemed safe, the treatment can be resumed at the next scheduled visit. During the

discontinuation period, remote checks (eg, telephone calls) will take the place of on-site visits per the SoA (Section 1.3).

If the above emergency scenario occurs during the follow-up period, one or more follow up visits can be performed remotely with at least 1 contact (eg, via telephone call) at 4 weeks after planned EOT (for participants not entering OLE, visit 6 (Week 12) will be their planned EOT; for participants entering the OLE phase, Visit 12 (Week 52) will be their planned EOT), but at least one follow up visit should be performed on site (end-off study [EOS] visit)), even if the visit window needs to be extended. Remote follow up should be done according to local regulations and approved by the Sponsor.

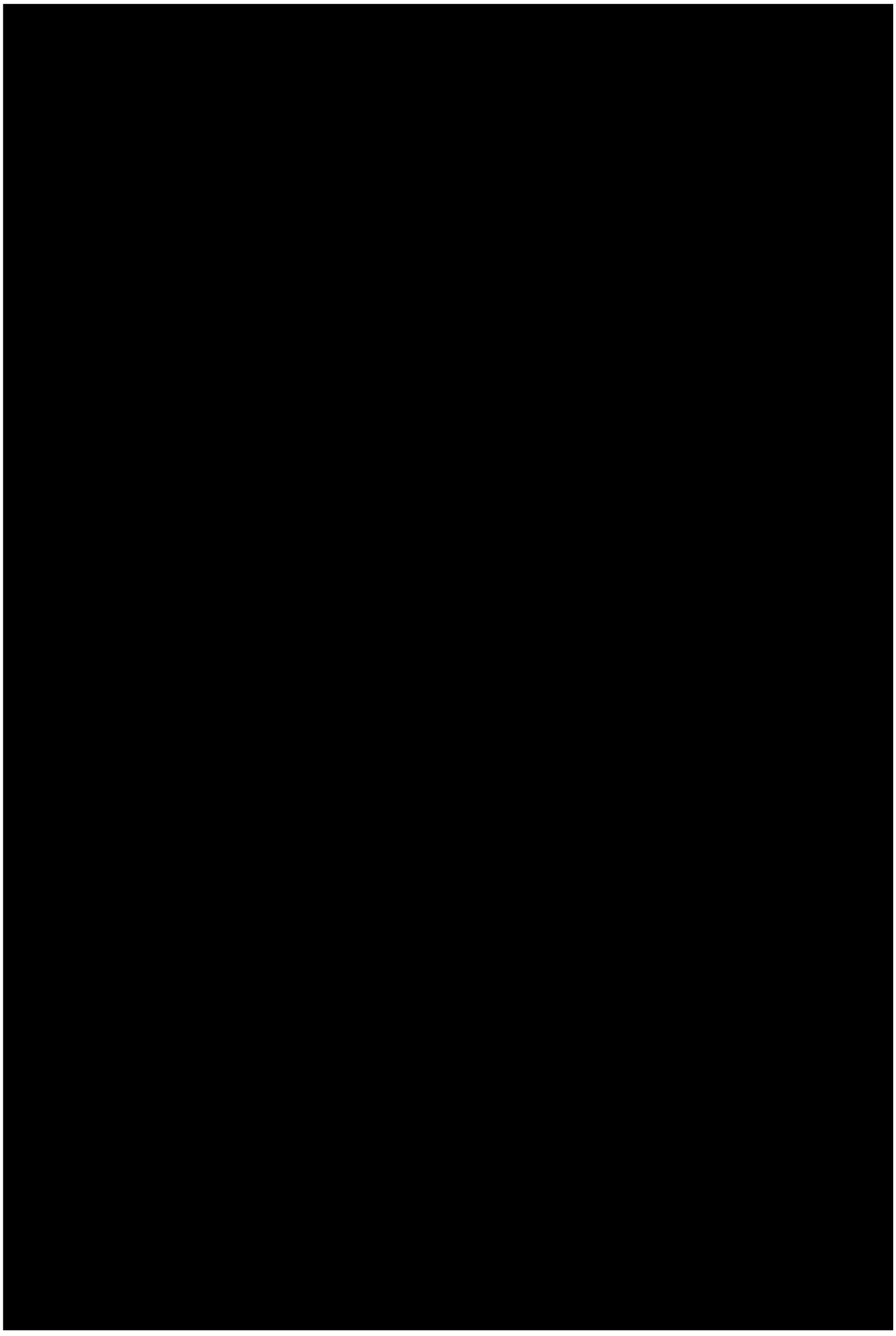
If the above emergency scenario leads to site closure or complete regional or national lock-down, the study may be suspended for the affected sites (Section 10.1.9).

