NCT05018806

AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A Phase 2, randomized, double-blind, placebo-controlled, multicenter proof-of-concept study evaluating efficacy and safety of rilzabrutinib in adult patients with moderate-to-severe atopic dermatitis who are inadequate responders or intolerant to topical corticosteroids**
Protocol number:	**ACT17207**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444671** **rilzabrutinib/Not available**
Brief title:	**Proof of concept study of rilzabrutinib in adult patients with moderate-to-severe atopic dermatitis**
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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Date: 24-Aug-2022 Total number of pages: 133

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 03	*All*	*24 August 2022. Version 1 (electronic 3.0)*
Amended Clinical Trial protocol 02	*All*	*03 January 2022. Version 1 (electronic 2.0)*
Amended Clinical Trial protocol 01	*All*	*08 July 2021, version 1 (electronic 1.0)*
Original Protocol		*14 May 2021, version 1 (electronic 2.0)*

Amended protocol 03 (24 August 2022)

This amended protocol 03 (amendment 03) 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:
  - To update the liver-related exclusion criterion to harmonize all protocols within the rilzabrutinib program whatever the indication by excluding patients with AST or ALT >1.5 x ULN (exclusion criterion E 03).
  - 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 02.
  - To modify the exclusion criterion E 04 to strengthen that all medical decisions in the clinical trial are under the responsibility of the investigator in line with ICH E6 (R2) principles.

- To update inclusion criteria as follows:
  - To allow patients with an EASI score ≥ 12 within screening period and at baseline (inclusion criterion I 04).
  - To allow Investigator documentation based on communication with the patient's pharmacist or the patient as acceptable documentation for inadequate response or intolerance to topical corticosteroids.

- To clarify that H2 receptor blocking drugs can only be taken once daily in the evening for the TID regimen since 2-3 hours must separate the H2-receptor blockers and the IMP.
- [redacted]

In addition, clarifications and corrections deemed necessary by the Sponsor will 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 1.1 Synopsis (Number of participants) Section 1.2 Schema Section 4.1 Overall design Section 9.2 Populations for analyses	Added in the wording “main study, “For the main study” or “(for main study only)” to clarify that this statement is applicable for the main study only.	Clarification and accuracy

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SOA)	Footnote d was reworded as follows: "Optional, only for participants who do not have a history of skin prick testing or RAST and at sites that have the capability to perform the test. The test will be done at Screening, and results should be collected in the corresponding electronic case report form (eCRF) page"	Clarification
	Added a row for "BSA" and an X under V1, V2, V3, V4, V5, V6, V7 and unscheduled visit.	Changes made for accuracy as BSA assessment will be performed.
	Added "and at V3" to footnote p	Changes made for accuracy
[redacted]	[redacted]	[redacted]
Section 2.2 Background	Updated "Clinical Experience" based on the new version of Investigator's Brochure (IB).	To include updated information and maintain consistency with the current IB.
Section 2.3.1 Risk assessment	Decreased AST and ALT exclusion threshold to > 1.5 x ULN in Table 1	To harmonize all protocols within the rilzabrutinib program whatever the indication
Section 4.1 Overall design	Added information related to Japan substudy.	Clarification and accuracy
	Revised information related to end of study (EOS): "The End of Treatment (EOT) visit is planned on Week 16 after the last dose of IMP (morning of Week 16 visit). The End of Study (EOS) visit will be 7 days after the last dose of IMP (refer to Section 7.1 in case of early discontinuation)."	Correction
	Added the following text: "At sites able to conduct RAST testing or skin prick testing." Cross-reference to section 1.3 footnote d is added.	Changes were made for consistency and accuracy.
Section 5.1 Inclusion Criteria	I 04 was reworded to allow patients with EASI score ≥ 12 during the screening phase and at baseline (instead of ≥ 16) and added footnote a for the possibility of EASI score re-testing at screening: a. Patients with EASI score between 10 to 12 may be re-tested once during screening phase if, per investigator's judgement, the results may evolve up to ≥12 during screening	Changes were made to harmonize the threshold value between screening and baseline. This modification is aimed at decreasing the number of screened failures due to EASI score that has not increased up to 16 between screening and baseline. It nevertheless: - does not modify the targeted population of moderate to severe AD defined with an

Section # and Name	Description of Change	Brief Rationale
		EASI score ≥ 7.1 and an IGA score ≥3 (inclusion criterion I.05)[a] - does not jeopardize the study results since the Minimal Clinically Important Difference (MCID) for change in absolute EASI (almost 7 points) can still be assessed by this EASI score threshold of 12 at baseline (Schram, 2012)
	Update footnote b in I 07 as follows: "Acceptable documentation includes contemporaneous chart notes that recorded TCS prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician, the **patient's pharmacist, or the patient**."	Changes were made to increase the flexibility of this documentation by allowing fulfillment based on Investigator's assessments using pharmacy confirmation, or even discussion with the patients themselves.
Section 5.2 Exclusion Criteria	Removal of the statement "~~and the Sponsor Medical Monitor~~" within exclusion criterion E04 to let the investigator be the sole judge for considering serious infections requiring intravenous therapy with the potential for recurrence.	To reinforce that all medical decisions in the clinical trial are the responsibility of the investigator in line with ICH E6 (R2) principles.
	Updated E 02 to provide examples on clinically significant disease, conditions, or medical history. "Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with participant safety, trial evaluations, and/or trial procedures. 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), hepato-biliary conditions such as 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, active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases."	Clarification

Section # and Name	Description of Change	Brief Rationale
	Revised text for E 03: • Decreased AST and ALT exclusion threshold to >1.5 x ULN: "Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)". • Added the following text: "Note: a one-time retest at screening may be performed by the Investigator if abnormal laboratory test values are found".	To harmonize all protocols within the rilzabrutinib program whatever the indications Changes were made to give the Investigator the possibility of one-time retest at screening for abnormal laboratory values
Section 5.2 Exclusion Criteria Section 6.8 Concomitant therapy	Added the word "systemic" to "strong-to-moderate" in E20 and in concomitant therapy section to specific that only systemic moderate or strong inhibitors and inducers of CYP3a are prohibited.	Changes were made for clarification and accuracy.
Section 6 Study intervention (s) and concomitant therapy	Revised text to clarify that a question about food intake will be administered at end of treatment: "Participants will administer rilzabrutinib by mouth twice daily or 3 times a day with or without food starting on Day 1. The frequency and/or severity of gastrointestinal AEs may be improved if rilzabrutinib is taken with food. **A question about intake with food will be administered at end of treatment.**"	Added information about an additional question that will be asked at the end of treatment
Section 6.4 Study intervention compliance	Added the following text: "for the main study. [redacted]	Changes made for clarification and accuracy.
Section 6.8 Concomitant therapy	Revised information related to Histamine 2 (H2) receptor blocking drugs as follows: "Histamine 2 (H2) receptor blocking drugs ~~(ranitidine or famotidine) and antacids~~ are permitted provided they can be given 2-3 hours after administration of rilzabrutinib or placebo. For participants receiving the IMP three times a day, H2-receptor blockers must be taken once daily only, 2-3 hours after the evening dose of rilzabrutinib or placebo."	Changes were made to clarify that, for the TID cohort, H2 receptor blocking drugs can only be taken once daily in the evening to ensure there should be 2-3 hours between the H2-receptor blockers administration and the IMP administration.
	Information related to Antacids are added as a separate bullet point: "Antacids are permitted provided they are given 2 hours or more apart from rilzabrutinib or placebo".	Clarification
Section 6.8 Concomitant Therapy	Deleted the word "Sponsor" from the following text: "Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator ~~and Sponsor~~, the medication will not interfere with the study."	To reinforce that all medical decisions in the clinical trial are the responsibility of the investigator in line with ICH E6 (R2) principles.
Section 8.2.4 Clinical Safety laboratory assessments	In the last bullet point; cross reference to Section 10.3 and Section 10.6 is added.	Changes made for clarification.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.7 Adverse event of special interest	Updated bullet point related to ALT as follows: "Increase in ALT >3 × ULN **confirmed by retest within 72 hours of initial sample**; see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6) that recommends to also measure total bilirubin upon reconfirmation of ALT >3 x ULN."	Changes were made for clarification.
Section 1.1 Synopsis (Objectives and endpoints) Section 3 Objectives and endpoints Section 9.3.3.2 Other secondary endpoint(s)	Added the following secondary endpoint: Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by ≥ 50% or 75% or 90% from baseline) at Week 16.	To explore the assessment of AD by using IGA*BSA as an alternative measure of the disease severity and improvement overtime in participants with AD.
Section 9.3.4 Exploratory endpoint(s)	Update the below endpoint as: Change and percent change in EASI score and PP-NRS in subgroups of participants with Screening IgE level< or ≥ 300 UI/ml from baseline to Week 16.	Changes to clarify this exploratory endpoint
Section 10.2 Appendix 2: Clinical laboratory tests-Table 7	Added RAST or skin prick test	Changes made for accuracy
[redacted]	[redacted]	[redacted]
Section 10.11.2 Non-exhaustive list of live (attenuated) vaccines-Table 13	In footnote a, the word "Sringrix" changed to "Shingrix"	Typo correction

In addition, other minor editorial changes were implemented throughout the protocol.

a Y.A. Leshem, T. Hajar, J.M. Hanifin and E.L. Simpson. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. British Journal of Dermatology 2015; 172:1353.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2, randomized, double-blind, placebo-controlled, multicenter proof-of-concept study evaluating efficacy and safety of rilzabrutinib in adult patients with moderate-to-severe atopic dermatitis who are inadequate responders or intolerant to topical corticosteroids

Brief title:

Proof of concept study of rilzabrutinib in adult patients with moderate-to-severe atopic dermatitis

Rationale:

Rilzabrutinib (also known as SAR444671 or PRN1008), a selective Bruton's tyrosine kinase (BTK) inhibitor, is an investigational drug being developed as an oral agent for the treatment of immune-mediated dermatological diseases. This study will explore the efficacy and safety of rilzabrutinib in participants with moderate to severe atopic dermatitis (AD). See Study Rationale, Section 2.1.

Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess the efficacy of rilzabrutinib in participants with atopic dermatitis (AD)	• Percent change from baseline to Week 16 in Eczema Area and Severity Index (EASI) score.
Secondary	
• Assess the efficacy of rilzabrutinib at different time points	• Proportion of participants with Investigator's Global Assessment (IGA) of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16. • Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16. • Proportion of participants with reduction of weekly average of daily peak pruritus Numerical Rating Scale (PP-NRS) of ≥4 points from baseline at Week 16. • Time to onset of effect on pruritus (≥ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period). • Absolute change from baseline to Week 16 in EASI score. • Proportion of participants achieving EASI-50/90 (reduction of EASI score by ≥ 50% or ≥90% from baseline) at Week 16.

	• Change from baseline to Week 16 in percent body surface area (BSA) of EASI. • Change (absolute and percent change) on weekly average of daily PP-NRS based on daily participant assessments documented in their electronic diary (e-diary) from baseline to Week 16. • Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by ≥ 50% or 75% or 90% from baseline) at Week 16.
• Assess the safety of rilzabrutinib	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) from baseline to Week 16. • Incidence of study investigational medicinal product (IMP) discontinuation and withdrawals due to TEAEs from baseline to Week 16.

Overall design:

This is a parallel, treatment, Phase 2, double-blind, 2-arm, placebo-controlled study with 2 staggered cohorts (2 arms in each cohort) to evaluate the efficacy and safety of rilzabrutinib in adult participants (aged at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to topical corticosteroids (TCS).

An optional substudy will be proposed to participants for skin tape strip samples to be taken at baseline and Week 16 for exploratory biomarkers analysis.

[redacted]

Brief summary:

This is a parallel, treatment, Phase 2, double-blind, 2-arm, placebo-controlled study with 2 staggered cohorts (2 arms in each cohort) in adult participants (aged at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to TCS.

Participants will be enrolled into 2 staggered dose regimen cohorts, twice a day (BID) cohort and three times a day (TID) cohort, starting with the BID cohort. These 2 dose regimen cohorts will be evaluated with the same double-blind fashion and planned assessments in this study.

Adult participants who meet the inclusion/exclusion criteria will be stratified by immunoglobulin E (IgE) levels (< or ≥300 UI/mL) at Screening and will be randomized in a 3:2 allocation ratio to receive either rilzabrutinib or matching placebo on Day 1 (Week 0, Visit 2). The total study duration per participant is expected to be approximately 21 weeks: including up to 4 weeks for Screening, 16 weeks on-treatment double-blind period, and 1-week post-treatment follow-up. Visits during the on-treatment period will be at Week 0, 2, 4, 8, 12 and 16.

Number of participants:

Approximately 120 adult participants will be enrolled in the main study and randomized in a 3:2 allocation ratio to receive either rilzabrutinib or matching placebo on Day 1 (Week 0, Visit 2) in the BID and TID cohorts, respectively. In the BID cohort, approximately 50 participants will receive either rilzabrutinib (n = 30) or matching placebo (n = 20) twice a day, and in the TID cohort, approximately 70 participants will receive either rilzabrutinib (n = 42) or matching placebo (n = 28) three times a day.

[redacted]

- Rilzabrutinib TID (morning, midday and evening) for participants enrolled in rilzabrutinib TID arm.
- Rilzabrutinib BID (morning and evening) and matching placebo QD (midday) for participants enrolled in rilzabrutinib BID and placebo QD arm.
- Matching Placebo TID (morning, midday and evening) for participants enrolled in matching Placebo TID arm.

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

The total study duration per participant is expected to be approximately 21 weeks, including:

- Screening: up to 4 weeks
- Double-blind investigational medicinal product (IMP) treatment period: 16 weeks ± 3 days
- Post-treatment follow-up: 1 week ± 3 days.

Study intervention(s)

Investigational medicinal products: Rilzabrutinib and placebo

Rilzabrutinib (SAR444671)

- Formulation: tablets (modified-capsule shaped tablets / caplets)
- Route of administration: oral
- Dose regimen: 400 mg BID (morning and evening) or TID (morning, midday and evening).

Placebo

- Formulation: tablets (modified-capsule shaped tablets / caplets) (identical in appearance and contain the same inactive ingredients as that of the rilzabrutinib formulation, but do not contain rilzabrutinib)
- Route of administration: oral

- Dose regimen: BID (morning and evening) or TID (morning, midday and evening).

Rilzabrutinib or placebo may be taken with or without food (gastrointestinal tolerability may be better if given with food). Consecutive doses should ideally be administered 12 hours apart (and not less than 8 hours apart) for BID dosing, and ideally at least 6 hours apart (and not less than 4 hours apart) for TID dosing.

Noninvestigational medicinal products: Not applicable.

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

Statistical considerations:

Sample size consideration

Sample size calculations were performed to ensure reasonable accuracy for the estimation of the treatment difference in percent change in Eczema Area and Severity Index (EASI) score from baseline to Week 16 between rilzabrutinib and placebo. For the BID cohort, a sample size of 50 participants enrolled with a ratio of 3:2 between rilzabrutinib and placebo and a common standard deviation (SD) of 40 will provide a half-width for the 2-sided 90% confidence interval (CI) of less than or equal to 19.0%. For the TID cohort, a sample size of 70 participants enrolled with a ratio of 3:2 between rilzabrutinib and placebo and a common standard deviation (SD) of 40 will provide a half-width for the 2-sided 90% confidence interval (CI) of less than or equal to 16.1%.

[redacted]

Randomization

Approximately 50 participants will be randomized (3:2) in the BID cohort to the following treatment groups: rilzabrutinib 400 mg BID and placebo. The randomization will be stratified by IgE levels (< or ≥ 300 UI/mL) at Screening.

Approximately 70 participants will be randomized (3:2) in the TID cohort to the following treatment groups: rilzabrutinib 400 mg TID and placebo. The randomization will be stratified by IgE levels (< or ≥ 300 UI/mL) at Screening.

[redacted]

General consideration

The BID cohort and TID cohort will be analyzed separately. A pooled analysis of the BID and TID cohort may also be performed as appropriate. [redacted] The details will be described in the SAP.

Primary endpoint

The primary endpoint is percent change from baseline to Week 16 in EASI score.

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

- Treatment: rilzabrutinib and placebo
- Population: Intent-to-treat (ITT) population
- Endpoint: percent change from baseline to Week 16 in EASI score
- Intercurrent events handling strategy:
  - Discontinuation of study intervention

    For participants who discontinue the study intervention, all data collected after discontinuation will be used in the analysis (treatment policy strategy).
  - Receiving selected rescue medications

    For participants who receive high potency TCS or systemic medication as rescue treatment (see Section 6.8.1 for rescue) before Week 16, data collected post the rescue treatments will be set to missing. The worst postbaseline value on or before the time of the rescue treatments will be used to impute missing Week 16 value (for participants whose postbaseline values are all missing, the baseline will be used to impute) (hypothetical strategy).
- Population-level summary (analysis and missing data handling):
  - Mean percent change difference between rilzabrutinib and placebo from analysis of covariance (ANCOVA).
  - The missing data are handled as follows:

    After discontinuation of the study intervention due to lack of efficacy prior to Week 16: “worst observation carried forward” 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 16: multiple imputation (MI) approach will be used to impute missing endpoint value, and this MI will use all participants excluding participants who have been rescued with the high potency TCS or systemic medication (see Section 6.8.1 for rescue) prior to Week 16 and excluding participants who discontinue due to lack of efficacy prior to Week 16.
  - Each of the imputed complete data will be analyzed using ANCOVA model with percent change in EASI score from baseline to Week 16 as response variables, treatment and randomization stratification of Screening IgE level ($< \text{or} \geq 300$ UI/mL) as fixed effects, and baseline EASI score as covariates. 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) means will be provided. In addition, difference in LS means and the corresponding 90% CI will be provided along with the p-values.

Main secondary endpoints

- Proportion of participants with Investigator's Global Assessment (IGA) of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16

- Proportion of participants achieving EASI-75 (reduction of EASI score by ≥ 75% from baseline) at Week 16
- Proportion of participants with reduction of weekly average of daily peak pruritus Numerical Rating Scale (PP-NRS) of ≥4 points from baseline at Week 16

The main secondary efficacy endpoints will be analyzed using the Cochran-Mantel- Haenszel (CMH) test adjusted by randomization stratification of Screening IgE level (< or ≥300 UI/mL) in the ITT population. For the binary efficacy endpoints, if high potency TCS or systemic medications are used, the participant will be specified as a non-responder from the time the rescue is used. If a participant withdraws from the study, this participant will be counted as a non-responder for endpoints after withdrawal.

Multiplicity considerations

No adjustments for multiplicity are planned for this Phase 2 study. More specifically, no adjustments will be made in comparing the treatment groups based on the secondary efficacy endpoints and no adjustments will be made for the subgroup analyses. Reported p-values for the secondary endpoints will be nominal p-values.

Interim analysis

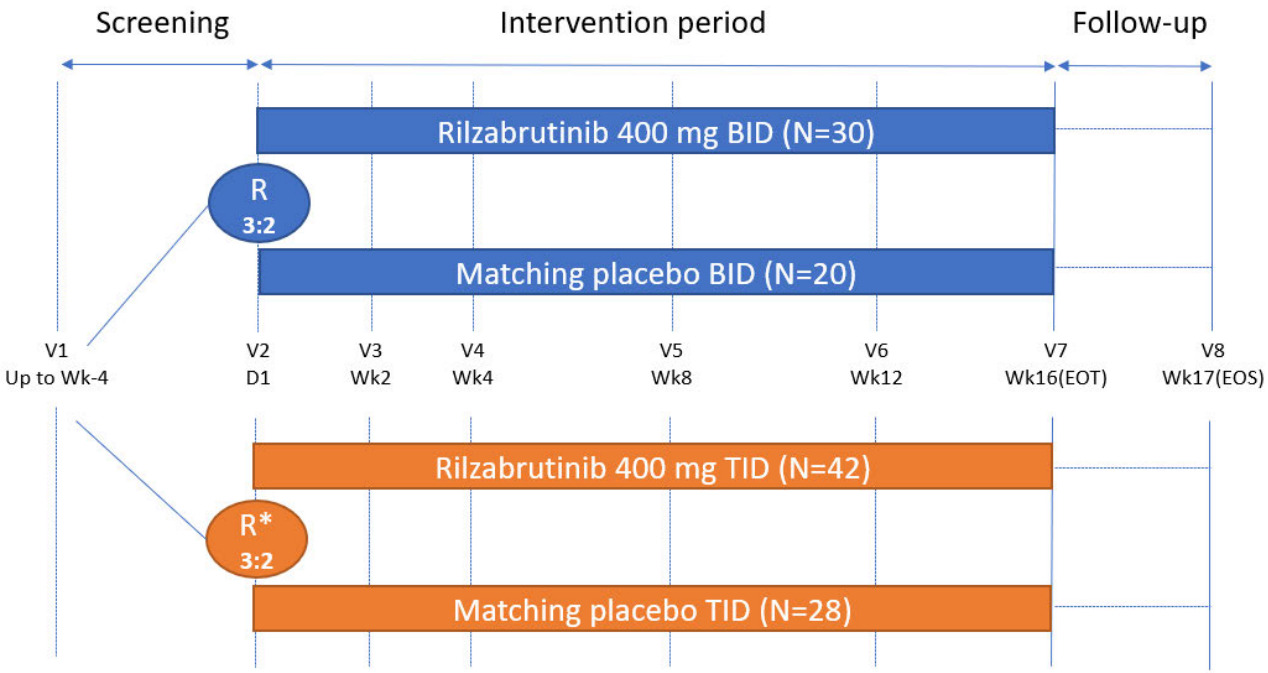
Interim analysis may be performed before the final database lock for this study. The details will be described in the statistical analysis plan (SAP).

Data Monitoring/Other committee: No

1.2 SCHEMA

:

Figure 1 - Graphical study design (For main study only)



R*: the randomization of TID cohort will start after the enrollment of the BID cohort.
BID: twice a day; D: Day; EOS: End of Study; EOT: End of Treatment; N: number of participants; R: randomization; TID: three times a day; V: visit; Wk: week.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before Day 1)	Intervention Period (16 Weeks)						Follow-up (7 days after last IMP dose)	Unscheduled visit (if applicable)[a]
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (EOT)[y]**	**V8 (EOS)**	**V100**
Week (Wk)		**Wk0**	**Wk2**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk17**	
Day (D)	**D-28 to D-1**	**D1**	**D15±3d**	**D29±3d**	**D57±3d**	**D85±3d**	**D113±3d**	**D120±3d**	
Informed consent[b]	X								
Inclusion and exclusion criteria	X	X[c]							
Randomization		X							
Demographics	X								
Medical history and prior medications	X								
Skin prick testing/RAST[d]	X								
Treatment									
Dispense IMP		X	X	X	X	X			(X)[x]
e-diary training	X								
e-diary daily completion by participant[e]	←----------							----------→	X
e-diary review		X	X	X	X	X	X		X
Concomitant medications		X	X	X	X	X	X	X	X
Safety									
Complete physical examination including height and weight[f]	X								
Abbreviated physical examination including weight[g]		X	X	X	X	X	X	X	X
Adverse events	←----------							----------→	X
Hematology[h]	X	X	X	X	X	X	X	X	X
Coagulation[i]	X	X	X	X	X	X	X	X	X
Serum chemistry[j]	X	X	X	X	X	X	X	X	X
Urinalysis[k]	X								
Vital signs[l]	X	X	X	X	X	X	X	X	X

Procedure	Screening (up to 28 days before Day 1)	Intervention Period (16 Weeks)						Follow-up (7 days after last IMP dose)	Unscheduled visit (if applicable)[a]
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7 (EOT)[y]**	**V8 (EOS)**	**V100**
Week (Wk)		**Wk0**	**Wk2**	**Wk4**	**Wk8**	**Wk12**	**Wk16**	**Wk17**	
Day (D)	**D-28 to D-1**	**D1**	**D15±3d**	**D29±3d**	**D57±3d**	**D85±3d**	**D113±3d**	**D120±3d**	
12-lead ECG	X						X		
Hep B and C[m], HIV testing	X								
COVID-19 testing[n]	X								
QuantiFERON (TB)[o]	X								
Pregnancy test (WOCBP only)[p]	X	X		X	X	X	X	X	
Biomarker									
Total IgE, total IgG, and total IgM	X[q]	X	X		X		X		
Sampling for soluble biomarker assays[r]		X	X		X		X		
Sampling for BHRA assay		X						X	
Blood draw for Immune cell phenotyping[s]		X	X		X		X		
BTK occupancy sample[t]		X	X	X	X	X	X		X
Serum and plasma sample for future use (optional)		X					X		
Whole blood sample for RNA extraction for future use (optional)[u]		X					X		
Skin tape strip (optional)		X					X		
PK									
PK sampling[v]		X	X	X	X	X	X		X
Efficacy Outcome Assessment									
EASI	X	X	X	X	X	X	X		X
BSA	X	X	X	X	X	X	X		X
IGA		X	X	X	X	X	X		X
Pruritus NRS[e, w]		X	X	X	X	X	X		X
Optional AD area photographs		X					X	X	

Abbreviations: AD = atopic dermatitis; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BHRA = Basophil Histamine Release Assay; BTK = Bruton's tyrosine kinase; COVID-19 = coronavirus disease 2019; CPK = creatine kinase; D = day; EASI = eczema area and severity index; eCRF = electronic case report form; e-diary =

electronic diary; ECG = electrocardiogram; ED = early discontinuation; EOS = End of Study; EOT = End of Treatment; Hep B (HBV) = hepatitis B virus; Hep C (HCV) = hepatitis C virus; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IGA =Investigator's global assessment; IgE = immunoglobulin E; IgG = immunoglobulin G; IL = interleukin; IMP = investigational medicinal product, INR = international normalized ratio; LDH = lactate dehydrogenase; NRS = Numerical Rating Scale; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cell; QFT = QuantiFERON test; RAST = radioallergosorbent test; RBC = red blood cell; TARC = thymus and activation regulated chemokine; TB = tuberculosis; TBNK = T, B, and natural killer cells; WBC = white blood cell; WOCBP = woman of childbearing potential; V = visit; Wk = week.

a Unscheduled visit may be used for early discontinuation (ED) or when participant needs a rescue medication for atopic dermatitis (AD). When this visit is used for ED, all scheduled EOT assessments should be performed.

b Informed consent will cover the consents of optional skin tape strip substudy, the optional serum and plasma sample for future use, and the optional photographs of AD area.

c Prior to randomization.

d Optional, only for participants who do not have a history of skin prick testing or RAST and at sites that have the capability to perform the test. The test will be done at Screening, and results should be collected in the corresponding electronic case report form (eCRF) page.

e Participants will record pruritus Numerical Rating Scale (NRS) scores and background topical treatment (ie, moisturizers/emollients) in the e-diary everyday from Screening visit up to the EOT. Participants will record rilzabrutinib dosing times and the compliance with rilzabrutinib and background topical treatment in the e-diary everyday during the intervention period of the study. Participants should also record all temporary intervention discontinuations in the e-diary everyday (when applicable) during the study intervention period.

f Complete physical examination includes, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems, height and weight.

g Abbreviated physical examination includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and weight.

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

i Coagulation includes international normalized ratio (INR) test and activated partial thromboplastin time (aPTT).

j Serum chemistry includes aspartate aminotransferase (AST); alanine aminotransferase (ALT); total, direct, and indirect bilirubin; alkaline phosphatase (ALP); lactate dehydrogenase (LDH); creatinine; blood urea nitrogen; high-sensitivity C-reactive protein (hs-CRP) and creatine kinase (CPK). Liver function test (ie, ALT, AST, total, direct, & indirect bilirubin and ALP) will be tested at each visit; LDH, creatinine, blood urea nitrogen and hs-CRP will be tested at baseline, Week 8 and Week 16; CPK will be tested at baseline and Week 16.

k Urinalysis includes pH, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes by dipstick and specific gravity. Microscopic examination will be performed if dipstick analysis of blood or protein is abnormal.

l Vital signs include systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), and body temperature (°C).

m Hep 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 3 months prior to the Screening visit [redacted]

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 final dose of the vaccine.

o To be performed for participants without documented negative screening for TB via a negative QFT within 3 months prior to Screening (and if required per local standard of care, a chest X-ray).

p Only for WOCBP: serum pregnancy test (β-HCG test) at Screening/V1 and urine pregnancy tests at every visit except at Screening and at V3. 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 study intervention discontinuation in all cases.

q During Screening, total serum IgE and IgG will be tested. Participants will be stratified by this IgE levels (< or ≥300 UI/mL) upon randomization.

[redacted]

u Whole blood sample is drawn into Paxgene RNA tubes for RNA stabilization.

v On Week 0, 4, 12 visits, PK samples will be collected at predose (1 hour within clinical visit dose for week 4 and 12 samples) and 2 hours (±15 minutes) post-dose. On Week 2, Week 8, and Week 16 visits, PK samples will be collected at predose (1 hour within clinical visit dose). At unscheduled visits (if any), samples will be taken at random times after last dose (with time of last dose recorded on eCRF). For predose PK collection: morning clinical visits are preferred, and participants should take the morning dose at the clinic. If morning visits are not possible, morning dosing time should be recorded in e-dairy as accurate as possible

w The pruritus NRS scores are assessed by the Investigator at the baseline visit (using the data collected by participant on the e-diary beginning 7 days preceding the baseline visit), and at visits during the on-treatment period (including the unscheduled visits, if any).

x If needed, according to Investigator (eg, end of temporary discontinuation, etc).

y The last dose of IMP should be taken in the morning of Visit 7 (Week 16).

2 INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, relapsing, pruritic, inflammatory skin disease. It is characterized by xerosis and acute (erythematous papules, vesicles, edema, exudation, crusting), subacute and chronic (scaly, erythematous papules and plaques, lichenification, excoriations, fissuring) eczematous skin lesions (1,2,3,4,5). Itching is the central and debilitating manifestation, aggravated by mechanical injury inflicted by uncontrolled scratching and leading to bacterial, fungal and viral infections (particularly staphylococcus aureus and herpes simplex type 1) (6). Intense pruritus has a considerable negative impact on quality of life (QoL), sleep, and possible mental health disorders including anxiety and depression.

Typically, AD presents with an age-related morphology and distribution (2,3). The global prevalence of AD is estimated to be approximately 2-10% in adults. The incidence has increased by 2- to 3-fold during the past 3 decades in industrialized countries. The proportion of adult patients with childhood-onset and adult-onset AD is approximately 4 to 1. Those patients having suffering from AD since childhood commonly present with comorbidities, including food allergy, asthma, and allergic rhinitis and those with adult-onset AD are at risk for systemic complications, including rheumatoid arthritis and inflammatory bowel disease (7).

The pathogenesis of AD is multifactorial and includes abnormalities of the skin barrier, defects in the innate and adaptive immune response and alterations in the resident skin microflora (4):

- Dysregulation of the innate immune system include changes in antimicrobial peptide (AMP) levels, reduced toll-like receptor (TLR) function, increased mast cells in the skin, increased levels of serum IgE, IgE-mediated degranulation and cytokine production, increased thymic stromal lymphopoietin (TSLP) by keratinocytes, increase in eosinophil infiltrates, dermal dendritic cell involvement, and basophil recruitment and activation (4,8,9).
- Abnormalities of the adaptive immune system include an increase in TH2 lymphocytes, increased TH2 cytokine activity A (interleukin-4 [IL-4] and IL-13) which initiates B-cell IgE class switching, increase in TH1, TH17, and TH22 cells and their related cytokine and chemokine production (9). Levels of thymus and activation-regulated chemokine (TARC/CCL17), a member of the T-helper 2 chemokine family, are associated disease activity and sensitively reflect short-term changes in skin conditions (10).

The association between atopy and autoimmune diseases has gained interest in the last decades, likely because the incidences of both allergic- and autoimmune are rising worldwide. Although many studies show an association between IgE autoreactivity and severity of clinical symptoms of AD, the clinical relevance of these IgE autoantibodies in AD is still to be demonstrated since elevated IgE are not specific. About half of the population without AD have elevated IgE and IgE may also be elevated in multiple nonatopic conditions (eg, parasitic infection and certain cancers and autoimmune diseases). For some authors, at least two AD subtypes can be distinguished: the first type is characterized by a strong type 2 mediated response with high levels of serum IgE and the second is a nonallergic type characterized with normal IgE levels (11). The presence of these antibodies in patients with severe and chronic AD may suggest a progression from allergic

inflammation to severe autoimmune processes against the skin. For some others, it is still unclear whether IgE autoreactivity could be an endotype of AD or an epiphenomenon considering that the total IgE level does tend to vary with disease severity (12). Increased knowledge on the clinical relevance and the pathophysiologic role of IgE autoantibodies in AD can have consequences for diagnosis and treatment.

2.1 STUDY RATIONALE

Topical treatments (eg, emollients, corticosteroids, calcineurin or phosphodiesterase 4 inhibitors) are the mainstay of AD therapy. Phototherapy is a second-line treatment, after failure of first-line treatment. Systemic immunomodulating medications are recommended in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or when QoL is substantially impacted.

Topical steroids have to be used intermittently to reduce the localized adverse effects such as skin atrophy, purpura, telangiectasis, and dyspigmentation (9). Furthermore, depending on the body surface area to treat, these topically applied corticosteroids, particularly high- and very high potency agents, can be absorbed at a degree sufficient to cause systemic side effect. Topical calcineurin inhibitors (TCIs) have been used in AD as a steroid sparing treatment, however, these agents include a Food and Drug Administration (FDA) black box warning of a potential increase in the risk of lymphoma. In addition, the use of TCIs has been limited by their inferior efficacy compared to the topical steroids. The most recently FDA approved topical therapy for AD is crisaborole ointment, a cyclic adenosine monophosphate (cAMP) specific phosphodiesterase-4 inhibitor but its moderate efficacy combined with localized adverse effects (significant localized burning and stinging at the site application) has led to the reduced use of crisaborole over TCIs and topical steroids (13).

Repeated application of any topical therapy over a long period of time or too large surface areas may lead to reduced patient compliance and is not recommended due to side effects. These patients therefore need systemic drugs for reducing skin pruritis and inflammation. First generation antihistamines are widely prescribed for acute symptomatic treatment of pruritus, although their effectiveness is limited and largely attributed to their sedating effect. Systemic glucocorticoids are effective, but are associated with side effects such as diabetes, hypertension, and osteoporosis, thus limiting their use to short courses and/or intermittent therapy exposing patients to a risk of rebound after steroid discontinuation.

Only a few systemic therapies have been approved so far for AD:

- Ciclosporin, oral systemic agent approved for severe patients only, and recommended only for intermittent use due its safety profile,
- Dupilumab, a fully human monoclonal antibody directed against the IL-4 receptor α subunit that blocks signaling of both IL-4 and IL-13, key Th2 cytokines. It has the inconvenience of having to be administered subcutaneously every other week with > 10% of patients experiencing site injections reactions. Other common side effects, when used for AD, are conjunctivitis and blepharitis.

- Baricitinib, a Janus kinase (JAK) inhibitor with selectivity for JAK2 and JAK1, and less potency for JAK3 or non-receptor tyrosine-protein kinase (TYK2), or any other JAKi. The JAKs and their associated signal transducers and activators of transcription (STAT) are major intracellular pathways that control the magnitude and duration of signaling for cytokines that bind to Type I and Type II cytokine receptors. Baricitinib has the advantage of once daily oral dosing. However, its safety profile includes increased risk for infections, malignancy and thrombosis, as well as an increased rate in increased low-density lipoprotein (LDL) cholesterol and herpes simplex infection in AD patients compared to rheumatoid arthritis (RA).

Many of the other systemic drugs for moderate-to-severe AD are given off-label, demonstrating a continued unmet need for a safe, effective, and easy to use oral drug in this field. AD is a Th2 inflammatory disease with multiple BTK innate dependent mechanisms (eosinophils infiltration, basophil recruitment and activation, mast cells increase (IgE mediated degranulation and cytokine production), dermal dendritic cells involvement through IgE/FcεR mechanisms). Several orally administered BTK inhibitors, including rilzabrutinib, evobrutinib, and fenebrutinib, are currently in clinical development for a range of immune-mediated diseases such as pemphigus, chronic spontaneous urticaria (CSU), multiple sclerosis (MS), systemic lupus erythematosus (SLE), and RA. The objective of this study is to further assess the efficacy and safety of rilzabrutinib, an oral BTK inhibitor, in patients with moderate-to-severe AD who are inadequate responders or intolerant to topical glucocorticoids.

2.2 BACKGROUND

Bruton's tyrosine kinase (BTK) is an essential signaling element downstream of the B cell receptor (BCR), Fc-gamma receptor (FcγR), and Fc-epsilon receptor (FcεR). BTK is a non-receptor tyrosine kinase and is a member of the TEC tyrosine protein kinase family of kinases (14). BTK activation is critical for B cell differentiation, activation, and maturation. BTK also regulates the activation of other hematopoietic cells, such as mast cells, macrophages, and neutrophils primarily through Fc receptor signaling (15). Platelets express high levels of BTK, which is involved in collagen/glycoprotein VI (GPVI) signaling; however, alternative signaling pathways exist with bypass BTK signaling to retain normal platelet functions and thrombus formation (16,17). BTK integrates BCR signalling to regulate B cell development. IgE antibodies bind FcεR on mast cells and basophils to trigger degranulation and acute inflammation, whereas IgG binds FcγR on macrophages, plasmacytoid dendritic cells (pDCs) and natural killer cells to promote cellular activation or phagocytosis. BTK positively regulates FcεR signalling in mast cells and basophils and FcγR signaling in macrophages or pDCs to internalize and deliver immune complexes to initiate and perpetuate overactive skin immune responses (18). Atopic dermatitis is a pruritic skin condition characterized by a chronic, relapsing form of skin inflammation, a disturbance of the epidermal-barrier function associated with immune changes in the skin, and a high prevalence of immunoglobulin E (IgE)-mediated sensitization to food and environmental allergens with pathogenic roles implicated for B-cells, mast cells and basophils in skin inflammation. BTK appears as an attractive drug target in reducing the inflammation of AD by inhibiting the dysregulated signaling and activation of these pathogenic cells.

BTK inhibition results in the down regulation of various immune cell activities including cell proliferation, differentiation, maturation, survival, cytokine production and the induction of apoptosis. Inhibition of BTK activity in B cells produces phenotypic changes consistent with blockade of the BCR, preventing activation, maturation, and antibody production. Inhibition of BTK in FcγR and FcεR expressing cells (such as macrophages or mast cells) blocks the inflammatory cytokine cascade driven by antibody cross-linking to the surface receptors (19,20). Deficiency or inhibition of BTK has been shown to reduce disease in several immune-mediated rodent models. Pertinent to the treatment of patients with immune-mediated diseases, inhibitors of BTK have been shown to be anti-inflammatory in several rodent models of arthritis (19,20,21,22,23), and lupus (22,24,25) with inhibition of proteinuria, kidney histopathology, nephritis, and cutaneous endpoints. BTK inhibitors also inhibit acute skin inflammation and vasculitis in antibody induced arthus reaction model and murine passive cutaneous anaphylaxis models (19).