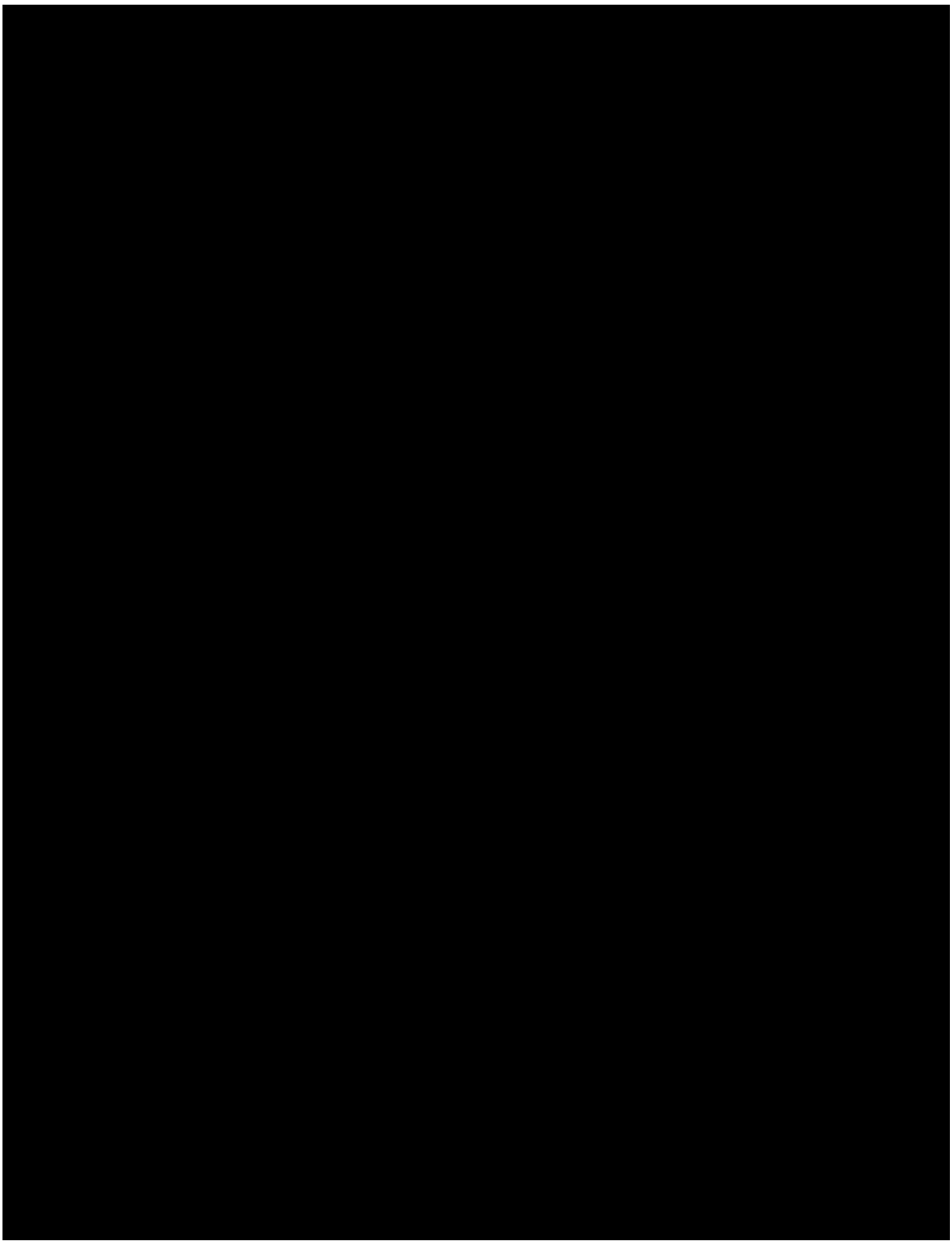
10.10 APPENDIX 10: ADDITIONAL APPENDICES