Nonclinical Experience

Rilzabrutinib (SAR444671) has been evaluated in various pharmacology, pharmacokinetic, and toxicology studies in mice, rats, and dogs primarily by the intended oral route of administration. Rilzabrutinib demonstrated blockade of the rat arthus reaction, full disease reversal of a rat collagen-induced arthritis model, and reduction in platelet loss in a mouse model of immune thrombocytopenia. The therapeutic effects of rilzabrutinib in pemphigus was studied in dogs with newly diagnosed, naturally occurring pemphigus foliaceus (PF) in an outpatient clinical trial. The drug safely controlled disease without the need for corticosteroid in 4 of 4 cases.

Please refer to the Investigator Brochure (IB) for more details.

Clinical Experience

In clinical studies as reported in the IB dated 15 August 2022, the cumulative exposure to rilzabrutinib in interventional clinical trials is 356 patients including 249 from unblinded studies (11 patients with immunoglobin G4-related disease (IgG4-RD), 78 patients with immune thrombocytopenia (ITP), 158 patients with pemphigus vulgaris (PV), and 2 patients with warm autoimmune hemolytic anemia (wAIHA) and 107 estimated from blinded studies (24 patients with (AD), 9 with asthma, 22 with CSU, and 52 with ITP) according to randomization ratio in Phase 2/3 studies. In addition to 301 healthy participants from Phase 1 studies, so a total of 657 study participants were exposed to rilzabrutinib in clinical development program as of the cut-off date of the most current edition of IB. A total of 153 participants have received rilzabrutinib/placebo (131 patients with Pemphigus and 2 patients with ITP) or placebo/other (20 healthy participants). The maximum administered daily dose is 1200 mg QD or 600 mg BID as immediate release tablets. Twenty-seven participants with pemphigus vulgaris (PV) in a Phase 2 study (PRN1008-005) used a starting dose of 400 mg BID which was shown to produce adequate BTK occupancies in all but one participant. One participant dose-escalated to 500 mg BID and two to 600 mg BID, with all other participants using the 400 mg BID dose. The primary endpoint of the study, “control of disease activity by the Week 4 visit on ≤0.5 mg/kg/day of prednisone (or equivalent corticosteroid)” was met by 53.8% (14/26) of participants who completed 4 weeks of treatment. Complete remission on ≤0.5 mg/kg/day of corticosteroid was achieved by 16.7% (4/24) of participants completing 12 weeks treatment.

Rilzabrutinib has been well-tolerated by healthy volunteers. In the pemphigus study, treatment-emergent adverse events (TEAEs) related to rilzabrutinib in ≥10% of participants were nausea (14.8%) and abdominal pain (11.1%). One serious adverse event (SAE) of Grade 3 "cellulitis" considered related to rilzabrutinib therapy occurred, resulting in a 3-day interruption of rilzabrutinib therapy. This event resolved, and the participant continued therapy for two further months without recurrence of the event.

Overall, results from Phase 1 and Phase 2 studies demonstrate that rilzabrutinib has an acceptable safety profile and is well tolerated in healthy subjects and participants with PV, ITP, and IgG4-RD. A detailed summary of the chemistry, pharmacology, efficacy, and safety of rilzabrutinib is provided in the IB.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of rilzabrutinib may be found in the IB.

2.3.1 Risk assessment

Based on the review of the cumulative data, there are no important identified risks for rilzabrutinib. Two important potential risks have been recognized for rilzabrutinib include:

- Increased risk of infections
- Liver enzyme elevation

Details of the potential risks together with a summary of the cumulative nonclinical and clinical safety data are provided in Table 1 below.

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Infection	The BTK enzyme plays an important role in immune modulation. Inhibition of the BTK pathway modulates B-cell function but does not deplete B cells or impact existing plasma cells. It also aids in reducing inflammation through actions on macrophages and neutrophils, although it has no direct action on T-cells that are instrumental to the body's immune system. Rilzabrutinib may increase the risk of infection due to inhibition of human B-cell activation and antibody mediated activation of immune cells via Fc receptor signaling. Cumulatively, one serious adverse reaction (SAR) of	Testing for SARS-CoV-2 infection during screening will be determined by the Investigators and Sponsor based on local guidelines and coronavirus disease 2019 (COVID-19) prevalence at each site. Participants known to have had COVID-19 prior to study entry must be fully recovered in order to be eligible for participation. The impact of rilzabrutinib treatment on the severity of SARS-CoV-2 infection or generation of protective antibodies is not known. Participants with evidence suggestive of active tuberculosis or non-tuberculous mycobacterial infections are excluded. Participants with history of serious infections requiring intravenous therapy with the potential for recurrence are excluded.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	cellulitis has been reported during the clinical development program of rilzabrutinib.	Participants are to be vaccinated per local guidelines. To allow for an optimal immune response to all required vaccinations, it is strongly recommended that study participants receive their **live** vaccines (per local requirements) a minimum of 28 days prior to receiving the first dose of study medication. Patients who received live vaccine in less than 4 weeks before first dose will be excluded[E 06]. Live vaccines are not allowed during treatment. To allow for an optimal immune response as well as protection against COVID-19, it is strongly recommended that study participants receive their COVID vaccine (per local requirements) a minimum of 14 days prior to receiving the first dose of study medication. The safety profile and effectiveness of COVID-19 vaccines on people with compromised immune systems or therapies (such as Rilzabrutinib) that modify or that suppress their immune response, is not yet established. While vaccination with an approved COVID-19 vaccine is widely recommended (26), this decision should only be made by the participant, after discussing with his/her physician as well as the investigator to assess the benefits and risks of receiving a COVID-19 vaccination during this study. If the vaccine is authorized, available, and recommended by the local regulatory health authority, it may be administered during the study and should be administered according to the label or local health authority recommendations.
Liver enzyme elevation	Cumulatively, one healthy volunteer experienced a reversible, Grade 2 elevation of alanine aminotransferase (ALT) (peak value 127 U/L, Upper Limit of Normal [ULN] 40 U/L), one patient with pemphigus with a past history of ALT elevations had a reversible Grade 2 elevation of ALT, and one patient with PV experienced a reversible Grade 1 ALT increase. One grade 3 TEAE of aspartate aminotransferase abnormal and one grade 3 TEAE of gamma-glutamyl transferase abnormal were reported in patients with immune thrombocytopenic purpura (ITP). None of these events	Patients with aspartate aminotransferase (AST)/ALT >1.5 × ULN will be excluded. Careful safety monitoring with regular liver function assessments and evaluation assessment for Hy's law cases.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	resulted in interruption of rilzabrutinib therapy.	

Potential risks reported with other BTK inhibitors

There are adverse events 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 (27).

These adverse events include:

- Cytopenia
- Bleeding
- Atrial fibrillation

Rilzabrutinib has characteristics that may solve many of the selectivity- and reversibility-related concerns accompanying currently available BTK inhibitors (28). Rilzabrutinib binds in a covalent manner, increasing selectivity by forming a chemical bond to a specific cysteine residue present in BTK. This durable covalent engagement allows for maximal efficacy. However, rilzabrutinib's unique binding mechanism provides the opportunity for a tailored residence time while reducing safety concerns associated with irreversible inhibitors. In addition, there are important differences between the background safety risk profiles of this study population versus the oncologic population (where these events have been observed). Taken together, it is postulated that there is a low probability of occurrence of the above-mentioned "BTK inhibitor Class" adverse events during the administration of rilzabrutinib.

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 moderate to severe AD. 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.

There is no identified risk associated with the use of rilzabrutinib. The important potential risks of "increased risk for infections" and "liver enzyme elevation" have been characterized and appropriate risk mitigation procedures have been defined. The adverse events seen with other BTK inhibitors (bleeding, cytopenia, and atrial fibrillation) will also be closely monitored for.

The design of the present study (ACT17207), including selection criteria of the study population, risk mitigation strategy, and monitoring of safety variables, should maintain the positive balance regarding the expected efficacy/safety ratio for rilzabrutinib in the treatment of participants with AD.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess the efficacy of rilzabrutinib in participants with atopic dermatitis (AD)	• Percent change from baseline to Week 16 in Eczema Area and Severity Index (EASI) score.
Secondary	
• Assess the efficacy of rilzabrutinib at different time points	• Proportion of participants with Investigator's Global Assessment (IGA) of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16. • Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16. • Proportion of participants with reduction of weekly average of daily peak pruritus Numerical Rating Scale (PP-NRS) of ≥4 points from baseline at Week 16. • Time to onset of effect on pruritus (≥4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period). • Absolute change from baseline to Week 16 in EASI score. • Proportion of participants achieving EASI-50/90 (reduction of EASI score by ≥50% or ≥90% from baseline) at Week 16. • Change from baseline to Week 16 in percent body surface area (BSA) of EASI. • Change (absolute and percent change) on weekly average of daily PP-NRS based on daily participant assessments documented in their electronic diary (e-diary) from baseline to Week 16. • Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by ≥ 50% or 75% or 90% from baseline) at Week 16.
• Assess the safety of rilzabrutinib	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) from baseline to Week 16. • Incidence of study investigational medicinal product (IMP) discontinuation and withdrawals due to TEAEs from baseline to Week 16.

3.1 APPROPRIATENESS OF MEASUREMENTS

Efficacy is assessed using EASI, IGA, and PP-NRS. EASI is assessed by the investigator to measure severity and extent of AD. IGA is a static measure of disease severity used by the investigator. PP-NRS is a tool that patients used to report the intensity of their itch during a daily recall period using an electronic diary (e-diary). EASI, IGA and PP-NRS are validated scales and can be used reliably in clinical trials.

In terms of safety, TEAEs, SAEs, adverse events of special interest (AESIs), vital signs, electrocardiograms (ECGs), and laboratory analyses will be reported.

This study being primarily aimed at assessing efficacy and safety, PK and PD will be assessed as exploratory endpoints.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a global, multicenter, Phase 2, double-blind, 2-arm, parallel treatment, placebo-controlled randomized proof-of-concept (PoC) study with 2 staggered cohorts (2 arms in each cohort) evaluating the efficacy and safety of rilzabrutinib in adult participants (aged at least 18 years) with moderate-to-severe AD and intolerance or inadequate response to TCS.

Participants will be enrolled into 2 staggered dose regimen cohorts: a BID cohort and a TID cohort, starting with the BID cohort. These 2 dose regimen cohorts will be evaluated with the same double-blind fashion and planned assessments in this study.

[redacted]

An optional substudy will be proposed to all participants for skin tape strip samples to be taken at baseline and Week 16 for exploratory biomarkers analysis (Section 8.10).

The total number of participants in this study will be approximately 136, split in:

- For the main study: 120 adult participants who meet the inclusion/exclusion criteria will be stratified by immunoglobulin E (IgE) levels (< or ≥ 300 UI/mL) at Screening and will be randomized in a 3:2 allocation ratio to receive either rilzabrutinib or matching placebo on Day 1 (Week 0, Visit 2). In the BID cohort, approximately 50 participants will receive either rilzabrutinib (n = 30) or matching placebo (n = 20) twice a day, and in the TID cohort, approximately 70 participants will receive either rilzabrutinib (n = 42) or matching placebo (n = 28) three times a day.
- [redacted]

The study duration of the study for a participant is expected to be approximately 21 weeks and will include:

- A Screening period of up to 4 weeks
- Double-blind IMP treatment period of 16 weeks ± 3 days
- A post-treatment safety follow-up period of 1 week ± 3 days.

The End of Treatment (EOT) visit is planned on Week 16 after the last dose of IMP (morning of Week 16 visit). The End of Study (EOS) visit will be 7 days after the last dose of IMP (refer to Section 7.1 in case of early discontinuation).

For the main study, an interim analysis will be performed before the final database lock. The details will be provided in the SAP.

The list of randomized treatment kit numbers will be generated centrally by Sanofi. The IMPs are packaged in accordance with this list. Participants will be assigned a randomized study intervention by an interactive voice response system (IVRS) or an interactive web response system (IWRS). Participants who meet the entry criteria will be included and will be dispensed the treatment kits.

During the Screening period:

- Participants will be trained on using electronic questionnaires (e-diary) at the Screening visit (Visit 1). They will have to record pruritus NRS scores daily during the screening period for training purpose. Nevertheless, clinical site staff will only review pruritus NRS scores collected on the e-diary beginning 7 days preceding the baseline visit (Visit 2) and the data that are not reviewed by clinical site staff (between D-28 and D-7) will not be transferred to the Sponsor. Baseline PP-NRS score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For participants who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for Screening.
- Participants will be queried on personal and family history of allergy (aeroallergens, dust mites, cats, and mold). Results of historical skin testing (prick/puncture [percutaneous] or intradermal [intracutaneous] or RAST) should be collected. At sites able to conduct RAST testing or skin prick testing, participants who do not have a past history of skin testing should undergo RAST testing or skin prick testing at Screening and results should be collected in the corresponding electronic case report form (eCRF) page (See Section 1.3 footnote d).

During the intervention period:

- Participants will record pruritus NRS scores, rilzabrutinib dosing times, compliance with rilzabrutinib and background topical treatment (ie, moisturizers/emollients) every day during the intervention period of the study using e-diary.
- Participants will be assessed for efficacy (at on-site visits: baseline, Week 2, 4, 8, 12 and 16, and at unscheduled visits [if unscheduled visits occur]), safety (continuous assessment throughout the course of the study), PD and PK at different timepoints. As much as possible, morning visits are preferable to permit collection of pre-dose PK samples. On visit days, the participants will be invited to take their morning dose at the clinic, after pre-dose PK samples have been collected. Unless permanently discontinued from the study, all

participants will complete the scheduled study visits and assessments whether or not they complete study intervention treatment and whether or not they receive rescue treatment for AD.

- Participants may receive rescue therapy for AD at the discretion of the Investigator at any time during the study, if judged medically necessary. The participants will continue study intervention if rescue consists of the following medications: low to medium potency TCS, topical crisaborole, or TCIs. Topical calcineurin inhibitors may be used for rescue but should be reserved for problem areas only (eg, face, neck, intertriginous and genital areas, etc). If a participant receives rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study intervention will be immediately discontinued. After the treatment with these medications is completed, study intervention may be resumed if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of the rescue medication. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment with high potency TCS or systemic medications. An unscheduled visit may be used for this purpose if necessary. For the purpose of efficacy analysis, participants who receive high potency TCS or systemic medications during the study intervention period will be considered treatment failures.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Study design rationale

The 16 weeks blinded treatment duration selected for the current study is based on prior AD studies with other systemic and publicly available drugs (including dupilumab and baricitinib), and is sufficient to demonstrate clinically meaningful efficacy and to assess safety.

The double-blind design intends to mitigate potential bias and placebo control is necessary to assess the net effect of active rilzabrutinib treatment. Use of placebo is ethical in this context, since all participants in the trial have the possibility for rescue therapy based on the Investigator's judgment. The randomization ratio 3:2 is aimed at minimizing the participant number in the placebo group.

The stratification by serum levels of IgE autoantibodies is intended to assess the effect of rilzabrutinib based on whether the participants' AD is extrinsic or intrinsic.

4.3 JUSTIFICATION FOR DOSE

The rilzabrutinib dose regimens selected for this study are based on clinical results in patients with PV in Phase 2 Study PRN1008-005 and in patients with ITP in Phase 1/2 Study PRN1008-010, and the BTK target occupancy of rilzabrutinib collected in Phase 1 and Phase 2 studies. The current dosing regimen for the Phase 3 lead indication, immune thrombocytopenia, is 400 mg BID. This regimen has demonstrated to be an effective and safe clinical dose from Study PRN1008-010.

Dose-ranging in Phase 1 PK program in healthy volunteers collecting BTK occupancy of rilzabrutinib in circulating white blood cells showed that plasma concentration associated with a 400 mg BID dosing regimen with the tablet formulation was predicted to produce 91% BTK occupancy at peak (4-hour post-dose) and >70% BTK occupancy at trough (12 hours after the dose) at steady-state. BTK occupancy data from patients with PV (PRN1008-005) confirms adequacy of this dose with a trough BTK occupancy of approximately 80% at Day 2 pre-dose.

The dosing regimen of 400 mg TID was selected to match the daily maximal administered dose (600 mg BID) in study PRN1008-005 which was shown to be well tolerated. In contrast to autoimmune type 1-predominant diseases as per the Gell and Coombs classification which are driven by B cells, type 2-predominant inflammatory diseases such as AD, asthma and chronic urticaria are exacerbated by mast cell and basophil activity. The IC50 for basophil activation is higher compared to the IC50 for B-cell activation. Based on simulation data (n=1000 subjects), it is expected that 400 mg TID dosing to achieve ~79% or higher trough occupancy with less peak to trough variability compared to 400 mg BID dosing in AD patients. Thus, the higher dose is expected to ensure sufficient inhibition in mast cells and basophils which may lead to an augmented clinical response in Type 2 inflammatory diseases.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit/last contact of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

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 years of age, inclusive, or older at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. AD as defined by the American Academy of Dermatology Consensus Criteria (2).

I 03. History of AD for at least 12 months prior to baseline as determined by the Investigator through patient interview.

I 04. Eczema Area and Severity Index (EASI) score ≥12 during screening[a)] and at baseline.

a) Patients with EASI score between 10 to 12 may be re-tested once during screening phase if, per investigator's judgement, the results may evolve up to ≥ 12 during screening

I 05. IGA score ≥ 3 (on the 0 to 4 IGA scale) at baseline.

I 06. BSA* of AD involvement ≥ 10% at baseline.

*BSA estimated using the method described in Section 8.1.2.

I 07. Documented[b)] inadequate response[c)] or intolerance[d)] to TCS within 6 months prior to baseline visit

NOTE:

b) Acceptable documentation includes contemporaneous chart notes that recorded TCS prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician, the patient's pharmacist, or the patient.

c) Failure to achieve and maintain remission or low disease activity (eg, IGA 0 = clear to 2 = mild) despite treatment with TCS of medium to high potency (± topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever was shorter.
NOTE: Patients who failed systemic therapies intended to treat AD within 6 months

preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate will be also considered as surrogate for having inadequate response to topical therapy.

d) Important side effects or safety risks defined as those that outweighted the potential treatment benefits (eg, hypersensitivity reactions, significant skin atrophy, systemic effects, etc… or imminence thereof), assessed by the investigator or treating physician.

I 08. Baseline PP-NRS score for maximum itch intensity ≥4.

NOTE: Baseline PP-NRS score for maximum itch intensity will be determined based on the average of daily NRS scores for maximum itch intensity (the daily score ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum of 4 daily scores out of the 7 days is required to calculate the baseline average score. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening.

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 09. All 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 Contraceptive 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 Contraceptive and barrier guidance (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 of the protocol. 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 of the protocol (Section 10.1) 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).

Other inclusions

Substudy

I 11. Willingness to have 2 tape strips for comparison of baseline and treatment response.

I 12. Capable of giving signed informed consent specific to the substudy.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Skin comorbidities that may interfere with study assessments such as psoriasis, tinea corporis, lupus erythematosus.

E 02. Any other clinically significant disease, condition, or medical history that, in the opinion of the Investigator, would interfere with participant safety, trial evaluations, and/or trial procedures. 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), hepato-biliary conditions such as 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, active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases.

E 03. Any of the following laboratory abnormalities at the screening visit (identified by the central laboratory):

- Absolute neutrophil count < 1.5 x 10^9/L
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
- Total bilirubin > 1.5 x ULN, (isolated bilirubin > 1.5 x ULN is acceptable if total bilirubin is fractionated and direct bilirubin < 35%)
- IgG < 500 mg/dL
- Abnormal international normalized ratio (INR) test and activated partial thromboplastin time (aPTT) judged by the Investigator to be clinically significant
- A platelet count < 150 000/μL

Note: a one-time retest at screening may be performed by the Investigator if abnormal laboratory test values are found.

E 04. History of serious infections requiring intravenous 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).

E 05. 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 06. COVID-19 vaccine within 14 days prior to Study Day 1.

E 07. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant bowel resection that would preclude adequate rilzabrutinib/placebo absorption.

E 08. Donation of a unit or more of blood or blood products within 4 weeks prior to Day 1.

E 09. History of solid organ transplant.

E 10. A history of malignancy of any type within 5 years before Day 1, other than surgically excised non-melanoma skin cancers or in situ cervical cancer.

E 11. Conditions that may predispose the patient 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.

Prior/concomitant therapy

E 12. Initiation of prescription moisturizers (with or without additives such as ceramide, hyaluronic acid, urea, or filaggrin), topical anesthetics or antihistamines during the screening period.

NOTE: Participants may continue using stable doses of such drugs if initiated before the screening visit.

E 13. Use of TCS, topical calcineurin (tacrolimus, and/or pimecrolimus) or topical phosphodiesterase 4 inhibitor within 1 week prior to baseline and as concomitant medication.

E 14. Use of systemic corticosteroids within 4 weeks prior to baseline and as concomitant medication.

E 15. Phototherapy for AD or regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks prior to baseline or likely to be required as concomitant procedure during the study.

E 16. Use of mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin (IVIG), Kineret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion within 4 weeks prior to baseline.

E 17. Use of infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, IFN-γ, JAK inhibitors, dupilumab, and any other biologic or targeted-synthetic disease modifier drug not mentioned in this exclusion criterion or in exclusion criterion[E 16], as well as plasmapheresis within 12 weeks prior to baseline.

E 18. Use of anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics within 6 months prior to baseline (or shorter if there is documented B cell reconstitution for anti-CD20 drugs).

E 19. Use of proton pump inhibitor drugs such as omeprazole and esomeprazole within 3 days of baseline (it is acceptable to change participant to H2 receptor blocking drugs prior to baseline).

E 20. Concomitant use of known systemic strong-to-moderate inhibitors and inducers of cytochrome P450 3A (CYP3A) within 14 days or 5 half-lives (whichever is longer) prior to baseline (Section 10.11.1).

Prior/concurrent clinical study experience

E 21. Previous use of a BTK inhibitor.

E 22. Has received any investigational drug (or is currently using an investigational device) within the 30 days before baseline, or at least 5 times the respective elimination half-life time (whichever is longer).

Diagnostic assessments

E 23. Positive for human immunodeficiency virus (HIV) at Screening.

E 24. 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 10.9.10.1).

E 25. 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 ribonucleic acid (RNA) test is obtained.

E 26. Exclusion related to Tuberculosis (TB):

- Active TB or a history of incompletely treated TB regardless of screening Quantiferon test (QFT) result.
- Quantiferon positive patients (no active disease) unless the following conditions are met
  - Patients with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (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 QFT 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 QFT 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 TB 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 TB infection regardless of screening Quantiferon result.
- Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.

E 27. Electrocardiogram (ECG) 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 28. Sensitivity 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 29. History of drug abuse within the previous 12 months.

E 30. Alcoholism or excessive alcohol use, defined as regular consumption of more than approximately 3 standard drinks per day.

E 31. 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 32. 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-GCP Ordinance E6).

E 33. Any specific situation during study implementation that may raise ethics considerations.

E 34. 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

Study interventions can be given with or without food. Food does not alter bioavailability of rilzabrutinib based on the results from the preliminary food effect study. Gastrointestinal tolerability may be better if given with food.

Refrain from consumption of grapefruit or grapefruit juice, from 7 days before the start of study intervention until the completion of the final dose.

5.3.2 Caffeine, tobacco, and activity

No restriction of caffeine, tobacco or activity is required.

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.

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 re-screened one time for this study after notification of the Sponsor. A different participant identification number will be issued. There is no requirement for a waiting period between the screen-failure and the re-screening. Participants that are re-screened will be required to sign a new consent form. Visit 1 procedures must be repeated for re-screened participants.

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 10.10).

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.

Rilzabrutinib tablets are supplied ready for use; no preparation is needed. Participants will use study medication directly from the dispensed bottles.

Participants will administer rilzabrutinib by mouth twice daily or 3 times a day with or without food starting on Day 1. The frequency and/or severity of gastrointestinal AEs may be improved if rilzabrutinib is taken with food. A question about intake with food will be administered at end of treatment. Consecutive doses should ideally be administered 12 hours apart (and not less than 8 hours apart) for BID dosing, and ideally at least 6 hours apart (and not less than 4 hours apart) for TID dosing. Tablets should not be broken or crushed. Further details for dispensation and administration are provided in the Pharmacy Manual.

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

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 (modified-capsule shaped tablets / caplets)	Tablets (modified-capsule shaped tablets / caplets)
Unit dose strength(s)	400 mg	0 mg
Dosage level(s)	400 mg (1 tablet) BID or TID	1 tablet BID or TID
Route of administration	Oral	Oral
Use	Experimental	Placebo-comparator
IMP or NIMP	IMP	IMP
Packaging and labeling	Rilzabrutinib tablets will be supplied in white plastic bottles with child-resistant induction-sealed caps. The bottles will be labelled as required per country requirement.	Placebo tablets will be supplied in white plastic bottles with child-resistant induction-sealed caps. The bottles will be labelled as required per country requirement.
[Current/Former name(s) or alias(es)]	Rilzabrutinib (SAR444671)/PRN1008	Placebo

[redacted]

Table 4 - Arms and associated interventions

Arm name	Rilzabrutinib BID	Placebo BID	Rilzabrutinib TID	Placebo TID
Associated interventions (intervention label[s])	Rilzabrutinib	Placebo	Rilzabrutinib	Placebo

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: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.10).

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 the IMP and eliminate potential hazards.

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

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 interactive response technology (IRT). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Randomization will take place at Day 1 stratified by Screening IgE levels (< or ≥300 UI/mL).

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 (Section 1.3). 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.

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 data base 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.

Procedures 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 for 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) (Section 10.10).
  - The Investigator counts the number of tablets remaining in the returned kits and fills in the Accountability Log Form.
  - The monitor in charge of the study then checks the compliance data by comparing them with the IMP which he/she has retrieved and Accountability Log Form.

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 by the participant in a e-diary and by the site staff at each visit for the main study. [redacted] 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 rilzabrutinib 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

Dose modification will not be allowed.

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

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

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

The following medications / procedures are prohibited during the study:

- Immunosuppressive or immunomodulating drugs
- Live vaccines (see Section 10.11.2)
- Phototherapy or regular use (more than 2 visits per week) of a tanning booth/parlor
- Proton Pump inhibitors
  - Esomeprazole was shown to reduce the exposure of rilzabrutinib by approximately 50%, presumably due to a lack of an acidic environment on tablet dissolution. Participants who are on proton pump inhibitors should be changed to histamine (H2) receptor blocking drugs, if possible, or not be enrolled in the study.
- Known systemic strong-to-moderate inducers or inhibitors of CYP3A (see Section 10.11.1)

A non-exhaustive list of prohibited medications and therapies is provided in Appendix 10 (Section 10.11.3). All medications that are not listed as prohibited therapies are allowed during the study.

Any medication or vaccine (including over-the-counter or prescription medicines, 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 Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator, the medication will not interfere with the study.

Medications that have not been listed as exclusion criteria are permitted for use during the trial. These include the following:

- Prescription moisturizers (with or without additives such as ceramide, hyaluronic acid, urea, or filaggrin), topical anesthetics or antihistamines that have been initiated prior to the screening period are allowed to be continued if the doses are stable.
- Oral corticosteroid rinses (mouth washes), ocular or inhaled corticosteroids are allowed.
- Clinically relevant drugs that are substrates of CYP3A, including those considered to be sensitive CYP3A substrates (see Section 10.11.1) are permitted. Appropriate caution should be used when co-administering sensitive CYP3A substrates with rilzabrutinib and a benefit-risk assessment should be conducted for each medication. Consideration should also be given to avoidance of high doses, dose reduction, or replacement of sensitive and narrow therapeutic index CYP3A substrate drugs. Systemic strong or moderate inhibitors (including foods such as grapefruit juice) and inducers of CYP3A should be avoided.
- Histamine 2 (H2) receptor blocking drugs are permitted provided they can be given 2-3 hours after administration of rilzabrutinib or placebo. For participants receiving the IMP three times a day, H2-receptor blockers must be taken once daily only, 2-3 hours after the evening dose of rilzabrutinib or placebo.
- Antacids are permitted provided they are given 2 hours or more apart from rilzabrutinib or placebo.
- COVID-19 vaccines:

  To allow for an optimal immune response as well as protection against COVID-19, it is strongly recommended that study participants receive their COVID vaccine (per local requirements) a minimum of 14 days prior to receiving the first dose of study medication. The safety profile and effectiveness of COVID-19 vaccines on people with compromised immune systems or therapies (such as Rilzabrutinib) that modify or that suppress their immune response, is not yet established. While vaccination with an approved COVID-19

vaccine is widely recommended (26), this decision should only be made by the participant, after discussing with his/her physician as well as the investigator to assess the benefits and risks of receiving a COVID-19 vaccination during this study. If the vaccine is authorized, available, and recommended by the local regulatory health authority, it may be administered during the study and should be administered according to the label or local health authority recommendations.

6.8.1 Rescue medicine

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study participants at the discretion of the Investigator.

If possible, Investigators should attempt to limit the first step of rescue therapy topical medications with:

- low to medium potency TCS (see Section 10.11.4),
- crisaborole (cAMP-specific phosphodiesterase-4 inhibitor),
- calcineurin inhibitors (which should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas).

Participants will continue study intervention if rescue consists of these topical medications.

Only for participants who do not respond adequately after at least 7 days of this first step rescue therapy, Investigators may escalate to high potency TCS or systemic medications (corticosteroid or non-steroidal systemic immunosuppressive drugs such as cyclosporine, methotrexate, mycophenolate mofetil, aziathioprine, etc).

If a participant receives rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study intervention will be immediately discontinued. After the treatment with these medications is completed, study intervention may be resumed if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of the rescue medication. All participants will complete the schedule of study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment with high potency TCS or systemic medications. An unscheduled visit may be used for this purpose if necessary.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

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 patient 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 definitive study 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 participant's safety or data integrity. These include, but are not limited to
  - Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status.
  - Serum ALT >3 × ULN and total bilirubin >2 ULN (see Section 10.6).

Any clinically significant abnormal laboratory value will be immediately rechecked for confirmation after 24 hours before making a decision of definitive 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

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Section 10.6 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to/not taken by the participant.

If a participant receives rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study intervention will be immediately discontinued.

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 (Section 10.10: Contingency measures for a regional or national emergency that is declared by a governmental agency). All temporary intervention discontinuations should be recorded by the participant in the e-diary.

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(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 5).

When the participants temporarily discontinue the study intervention due to use of rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs, study intervention may be resumed after the rescue treatment is completed, if deemed appropriate by the Investigator and the medical monitor, but not sooner than 5 half-lives after the last dose of the rescue medication.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.10).

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

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 ED 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.

After discontinuation, participants will be encouraged to attend every remaining visit as per SoA (Section 1.3).

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.
- 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 450 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Section 10.11.5 provides representative examples of the EASI scoring system, estimation of BSA of EASI, NRS and IGA that will be used in this study.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency (Section 10.10).

8.1 EFFICACY ASSESSMENTS

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

The following efficacy parameters will be analyzed for assessing the primary and secondary efficacy endpoints.

8.1.1 Eczema Area and Skin Severity Index (EASI)

The EASI index is a validated Investigator-administered scoring system used to measure the severity of clinical signs in AD (29). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, upper limbs, and lower

limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

8.1.2 Estimation of body surface area (BSA) of EASI

Body surface area (BSA) affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [10%], trunk including genitalia [30%], upper limbs [20%], lower limbs [40%]) and will be reported as a percentage of all major body sections combined.

8.1.3 Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) during a daily recall period that has been used in clinical studies of AD (30).

Patients will be instructed on using the e-diary to complete the pruritus categorical scale daily. Clinical sites will receive alerts when patients do not complete e-diary items. Sites will be expected to contact patients who have missed 2 consecutive e-diary entries to encourage patient compliance.

The questions asked to patients are the following:

- For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch overall (on average) during the previous 24 hours?"
- For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?".

8.1.4 Investigator Global Assessment (IGA) of disease activity

Investigator Global Assessment (IGA) is a static 5-point measure of disease severity based on an overall assessment of the skin lesions on a 5-point scale (0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease).

8.1.5 Atopic Dermatitis Area Photographs

At selected study sites and in participants who consent, photographs may be taken of representative area(s) of AD involvement (eg, one or some of the lesional areas) used for EASI assessments on Day 1 / baseline (pre-dose). Area chosen for photographs will not comprise participant’s direct identifier (such as participant’s face, tattoos, identifiable jewelry, etc). Subsequent photographs of the same areas will be taken at Week 16 (EOT) and Week 17 (EOS). Instructions for taking the photographs are provided in the photography reference manual.

8.2 SAFETY ASSESSMENTS

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

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

8.2.1 Physical examinations

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological 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 also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

[redacted]

8.2.2 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained at Screening and Week 16 (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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 abnormal laboratory test values do not return to normal or 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 (Please refer to Section 10.3 and Section 10.6).

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 accordingly 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.

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

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

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

AE 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 the 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). 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, IRB/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 and 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 female partners of male participants will be collected after the start of study intervention and until 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 adverse event of special interest (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;
  - 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
  - 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 defined as a single ingestion of a dose equal to or greater than 1200 mg (3 times the indicated single dose of 400 mg), provided that it has been taken at once or over 2-hour period.
- Increase in ALT > 3 × ULN confirmed by retest within 72 hours of initial sample; see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6) that recommends to also measure total bilirubin upon reconfirmation of ALT > 3 x ULN.
- Other project specific AESI(s)
  - Severe infections including opportunistic infections
  - Tuberculosis or initiation of medications for suspected tuberculosis
  - Diagnosed and biologically proven SARS-CoV-2 infection
  - Major hemorrhagic events, including symptomatic bleeding in a critical area or organ such as the central nervous system (CNS), or intraocular bleeding, resulting in an SAE
  - Serious adverse events (or non-serious AEs with a severity level consistent with Grade 3 Common Terminology Criteria for AE [CTCAE]) of cytopenia
  - Atrial fibrillation

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 at each time point 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 PHARMACOGENOMICS

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

In addition, genomics/genetics will be evaluated in participants who consent to participate in the optional skin tape strip substudy (Section 8.10).

See Appendix 5 (Section 10.5) for information regarding genomic/genetic 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 serum, plasma, blood, and peripheral blood mononuclear cell (PBMC) samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).

- [redacted]

[redacted]

- 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)
- In addition, lesional and non-lesional skin samples may be collected in participants who consent to join optional skin tape strip substudy (Section 8.10)

Detailed descriptions of sample types, sample volumes and handling procedures will be provided in the laboratory manual.

8.7 IMMUNOGENICITY ASSESSMENTS

Antibodies to rilzabrutinib will not be evaluated in this study.

8.8 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and 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, mechanism of action, or possible 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 (leftover) and/or extra (additional) clinical samples, data and samples may be used 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.

Remaining leftover samples will be used only after the study ends (ie, end of study as defined in the study protocol). Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

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 in alignment with the information provided to participants in the ICF Part 2 (future research).

For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These 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).

Relating data and biological samples for future research will be stored for up to 25 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.

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).

8.10 OPTIONAL SUBSTUDY

Lesional and non-lesional skin samples for exploratory biomarker analysis (31), including RNA sequencing and quantitative reverse transcription polymerase chain reaction (qRT-PCR) validation of immune and barrier biomarkers, will be obtained using a tape stripping procedure at Day 1/baseline (Visit 2, predose) and at Week 16 (Visit 7, EOT) from participants who choose to participate in this optional sub-study and provide consent for participating in this optional substudy.

Skin tape strip samples for RNA isolation will be collected from all participants who have consented to participate in the substudy. Participants who do not wish to participate in the genomic/genetic research cannot participate in this substudy.

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

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

In the BID cohort, approximately 50 participants will be randomized in a 3:2 ratio to rilzabrutinib versus placebo. In the TID cohort, approximately 70 participants will be randomized in a 3:2 ratio to rilzabrutinib versus placebo.

Sample size calculations were performed to ensure reasonable accuracy for the estimation of the treatment difference in percent change in EASI score from baseline to Week 16 between rilzabrutinib and placebo. For the BID cohort, a sample size of 50 participants enrolled with a ratio of 3:2 between rilzabrutinib and placebo and a common SD of 40 will provide a half-width for the 2-sided 90% CI of less than or equal to 19.0%. For the TID cohort, a sample size of 70 participants enrolled with a ratio of 3:2 between rilzabrutinib and placebo and a common SD of 40 will provide a half-width for the 2-sided 90% CI of less than or equal to 16.1%.

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses in the main study are defined:

Table 5 - 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.
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), with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants in the placebo group will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.

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.

9.3 STATISTICAL ANALYSES

The SAP 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 main secondary endpoints.

9.3.1 General considerations

The BID cohort and TID cohort will be analyzed separately. A pooled analysis of the BID and TID cohort may also be performed as appropriate. The details will be described in the SAP.

Common definitions of baseline

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

General methods

- Descriptive analyses will include summarization of quantitative variables (using n, mean, standard deviation, inter quartile range, median, minimum, and maximum) and qualitative data (by reporting absolute and relative frequencies).
- Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **on-treatment period** is defined as the period from the first IMP administration to the last IMP administration +1 day.
- The **post-treatment period** is defined as the period from the end of the on-treatment period up to the follow-up visit.

Treatment emergent [TE] period includes both on-treatment period and post-treatment period.

9.3.2 Primary endpoint(s)

The primary estimand for the primary endpoint of percent change from baseline to Week 16 in EASI score is described in Table 6.

Table 6 – Summary of primary estimand for the primary endpoint

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To assess the efficacy of rilzabrutinib in participants with AD				
Primary endpoint	Percent change from baseline to Week 16 in EASI score.	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention: all data collected after discontinuation will be included in the analysis (treatment policy strategy). • Receiving selected rescue medications (see Section 6.8.1 for rescue) before Week 16: data collected post the rescue treatments will be set to missing and the worst postbaseline value on or before the time of the rescue treatments usage will be used to impute the missing Week 16 value (for participants whose postbaseline value are all missing, the baseline will be used to impute) (hypothetical strategy).	Mean percent change difference between rilzabrutinib and placebo from ANCOVA. The missing data are handled as follows: • After discontinuation of the study intervention due to lack of efficacy prior to Week 16: "worst observation carried forward" 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 16: MI approach will be used to impute missing endpoint value, and this MI will use all participants excluding participants who have been rescued with the high potency TCS or systemic medications (see Section 6.8.1 for rescue) before Week 16 and excluding participants who discontinue due to lack of efficacy prior to Week 16. Each of the imputed complete data will be analyzed by fitting the ANCOVA model with percent change in EASI score from baseline to Week 16 as response variables, treatment (rilzabrutinib and placebo) and randomization stratification of Screening IgE level (< or ≥300 UI/mL) as fixed effects, and baseline EASI score as covariates. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Descriptive statistics including the number of subjects mean, standard error, and LS means will be provided. In addition, difference in LS means and the corresponding 90% CI will be provided along with the p-values.