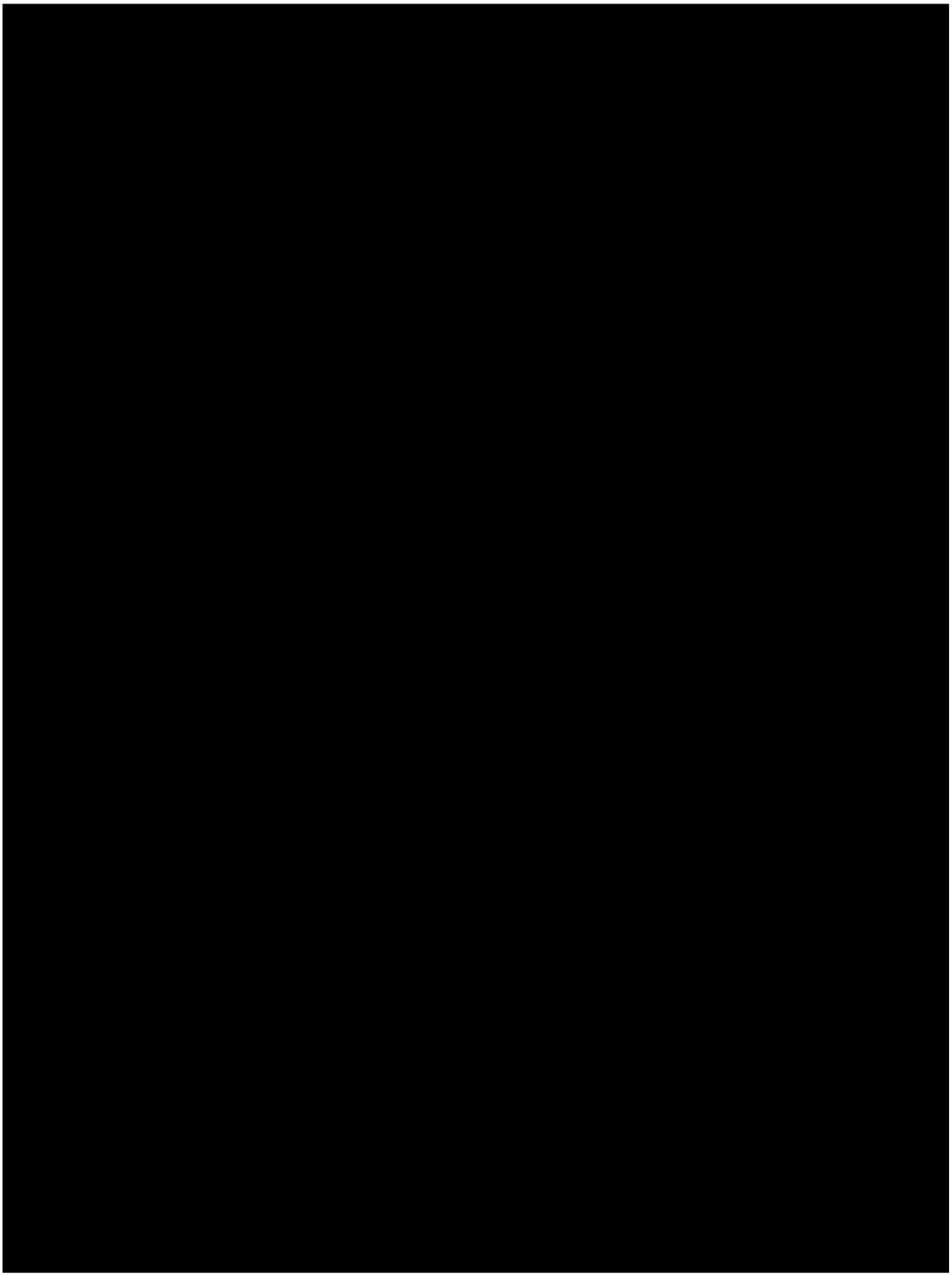
10.10.3 Clinician-reported outcomes and Patient-reported outcomes

[redacted]

[redacted]





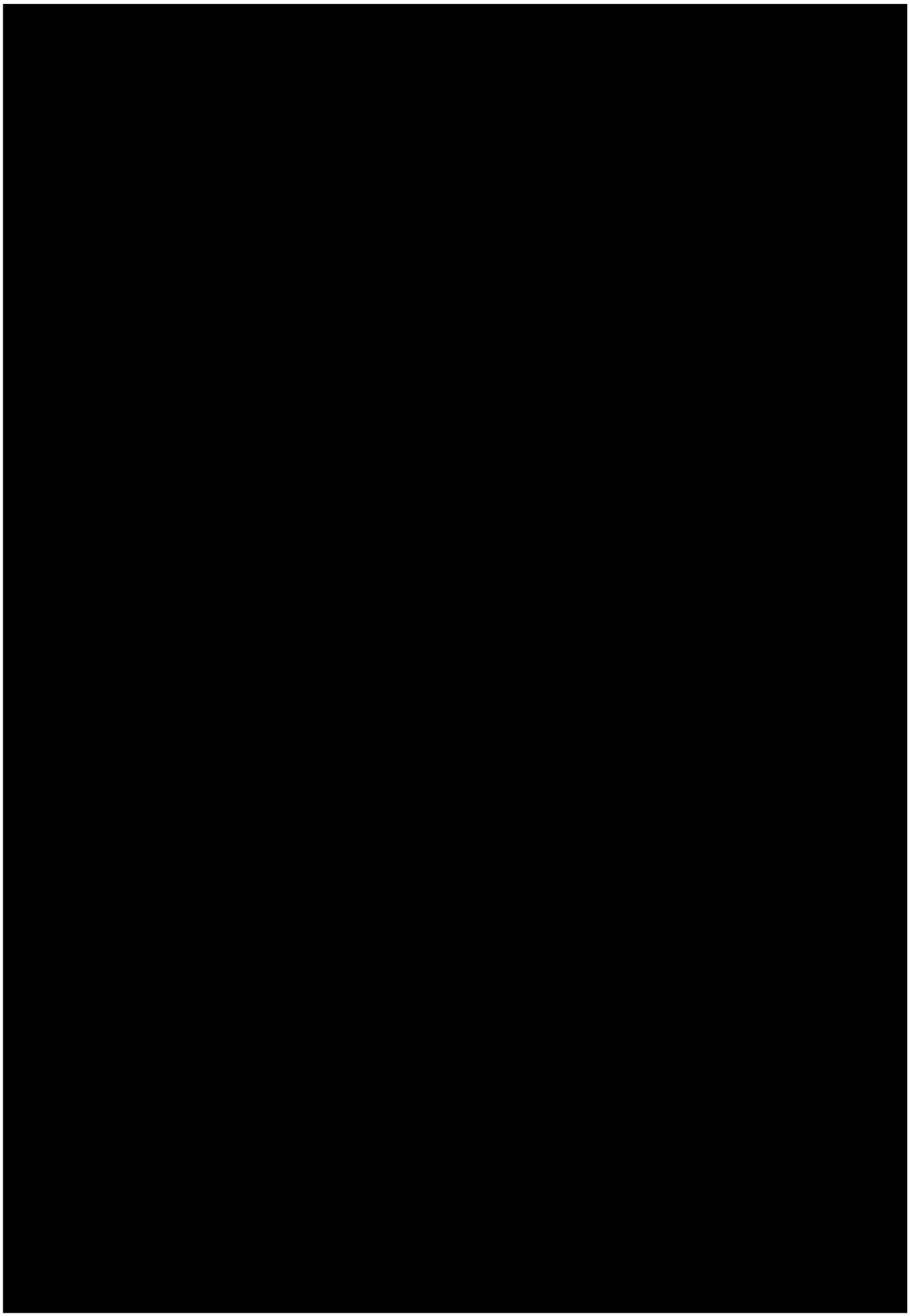


[redacted]

[redacted]

[redacted]

[redacted]



10.11 APPENDIX 11: ABBREVIATIONS AND DEFINITIONS

[redacted]

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotransferase
BCR:	B cell receptor
BID:	twice a day
BTK:	Bruton's tyrosine kinase
CI:	confidence intervals
CIU:	chronic idiopathic urticaria
COVID-19:	coronavirus disease 2019
CRF:	case report form
CS:	corticosteroid
CSU:	chronic spontaneous urticaria

[redacted]

DTP:	direct-to-participant
eCRF:	electronic case report form
EOS:	end-off study
FcεRI:	Fc-epsilon receptor 1
H1-AH:	H1 antihistamines
HBsAg:	hepatitis B surface antigen
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term

[redacted]

IA:	interim analysis
IB:	Investigator’s Brochure
ICF:	informed consent form
Ig:	immunoglobulin
IgG4-RD:	immunoglobin G4-related disease
IMP:	investigational medicinal product
INR:	international normalized ratio
ISS7:	weekly itch severity score
ITP:	immune thrombocytopenic purpura
ITT:	intent to treatment
LAR:	legally authorized representative
LS:	least squares

LTRA:	leukotriene receptor antagonist
MCID:	minimal clinically important difference
NIMP:	noninvestigational medicinal product
OCS:	oral corticosteroids
OLE:	open-label extension
[redacted]	
PRO:	patient-reported outcome
PT:	preferred term
PV:	pemphigus vulgaris
qd:	once per day
QPM:	once every evening
QTc:	QT corrected for heart rate
QTLs:	quality tolerance limits
SAE:	serious adverse event
SAP:	statistical analysis plan
SCIG:	subcutaneous immunoglobulin
SD:	standard deviation
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TBI:	tuberculosis infection
TEAE:	treatment-emergent adverse events
TESAE:	treatment-emergent serious adverse events
TID:	three times a day
UAS:	urticaria activity score
[redacted]	
ULN:	upper limit of normal
wAIHA:	warm autoimmune hemolytic anemia
WBC:	white blood cell