AD: atopic dermatitis; ANCOVA: analysis of covariance; EASI: Eczema Area and Severity Index; IgE: immunoglobulin E; TCS: topical corticosteroids; MI: multiple imputation; LS: least squares; CI: confidence interval.

Supplemental analysis

Data from historical studies which have similar target population and study design will be used as prior information supplementing the placebo arm, using a Bayesian approach. A prior distribution

for the mean percent change in EASI score from baseline to Week 16 of the placebo arm was determined based on the data observed in the historical studies.

Efficacy of rilzabrutinib will be based on the posterior probability that the mean percent change in EASI score from baseline to Week 16 of rilzabrutinib group is greater than that of the placebo group. A posterior probability of at least 95% will be considered significant.

Details on the analysis will be provided in the SAP.

9.3.3 Secondary endpoint(s)

9.3.3.1 The main secondary endpoints

- Proportion of participants with IGA of 0 or 1 (disease free or almost disease free) compared to placebo at Week 16
- Proportion of participants achieving EASI-75 (reduction of EASI score by ≥ 75% from baseline) at Week 16
- Proportion of participants with reduction of weekly average of daily PP-NRS of ≥ 4 points from baseline at Week 16

The binary endpoints at Week 16 will be analyzed using the CMH test adjusted by randomization stratification of Screening IgE level (< or ≥ 300 UI/mL) in the ITT population.

Account for the impact of selected rescue medications on the efficacy effect:

For the binary efficacy endpoints, if high potency TCS or systemic medications are used, the participant will be specified as a non-responder from the time the rescue is used.

If a participant withdraws from the study, this participant will be counted as a non-responder for endpoints after withdrawal.

9.3.3.2 Other secondary endpoint(s)

- Time to onsite of effect on pruritus (≥4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period).
- Absolute change from baseline to Week 16 in EASI score
- Proportion of participants achieving EASI-50/90 (reduction of EASI score by ≥50% or ≥ 90% from baseline) at Week 16
- Change from baseline to Week 16 in percent BSA of EASI
- Absolute and percent change on weekly average of daily PP-NRS based on daily participant assessments documented in their e-diary from baseline to Week 16
- Proportion of participants achieving IGA*BSA-50/75/90 (reduction of IGA*BSA by ≥ 50% or 75% or 90% from baseline) at Week 16

Time to onsite of the effect on pruritus (≥ 4 points reduction of weekly average of daily PP-NRS from baseline during the 16-week treatment period) will be analyzed using the Cox proportional hazard model with time to event as the dependent variable, and treatment, randomization stratification of Screening IgE level (< or ≥300 UI/mL) as covariates. The estimates of the hazard ratio and corresponding 90% CI and p-values will be provided for the rilzabrutinib versus the placebo group.

The continuous efficacy endpoints will be analyzed using the same analysis approach as for the primary endpoint.

The binary efficacy endpoints will be analyzed using the CMH test in the same fashion as for the main secondary endpoints.

[redacted]

9.3.5 Multiplicity considerations

No adjustments for multiplicity are planned for this Phase 2 study. More specifically, no adjustments will be made in comparing the treatment groups based on the secondary efficacy endpoints and no adjustments will be made for the subgroup analyses. Reported p-values for the secondary endpoints will be nominal p-values.

9.3.6 Safety analysis

All safety analyses will be performed using the safety population according to the intervention group to which the participants are exposed.

9.3.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 2 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment 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 AESIs (defined with a preferred term [PT] or a prespecified grouping), all treatment emergent SAEs, and all TEAEs leading to permanent study intervention discontinuation.

Adverse event incidence tables will present 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.

Deaths will also be analyzed.

9.3.6.2 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, 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, for laboratory variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

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

9.3.7 Other analysis

[redacted]

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.

9.4 INTERIM ANALYSES

Interim analysis may be performed before the final database lock for this study. The details will be described in the (SAP).

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, IB 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).
- 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.
- 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.

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 10.10).

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 participants 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 clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. 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: clinicalstudydatarequest.com.

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 eCRF 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.
- 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 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.

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.
- 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 and activated partial thromboplastin time (aPTT)
Clinical (serum) chemistry[a]	
	Blood urea nitrogen Creatinine high-sensitivity C reactive protein (hs-CRP) Creatine kinase (CPK) Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase (ALP)[b] Total, direct, and indirect bilirubin Lactate dehydrogenase (LDH)
Pregnancy testing	• Serum or highly sensitive urine beta human chorionic gonadotropin (β-HCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	• Total serum IgG • Serology (HIV antibody; and hepatitis B surface antigen [HBsAg], anti-HBc [total and IgM, followed by HBV DNA in case of anti-HBc positivity], and hepatitis C virus antibody [anti-HCV], and HCV RNA, if these tests have not been performed within 3 months prior to the Screening visit [redacted] • Urinalysis - Specific gravity - pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrites, leukocytes by dipstick - Microscopic examination (if blood or protein is abnormal) • Tuberculosis (TB)/QuantiFERON test (To be performed for participants without documented negative screening for TB via a negative QuantiFERON test within 3 months prior to Screening) • Coronavirus disease 2019 (COVID-19) test (if COVID-19 testing is required per local guidelines, to be determined for each site) • All study-required laboratory tests are planned to be performed by a central laboratory, with the exception of dipstick urinalysis, urine pregnancy test, RAST or skin prick test, and tests required to be done locally as specific to country requirements and regulations, eg, COVID-19 test.

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 6 (Section 10.6) Liver and other safety: Suggested actions and follow-up assessments. All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase (ALP) is elevated, consider fractionating.

c 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 adverse event is an adverse event that was not solicited 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 participant/ LAR(s) will be collected during interview with the participants/LAR(s) 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.

Events <u>meeting</u> 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 adverse event 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 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 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.

10.3.4 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.
- 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 the 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.

10.4 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 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 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 4 weeks and sperm up to 13 weeks
- 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 6 to 8 weeks 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:

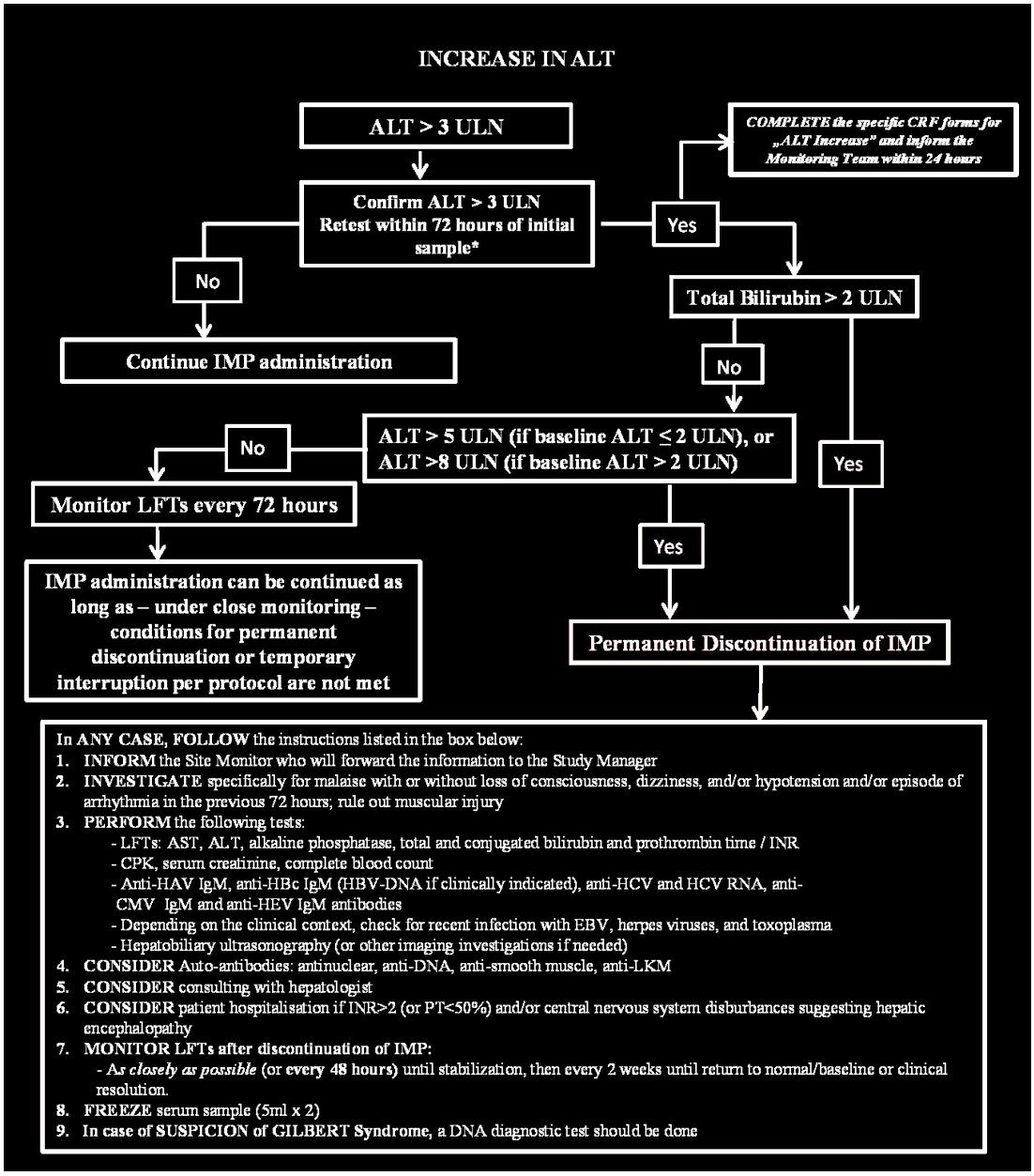
- The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be 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 6 to 8 weeks 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 10.3.4. 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 genomic/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 and skin tape strip samples will be collected for RNA/DNA analysis from consenting participants.
- RNA/DNA samples will be used for research related to rilzabrutinib or AD 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 AD. Genomic/Genetic research may consist of the analysis of one or more candidate genes or the analysis of genomic/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 genomic/genetic factors involved in the response to rilzabrutinib or drugs of this class to understand study disease or related conditions.
- The results of genomic/genetic 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



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

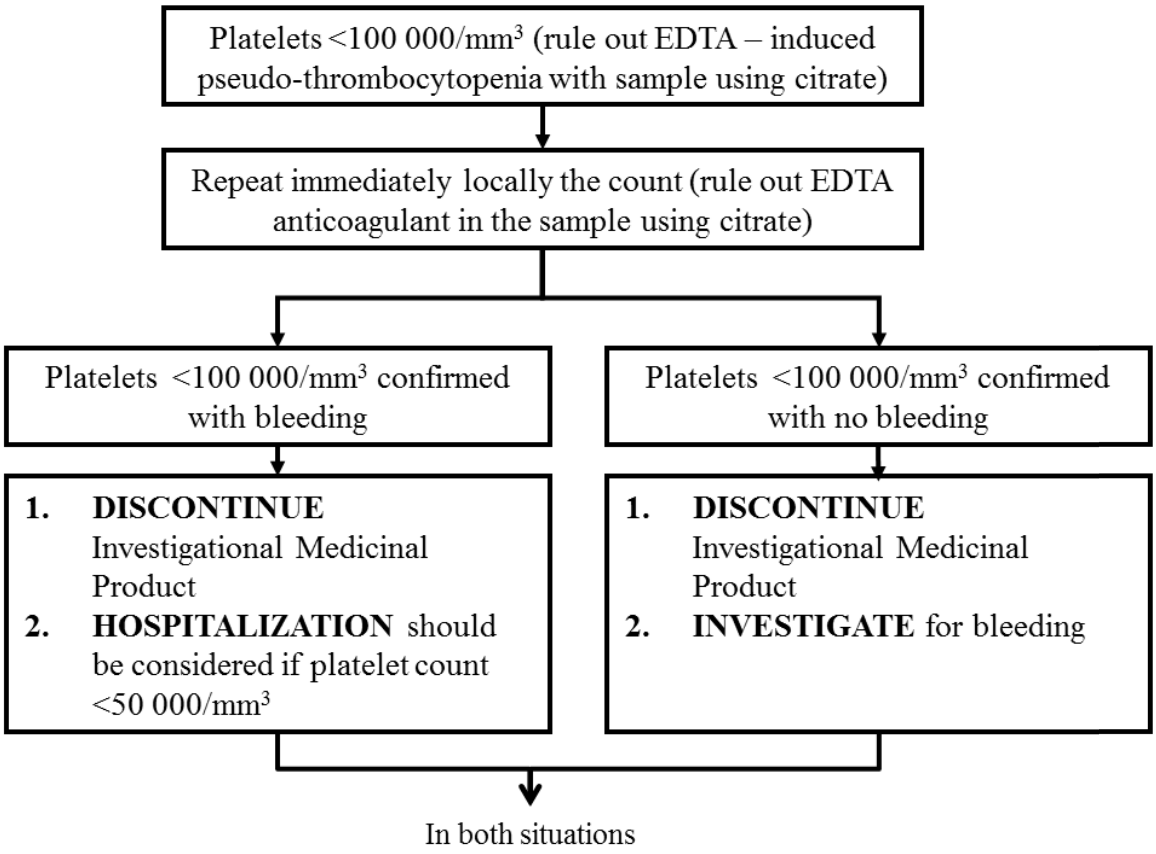
Note:

"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

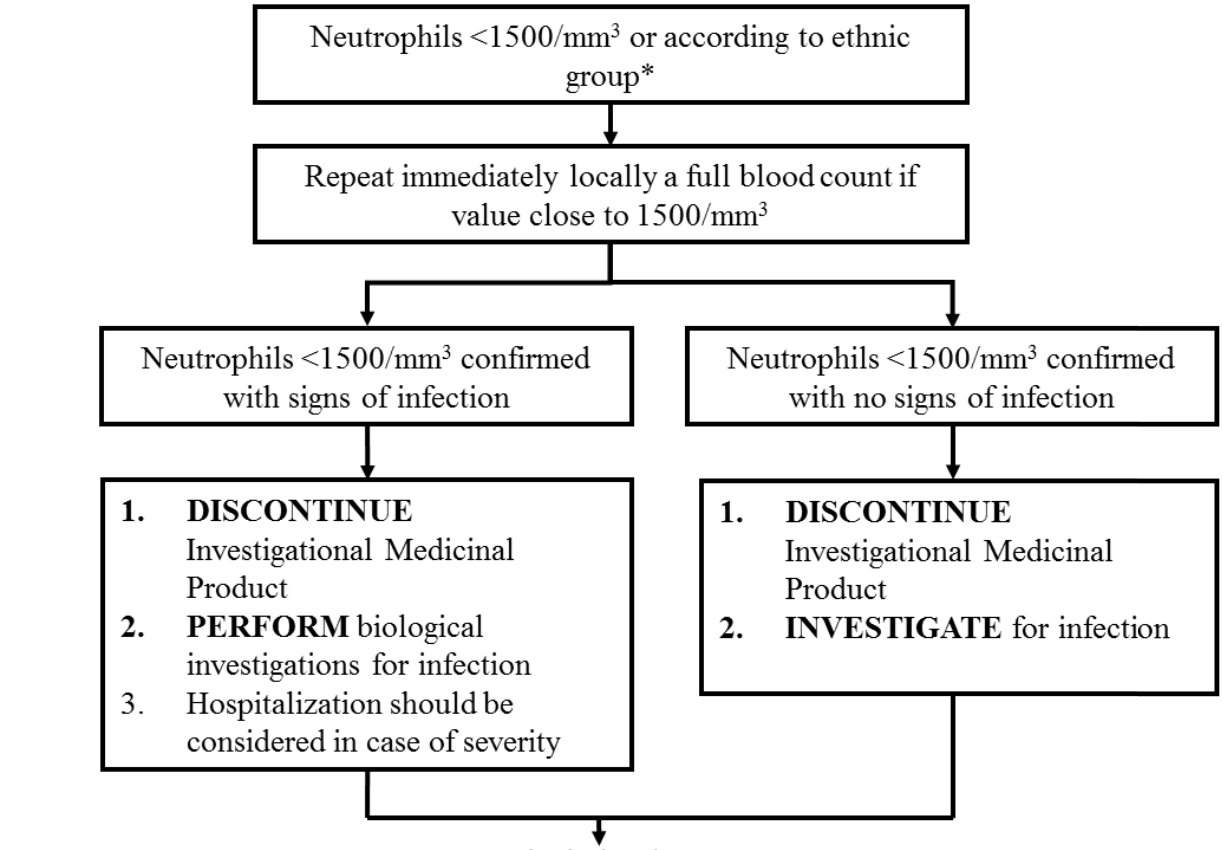
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

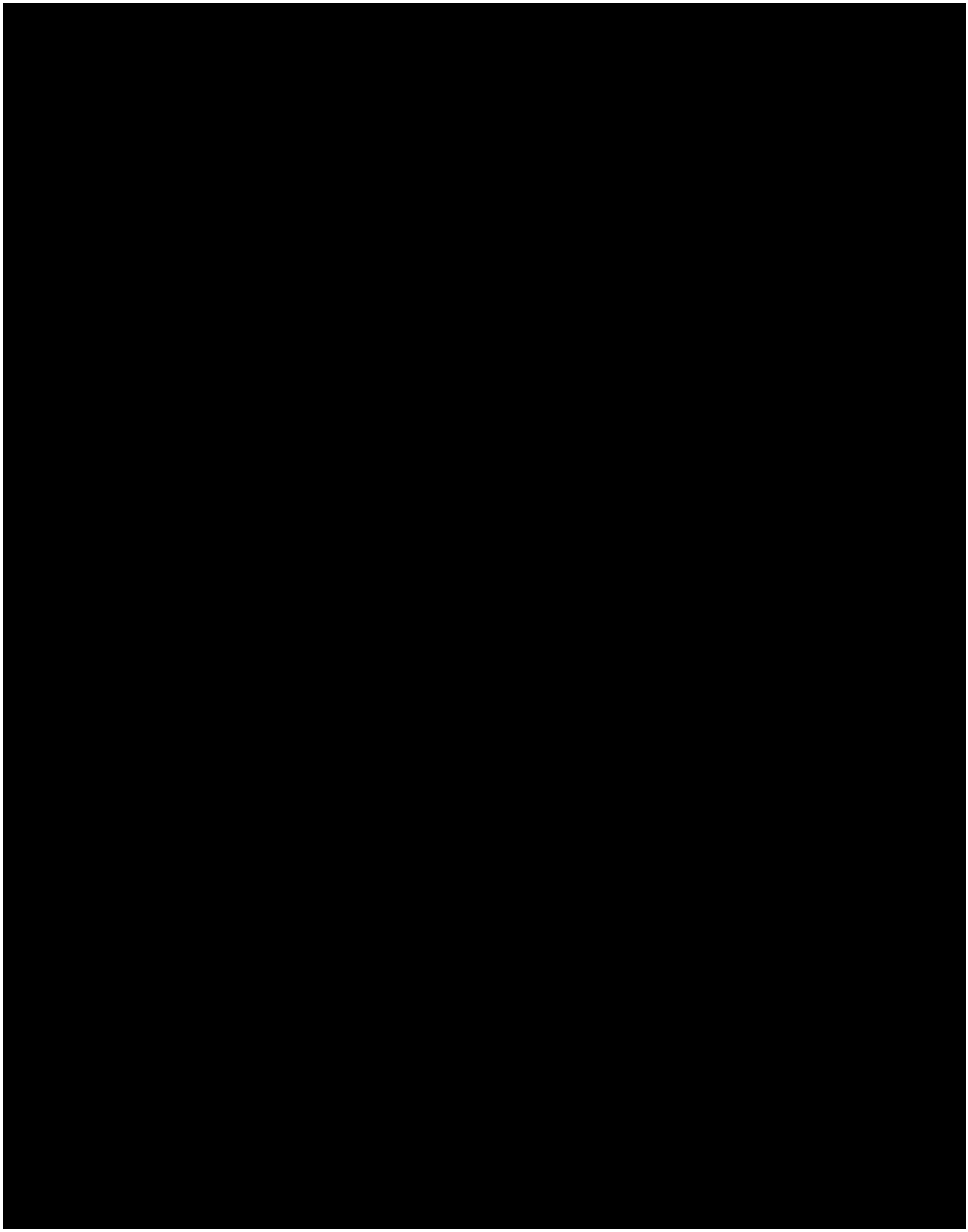
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