WOCBP:	woman of childbearing potential

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amended protocol 05 (07 June 2022)

This amended protocol 05 (amendment 05) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

[redacted]Other minor clarifications and corrections deemed necessary by the Sponsor will also be implemented.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page and throughout the protocol	Document formatting revisions were made. The header was updated. The amendment number was updated on the title page.	Administrative change to comply with Sanofi standard format.
Section 5.2 Exclusion Criteria	Removed "~~and the Sponsor Medical Monitor"~~ from exclusion criterion E.06 to let the Investigator be the sole judge for considering serious infections requiring intravenous therapy with the potential for recurrence.	Change was made to emphasize that all medical decisions in the clinical trial are under the responsibility of the investigator in line with ICH E6 (R2) principles.
[redacted]	[redacted]	[redacted]
Section 5.2 Exclusion Criteria	Cross-reference added for Section 10.8.3 to refer to Italy-specific requirements in E06	Clarification
Section 6 Study Intervention(s) and Concomitant Therapy	[redacted]	Clarification
Section 6.8 Concomitant therapy	[redacted]	
	[redacted]	[redacted]
Section 9.2 Population for analyses	Added "Open-label extension (OLE) population and its related description" to population for analyses in Table 6	Changes were made for accuracy.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.2.3 Supplementary analysis	Added the following text: "In addition to the comparison between each dose level of rilzabrutinib and placebo in a pairwise manner, a pooled analysis of the BID and TID doses may be performed as appropriate".	Clarfication as a pooled analysis of the BID and TID doses will be performed as appropriate.
[redacted]	[redacted]	[redacted]

In addition, other minor editiorial changes (eg, grammatical and minor typographical error corrections) were implemented throughout the protocol.

Amended protocol 04 (18 February 2022)

This amended protocol 04 (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to incorporate feedback from health authorities, expand the population to include omalizumab-incomplete responders, as well as other clarifications and corrections deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page Section 1.1 Synopsis Section 4.1 Overall design	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.
Section 1.1 Synopsis (Brief summary)	Revised text to add Week 14: "Due to the fact that some participants may be receiving rilzabrutinib for the first time, all participants will be monitored at **Week 14**,Week 16, Week 20, and Week 24".	Clarification.
Section 1.1 Synopsis (Number of participants) Section 4.1 Overall design	Revised text to add prior use of omalizumab as a stratification factor: **"**stratified by region **and prior use of omalizumab**".	Addition of stratification by omalizumab-treatment status at randomization to maintain balance between omalizumab-naïve and omalizumab-incomplete responders between arms.
Section 1.1 Synopsis (Duration of study period [per participant]) Section 4.1 Overall design	"Post double-blind IMP treatment period" was changed to "Follow-up period." "Post open-label IMP treatment period" was changed to "Follow-up period."	Clarification and accuracy.
Section 1.1 Synopsis	Revised text for formulation of Placebo: "Formulation: tablets (modified-capsule shaped tablets/caplets) (**Each placebo tablet contains the same ingredients as the rilzabrutinib tablets, except that the active ingredient is replaced with mannitol**)".	Consistency with Section 6.1.
Section 1.1 Synopsis	Text on oral corticosteriods was added to the non-investigational medicincal product.	Clarification.
Section 1.2 Schema	Added a footnote **"Omalizumab-incomplete responders will only be randomized to [redacted] mg BID, [redacted] mg TID or placebo".**	Footnote added for clarification of randomization of omalizumab-incomplete responders (see rationale below for further details).
Section 1.2 Schema Section 1.3 Schedule of activity Section 10.9 Appendix 9	Revised text to define the follow-up visit and planned EOT: "Follow up (28 days **after planned EOT**) Planned EOT: Visit 6 (W12), if participant is included in double-blind phase only, and Visit 12 (W52), if participant is included in open label extension (OLE)".	Clarification.
Section 1.3 Schedule of activity	Update SOA procedure header from "Pharmacokinetics" to "Pharmacokinetics / Pharmacodynamics".	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activity	Added **"IgG anti-IgE"** to footnote v.	Clarification.
Section 1.3 Schedule of activity	added a row for "screening IgG" and an X under screening.	Clarification.
Section 1.3 Schedule of activity Section 10.2 Appendix 2 (Table 7)	"Anti-HBs" was removed from Footnote l of SoA and table 7 and "Estradiol" was removed from Table 7.	Clarification because these lab tests are not needed in the study.
Section 2.1 Study Rationale	Revised to include the scientific rationale and benefits of including omalizumab-incomplete responders.	Changes to support the inclusion of omalizumab- incomplete responders to the study.
Section 2.2 Background	Updated "Clinical Experience" based on the new version of Investigator's Brochure (IB) Ed-12 dated 14 June 2021.	To include updated information and maintain consistency with the current IB.
Section 1.1 Synposis Section 3 Objectives and endopints	Deleted "Percentages of participants experiencing treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) during the double-blind phase**"** "Percentages of participants experiencing TEAEs or SAEs during the open-lable extension (OLE) phase**"** and replaced by: "**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".**	Clarification.
Section 4.2 Scientific Rationale for Study Design	The following text was added "who are either naïve to omalizumab or are incomplete responders to omalizumab".	Changes to align with the inclusion of omalizumab-incomplete responders to the study.
Section 4.3 Justification for Dose	[redacted]	PRN1008-010 study does not include 600 mg BID dose. Changes to provide rationale for randomizing the 400 mg BID and 400 mg TID doses only.
Section 5.1 Inclusion Criteria	The following text was added to I 05: **"OR omalizumab-incomplete responders (as determined by the Site Investigator and defined as inadequate control of CSU symptoms despite treatment with omalizumab 300 mg every 4 weeks for at least 3 months (minimum 3 injections). Note: Documentation of incomplete response must be documented in the patient's medical records)."**	Changes to align with the inclusion of omalizumab-incomplete responders to the study.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	[redacted]	
Section 5.1 Inclusion Criteria	[redacted]	For consistency with other rilzabrutinib studies.
Section 5.2 Exclusion Criteria	[redacted]	[redacted]
Section 5.2 Exclusion Criteria	[redacted] "E 10. Participant with any other medical or psychological condition including relevant laboratory or electrocardiogram (ECG) abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for participants excluded under this criterion will be noted in study documents (chart notes, CRF, etc)".	
Section 5.2 Exclusion Criteria	[redacted]	