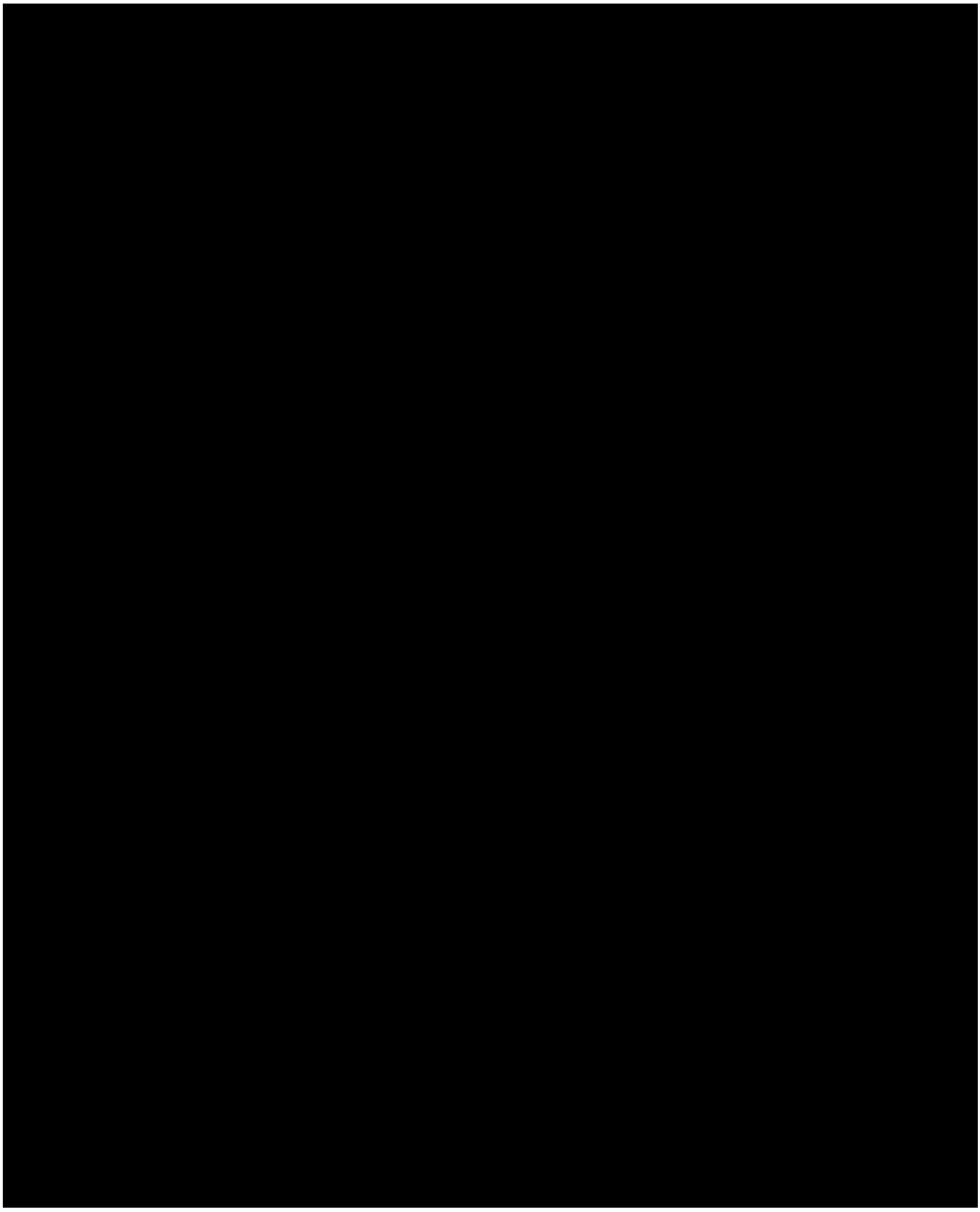
10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

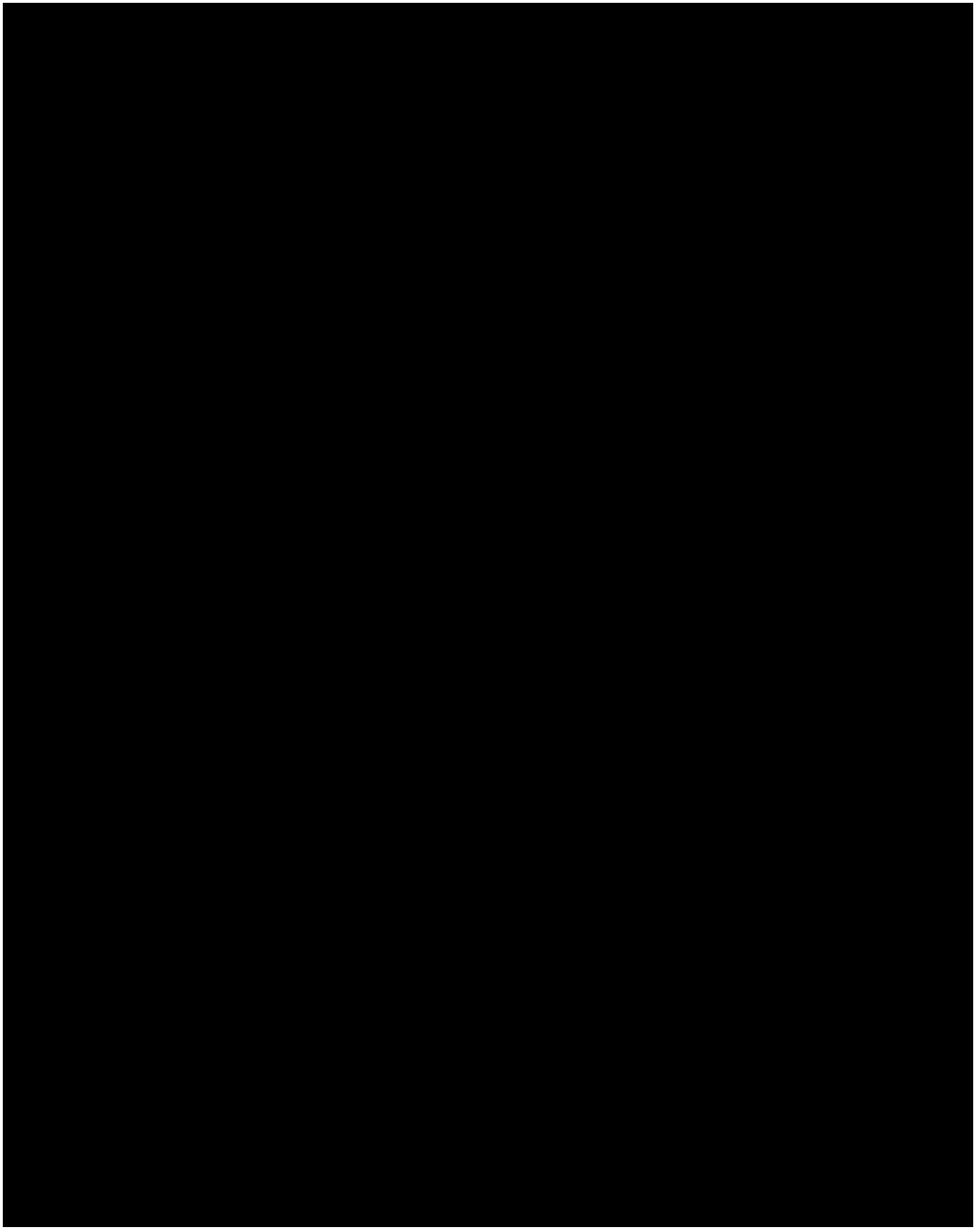
Not applicable.

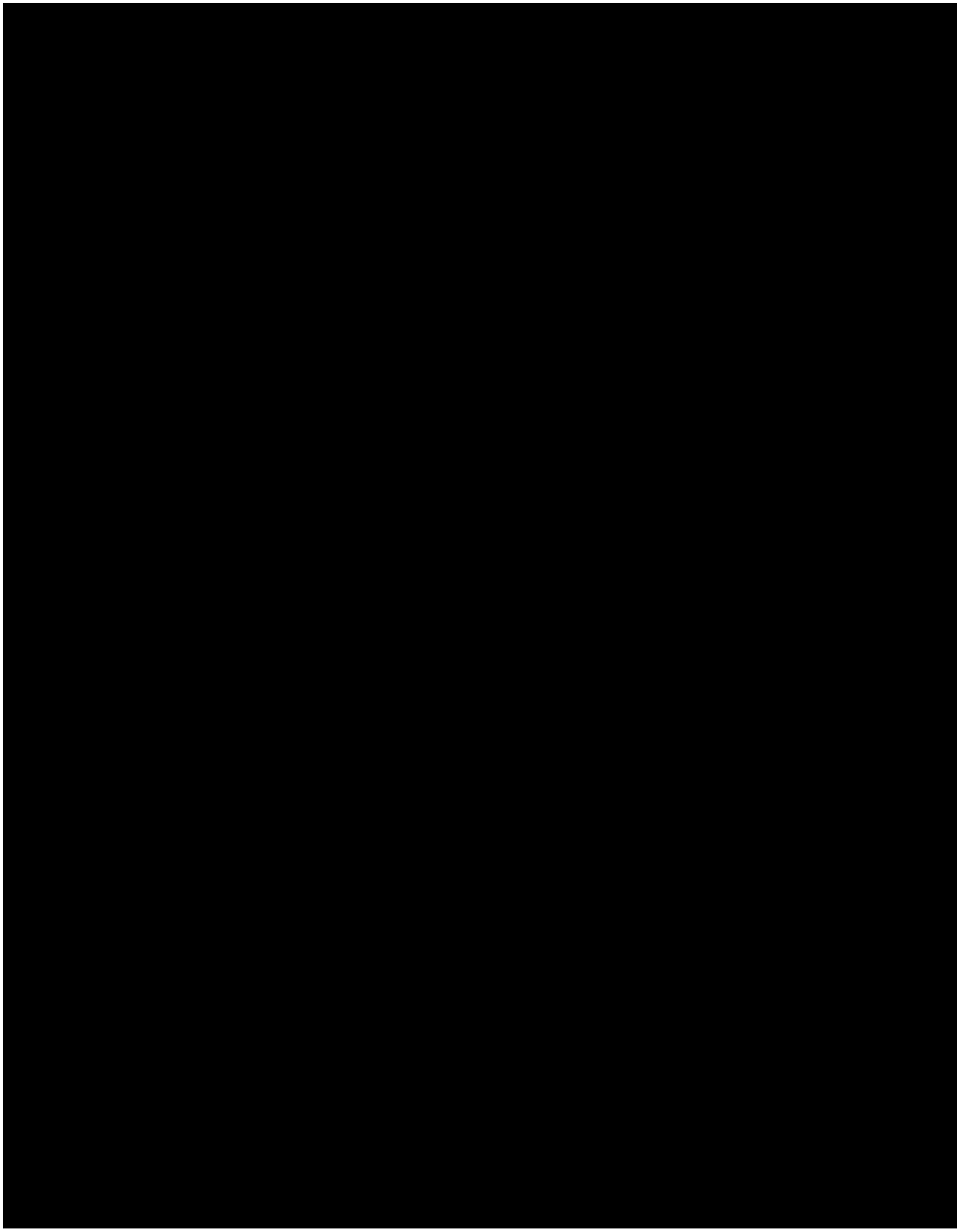
10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

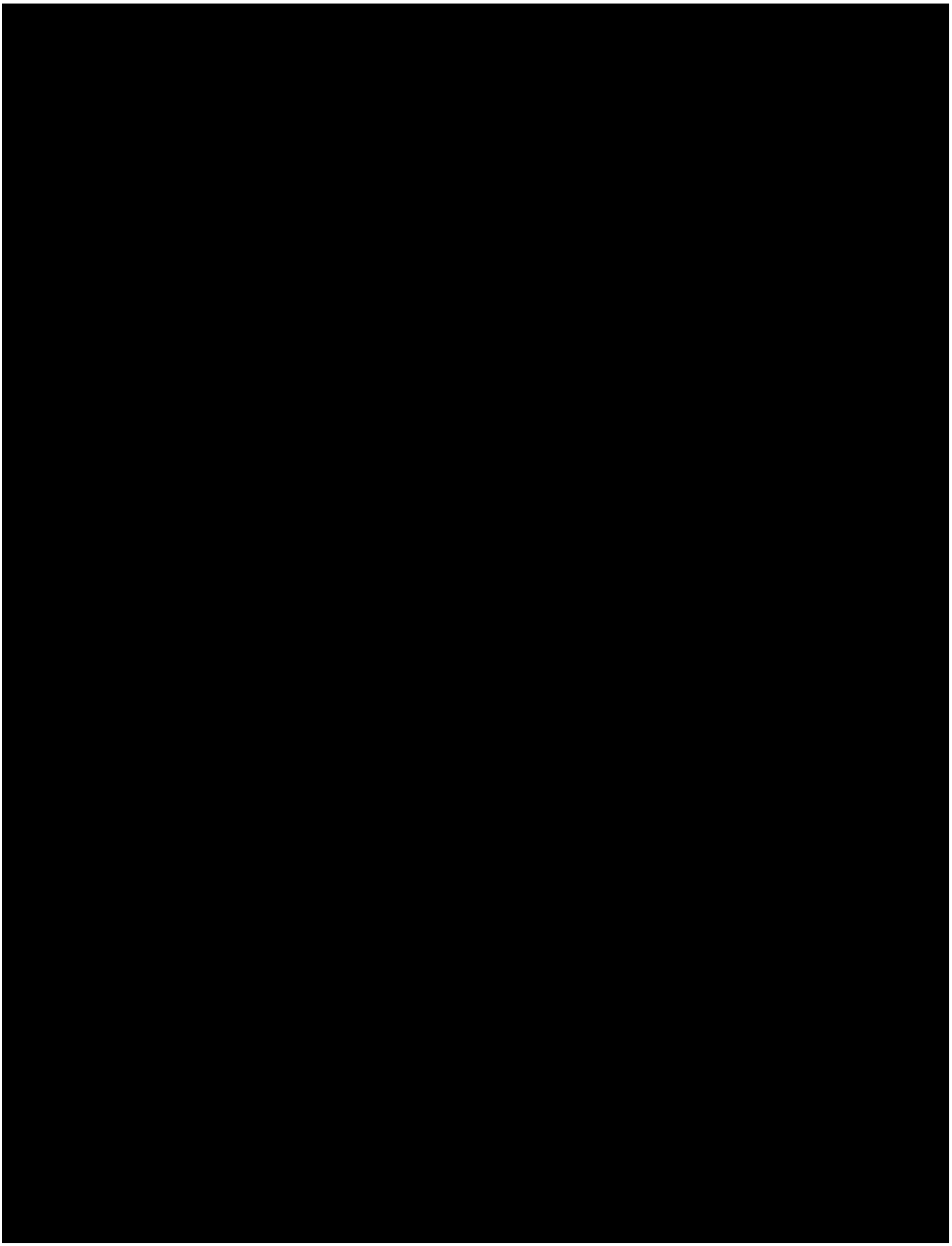
Not applicable.