Section # and Name	Description of Change	Brief Rationale
	[redacted]	
Section 5.2 Exclusion Criteria	[redacted]	Clarification.
Section 5.2 Exclusion Criteria	[redacted]	
Section 5.2 Exclusion Criteria		
Section 6.1 Study Intervention(s) administrated	Footnote a for quantitative composition of the study interventions added to table 3.	Clarification.
Section 1.1 Synopsis Section 6.1 Study Intervention(s) administered	[redacted]	
Section 1.1 Synopsis Section 6.1 Study Intervention(s) administered	[redacted]	

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Randomization) Section 6.3 Measures to minimize bias: randomization and blinding Section 9.1 Sample size determination	Revised text to add prior use of omalizumab as a stratification factor "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 (refer to Section 5.1 for definition of omalizumab-incomplete responders).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".	Addition of stratification by omalizumab-treatment status at randomization to maintain balance between omalizumab-naïve and omalizumab-incomplete responders between arms.
Section 6.4 Study Intervention Compliance	Removed the last bullet point "Proper placement of tear-off label for accounting purposes".	Deletion because not applicable to the study.
Section 6.8 Concomitant Therapy	Added Table 5 Prohibited Concomitant Therapy.	Clarification.
Section 6.8 Concomitant Therapy	[redacted]	
Section 8.1 Efficacy Assessments	Revised text to clarify when participants should return their e-diary: "the e-diary will be downloaded and returned to the site **at the end of the study participation".**	Clarification.
Section 8.2.2 Vital signs	Revised vital signs to add sitting position as follows: "Vital signs will be measured in a semi-supine or sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate".	Clarification.
Section 8.3.5 Pregnancy	Removed paragraph that mentions participants may continue study intervention after pregnancy under certain conditions. "Prior to continuation of study intervention following pregnancy, the following must occur: • The Sponsor and the relevant IRB/IEC give written approval. • The participant gives signed informed consent. • The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring".	Clarification for consistency with section 8.3.5 which states that : "Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study."
Section 8.3.6 Disease-related events and/or Disease-related outcomes not qualifying as AEs or SAEs	Inserted a cross-reference in Section 8.3.6 to Section 10.3.1 "for disease-related events not meeting the AE definition".	Clarification.
Section 8.3.7 Adverse event of special interest	Revised to clarify the definition of overdose with NIMP	Clarification.