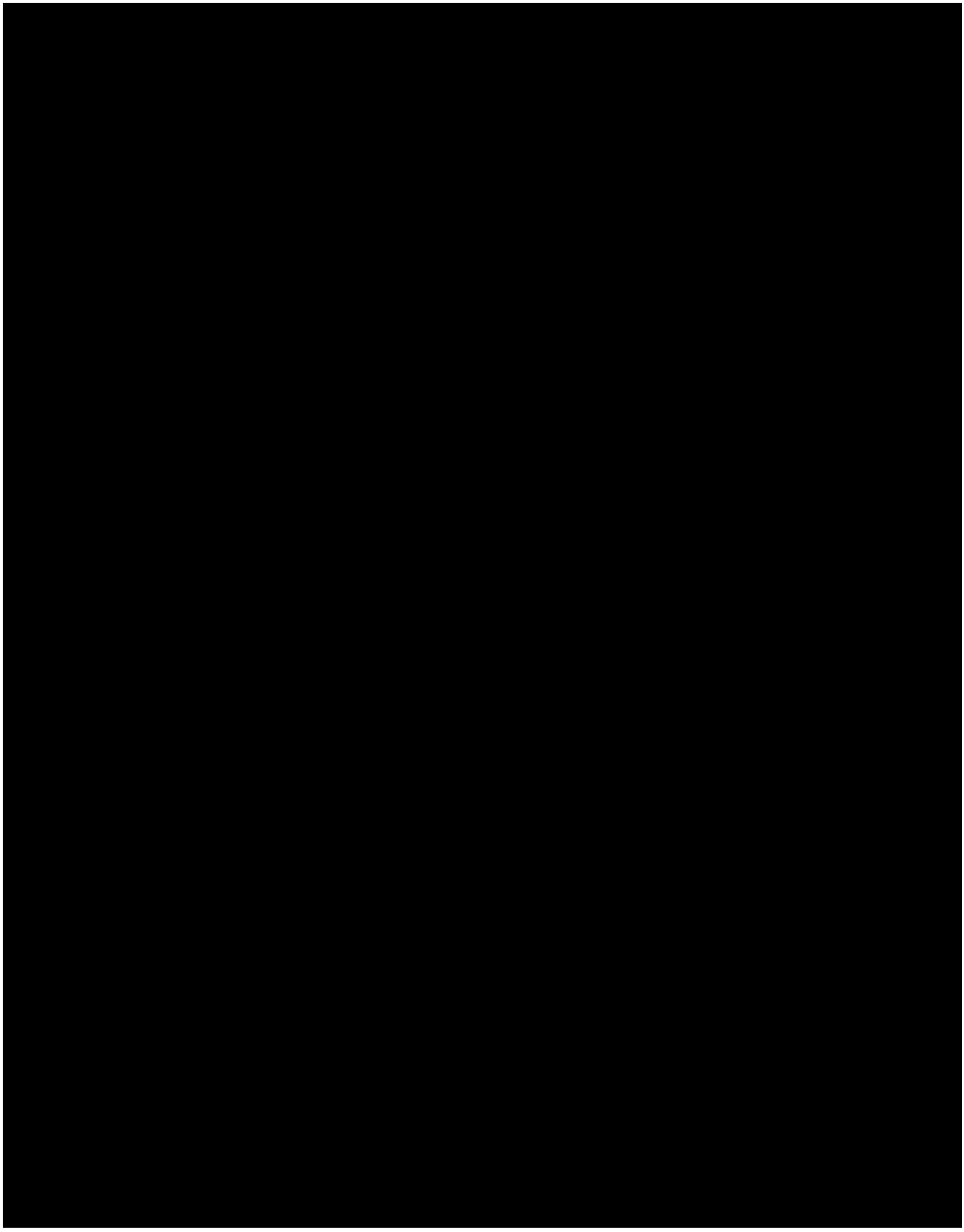


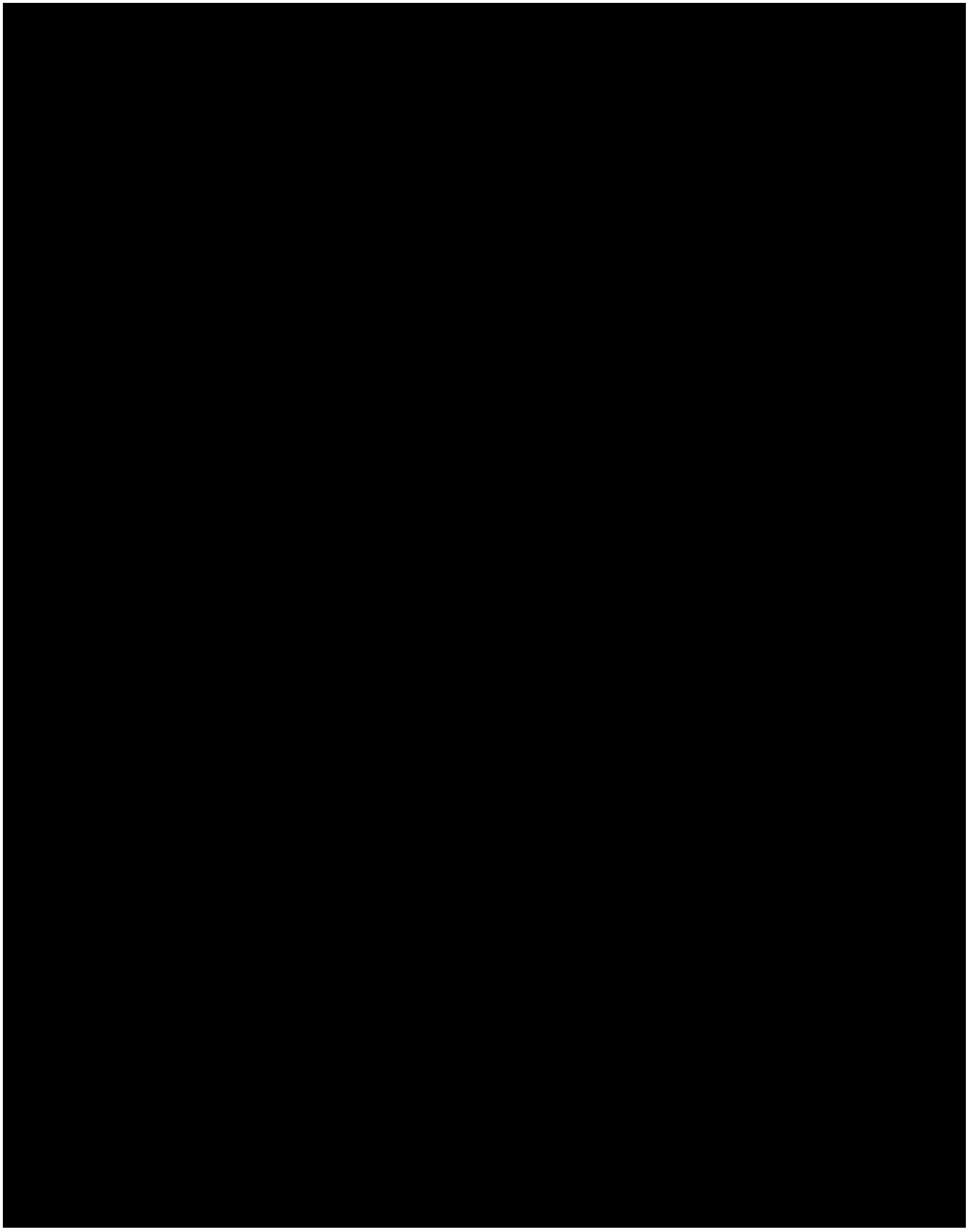


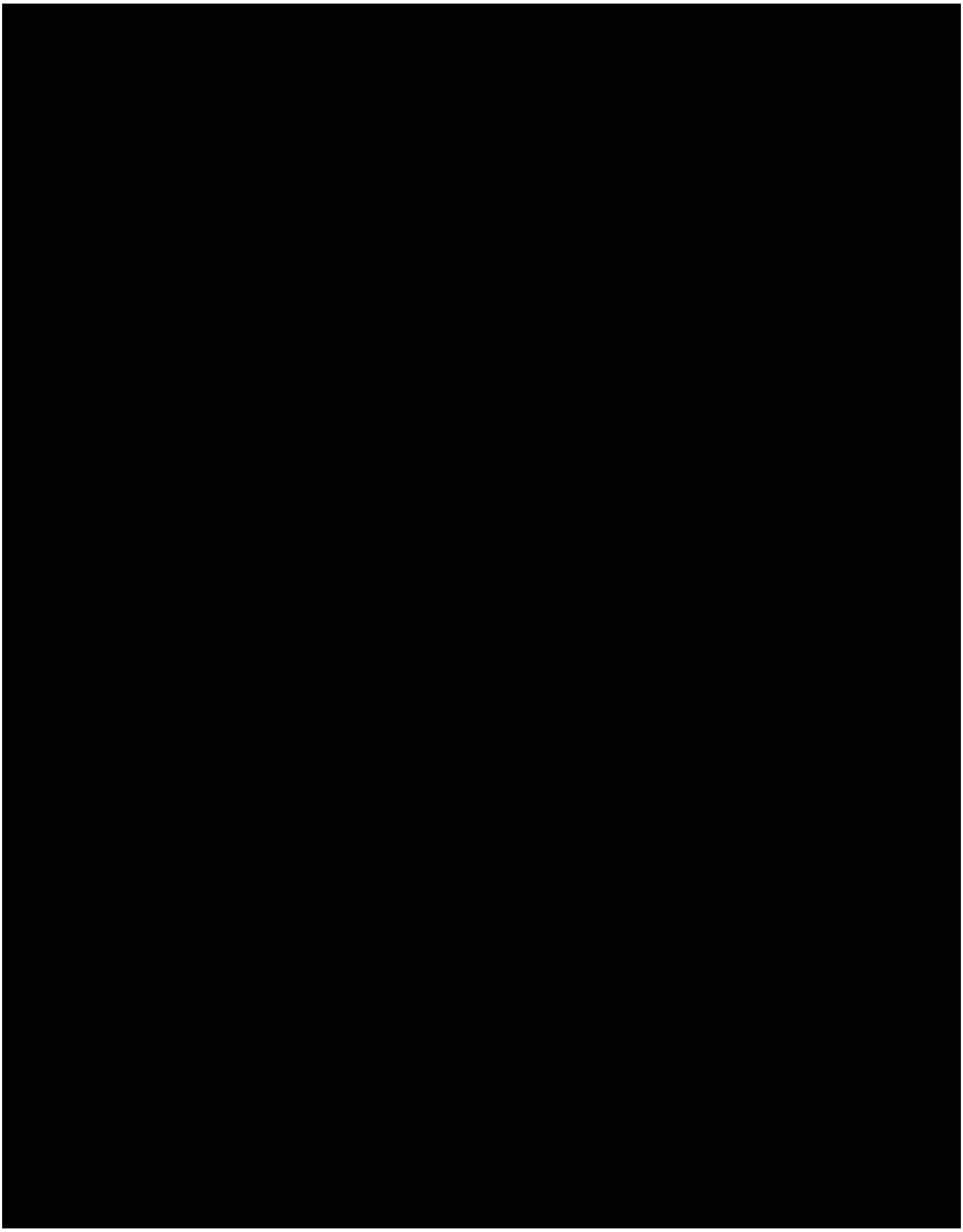


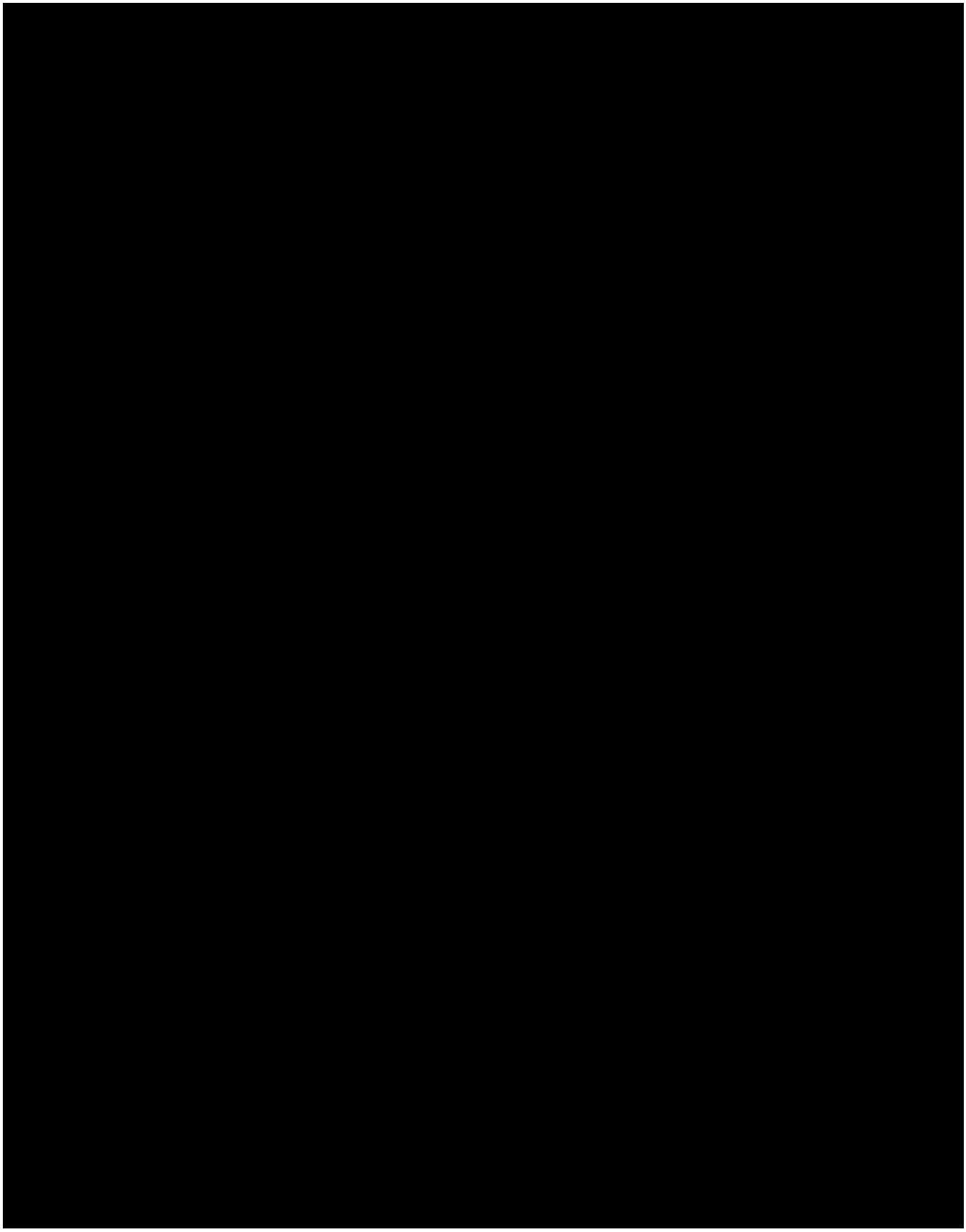












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10.10 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained). Contingencies implemented due to emergency will be documented.

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 to participant's home via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

Study assessments and procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Use of local clinic or laboratory locations may be allowed when central labs analyses cannot be performed due to a government declared national emergency.

If onsite visits are not possible:

- Remote visits (eg, phone call, virtual consultation, etc) or home visits (eg, home nurses, etc) may be planned for the collection of possible safety and/or efficacy data
- Visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension and duration of such extension must be

discussed on a case by case basis with the Sponsor considering first of all participants' safety and best interests.

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 study intervention 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 or unscheduled visit. During the discontinuation period, remote checks (eg, telephone/video 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 (eg, via telephone calls or video calls), but at least one follow up visit should be performed on site (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.

Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension).

10.11 APPENDIX 10: ADDITIONAL APPENDICES

10.11.1 List of CYP3A inhibitors and inducers, and sensitive CYP3A substrates

Table 11 - CYP3A Inhibitors and Inducers

	Strong	Moderate
CYP3A Inducers	Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, phenobarbital, primidone
CYP3A Inhibitors	Boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir and ombitasvir and/or dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole	Aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration. This list is not intended to be exhaustive and may be out of date. For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers or product labeling.

Table 12 - Sensitive CYP3A Substrate

Sensitive CYP3A Substrates
Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tolvaptan, tipranavir, triazolam, vardenafil

Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, U.S. Food and Drug Administration. This list is not intended to be exhaustive and may be out of date. For updated information, please refer to https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers or product labeling.

10.11.2 Non-exhaustive list of live (attenuated) vaccines

Table 13 - List of live (attenuated) vaccines

Live (attenuated) vaccines
Chickenpox (Varicella[a]), Intranasal influenza, Measles (Rubeola), Measles-mumps-rubella (MMR) combination, Mumps, Oral polio (Sabin), Oral typhoid, Rubella, Smallpox (Vaccinia), Shingles (Herpes zoster), Bacille Calmette-Guerin, Yellow fever.

Note: This list is indicative and not exhaustive.

a Shingrix is allowed for Shingles as a non-live Varicella vaccine.

10.11.3 Non-exhaustive list of prohibited medications and therapies

Table 14 - Non-exhaustive list of prohibited medications and therapies

Drug category	Non exhaustive list of Drugs
Immunosuppressive or immunomodulating drugs	**Immunosuppressant drugs** • mycophenolate mofetil • azathioprine • methotrexate • cyclosporine • dapsone • Intravenous immunoglobulin (IVIG) • anakinra (Kineret) • etanercept (Enbrel) • other immunosuppressant drugs **Biologic or targeted-synthetic disease modifier drug** • infliximab • adalimumab • golimumab • abatacept • tocilizumab • certolizumab • secukinumab • IFN-γ • JAK inhibitors • Dupilumab • Other biologic or targeted-synthetic disease modifiers **Anti-CD20 drugs or long-acting biologics** • rituximab • ofatumumab • other anti-CD20 drugs or long-acting biologics
Live vaccines	**See Section 10.11.2**
Phototherapy or regular use of tanning booth/parlor	**Phototherapy or regular use (more than 2 visits per week) of a tanning booth/parlor**
Proton Pump inhibitors	• omeprazole • esomeprazole • lansoprazole • pantoprazole • other proton pump inhibitors
Known strong-to-moderate inducers or inhibitors of CYP3A	**See Section 10.11.1**

This table provides a list of the most common medications within the classes of prohibited concomitant drugs. It is not exhaustive, and Site Investigators should contact the Medical Monitor if they are unsure about a specific medication that is not listed in this table.

10.11.4 Non-exhaustive list of corticosteroids of different relative potencies

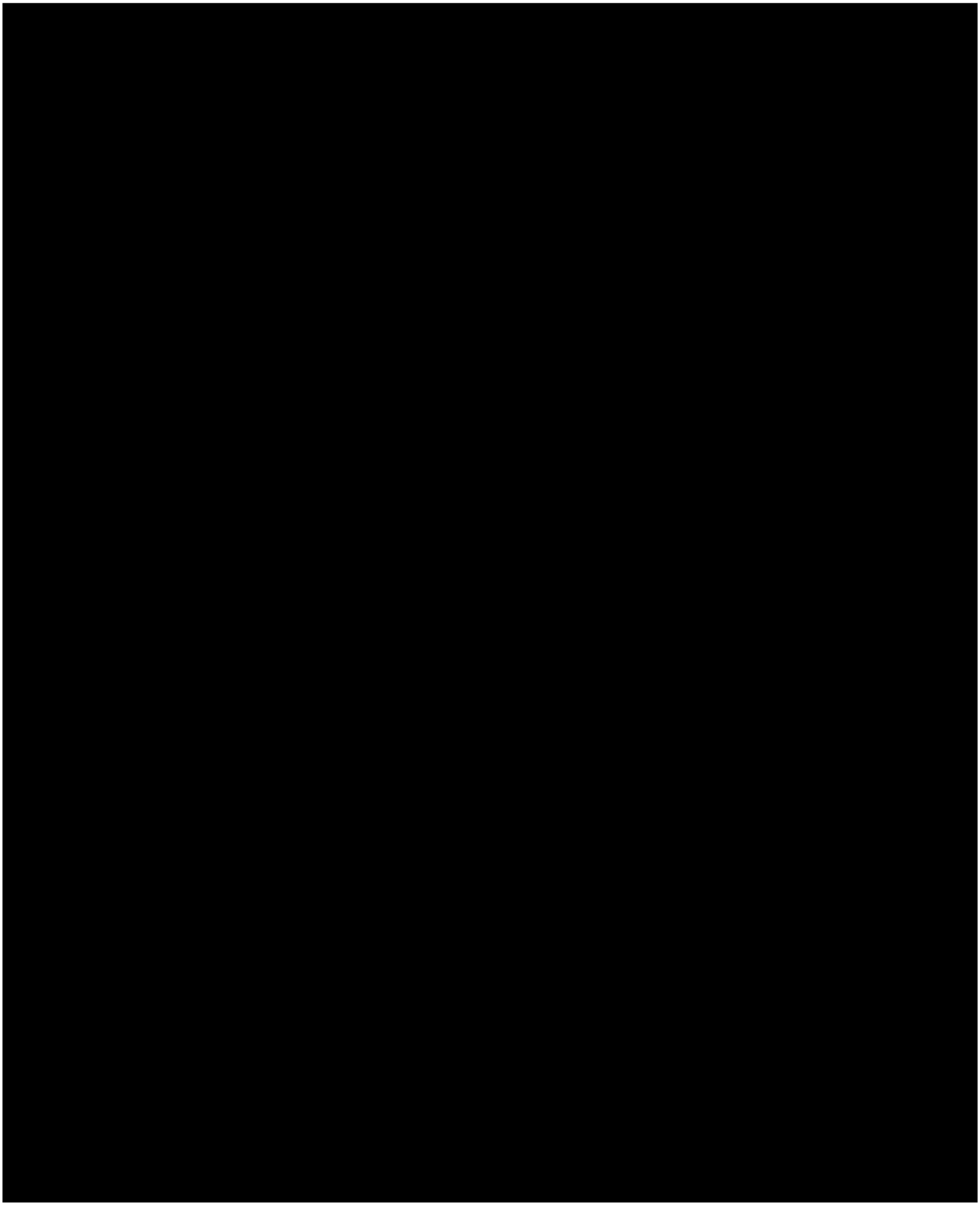
Table 15 - Relative potencies of topical corticosteroids