Section # and Name	Description of Change	Brief Rationale
	"An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the maximum allowed daily dose, within the intended therapeutic interval. **For H1-AH only, an overdose is defined as any dose that exceeds the maximum allowed daily dose in this protocol (see Section 6.1 and Section 6.8.1)".**	
Section 1.1 Synopsis Section 9 Statistical considerations (Multiplicity)	Added detailed information on how the efficacy of the investigational product will be assessed at each dose level.	Clarification.
Section 9.2 Population for analyses	Added "omalizumab-naïve" to table 6 and detailed description was added. The following text was added "The efficacy endpoints analyses will be primarily based on the omalizumab-naïve population. ITT population will be used as the supplementary analysis for selected efficacy endpoints".	Change to clarify that the primary analysis population remains as omalizumab-naïve participants only.
Section 9.3.1 General Consideration	Revised text for efficacy analyses as follows: "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".	Consistency with section 9.2 and clarification that ITT population will be used as supplementary analysis.
Section 1.1 Synopsis Section 9.3.2 Primary endpoints	Population was changed from "Intent-to-treat" to "Omalizumab-naïve".	Change to clarify that the primary analysis population remains as omalizumab-naïve participants only.
Section 9.3.2 Primary endpoints	The following text was deleted " In the ANCOVA model, comparison between each dose level of rilzabrutinib and placebo will be based on the trend test using below SAS example code Proc glm; class TRT01PN REGION; Model CHG = TRT01PN REGION BASE; Estimate 'High dose rilzabrutinib 400 mg TID vs. Placebo' TRT01PN -1 0 0 1; Estimate 'Medium dose rilzabrutinib 400 mg BID vs.Placebo' TRT01PN -1 0 1 0; Estimate 'Low dose rilzabrutinib 400 mg QPM vs.Placebo' TRT01PN -1 1 0 0; Run;	Removed SAS Coding from protocol as it is found to be unnecessary.

Section # and Name	Description of Change	Brief Rationale
	Note: TRT01PN values of 0,1,2 and 3 represent the Placebo, rilzabrutinib 400 mg QPM, rilzabrutinib 400 mg BID and rilzabrutinib 400 mg TID, respectively".	
Section 9.3.2.3 Supplementary analysis	Added a new section 9.3.2.3 for supplementary analysis and related content to clarify that as-observed analysis and other supplementary analysis will be performed.	Clarification.
Section 1.1 Synopsis Section 9.4 Interim analysis	[redacted]	
Section 10.1.7 Data quality assurance	Added text for Quality tolerance limits (QTLs).	Update in accordance with Sponsor's template.
Section 10.2 Appendix 2 -Table 7	Deletion of footnote b "If alkaline phosphatase is elevated, consider fractionating".	Fractionating of alkaline phosphatase is not performed by the central laboratory.
[redacted]		
Section 10.11 Abbreviation and Definitions	The abbreviation list was updated.	Changes made for accuracy.
Section 11 References	The references were updated and re-numbered in the list and body of amended protocol.	Changes made for accuracy.

In addition, other minor editorial changes (eg, grammatical and minor typographical error corrections) were implemented throughout the protocol.

Amended protocol 03 (19 October 2021)

[redacted]

OVERALL RATIONALE FOR THE AMENDMENT

[redacted]

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (E 06, E 34), 5.4 Screening Failures, 6.8 Concomitant Therapy	Cross-reference added for Section 10.8.3 to refer to Italy-specific requirements	Clarification

[redacted]

Amended protocol 02 (06 October 2021)

[redacted]

OVERALL RATIONALE FOR THE AMENDMENT

[redacted]

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
[redacted]		

[redacted]

Amended protocol 01 (15 September 2021)

This amended protocol 01 (amendment 01) version 2, based upon the request of German Ethics Committee and Health Authority, is applicable in Germany only and is considered to be substantial, based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to meet German requirements to be consistent with the German GCP ordinance (§ 12 (4) GCP-V).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
[redacted]		

Section # and Name	Description of Change	Brief Rationale
Version 1		
[redacted]		
Version 2		
[redacted]		

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