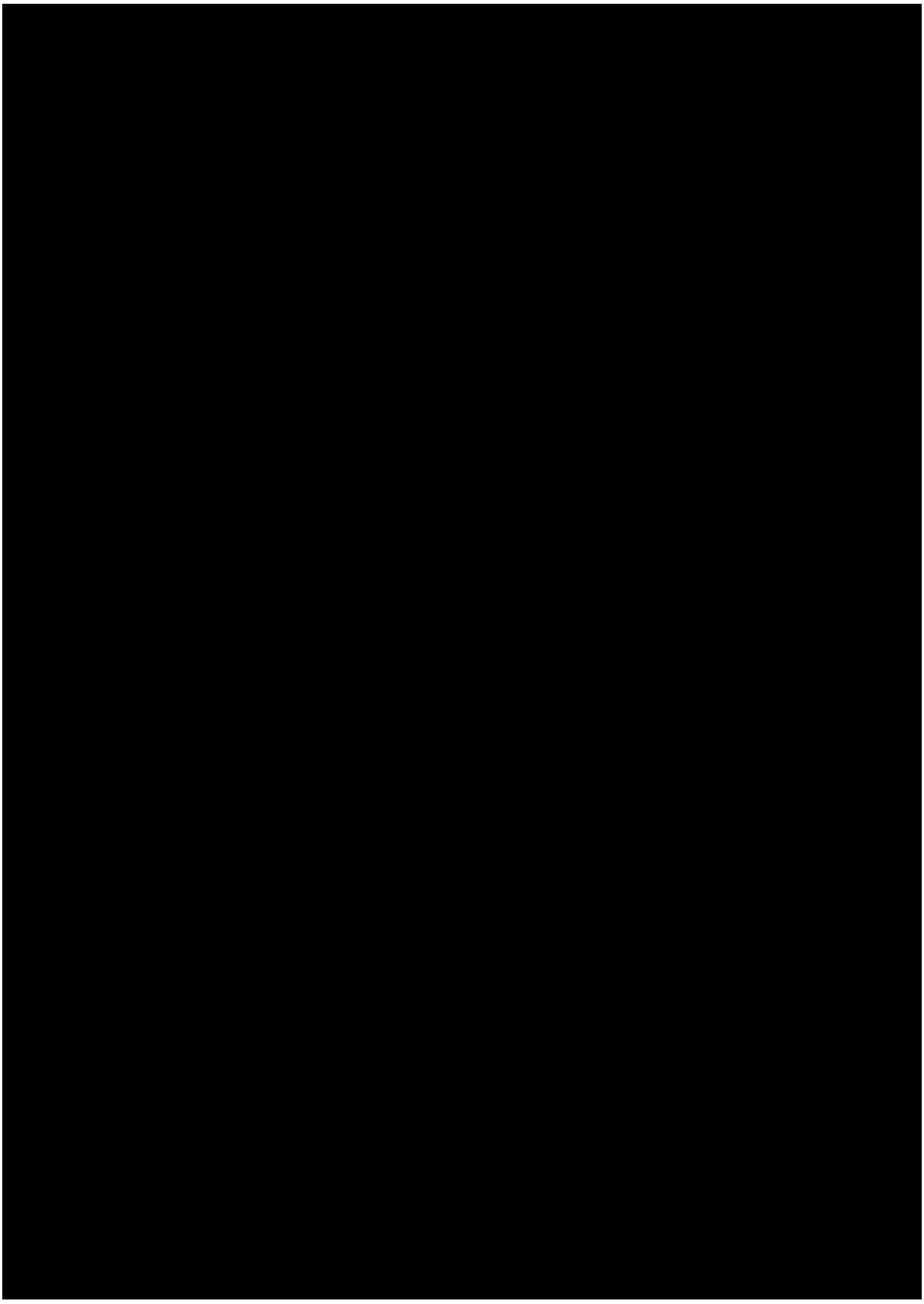
Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

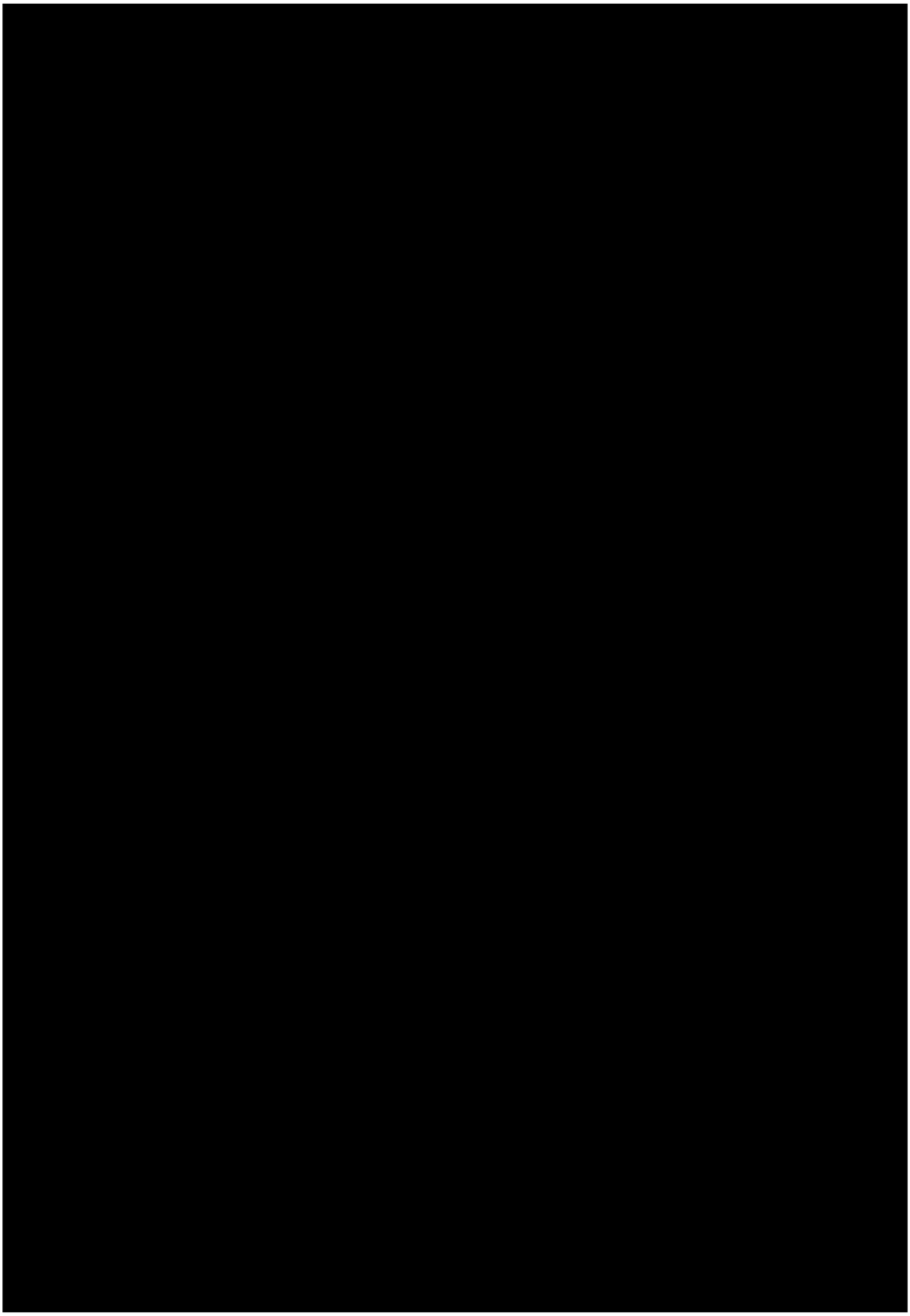
Includes representative examples and not all available agents.
This table is sourced from literatures (32, 33).

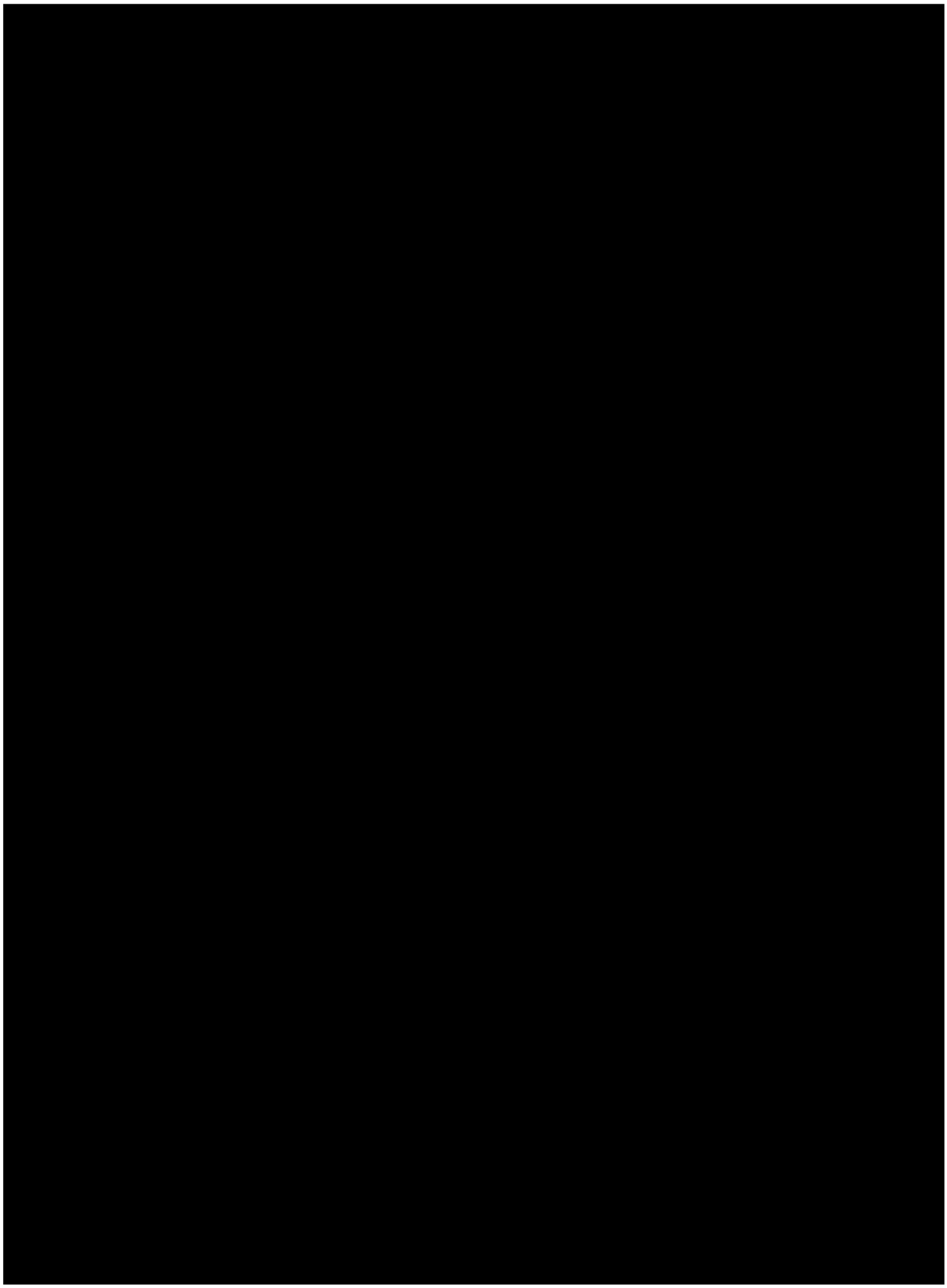
10.11.5 Clinicians-reported outcomes and patient-reported outcomes

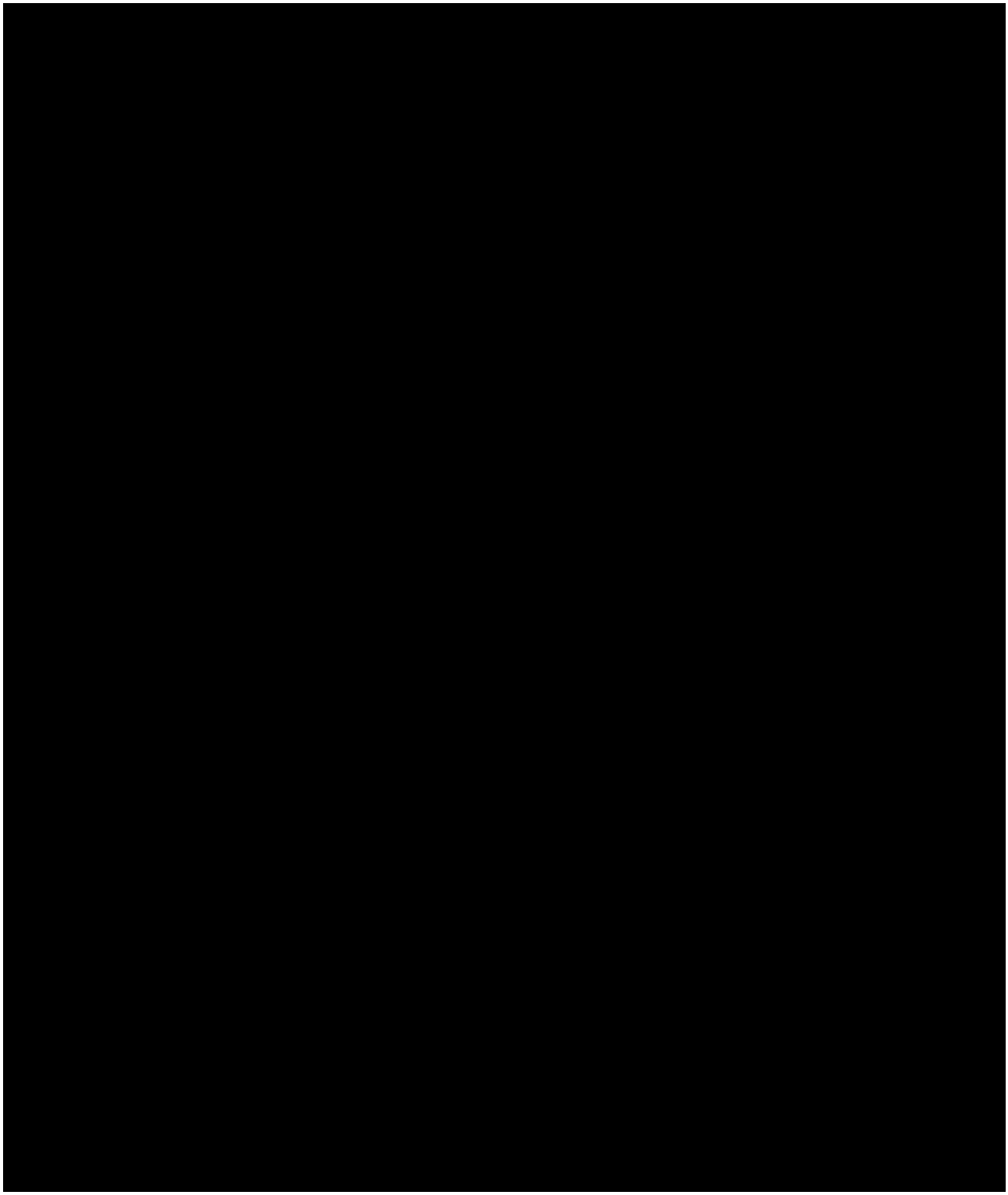
10.11.5.1 Eczema Area and Severity Index (EASI)

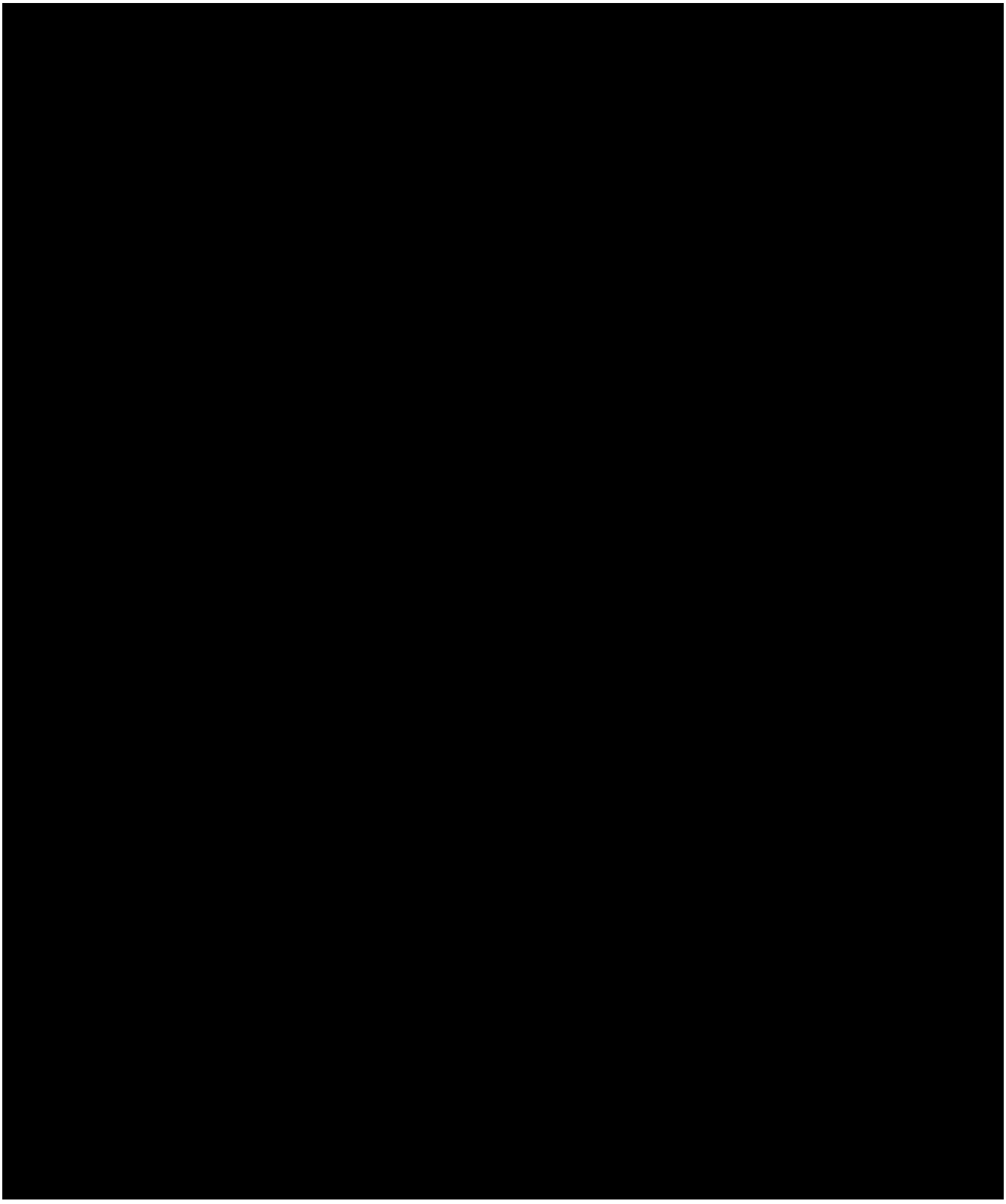


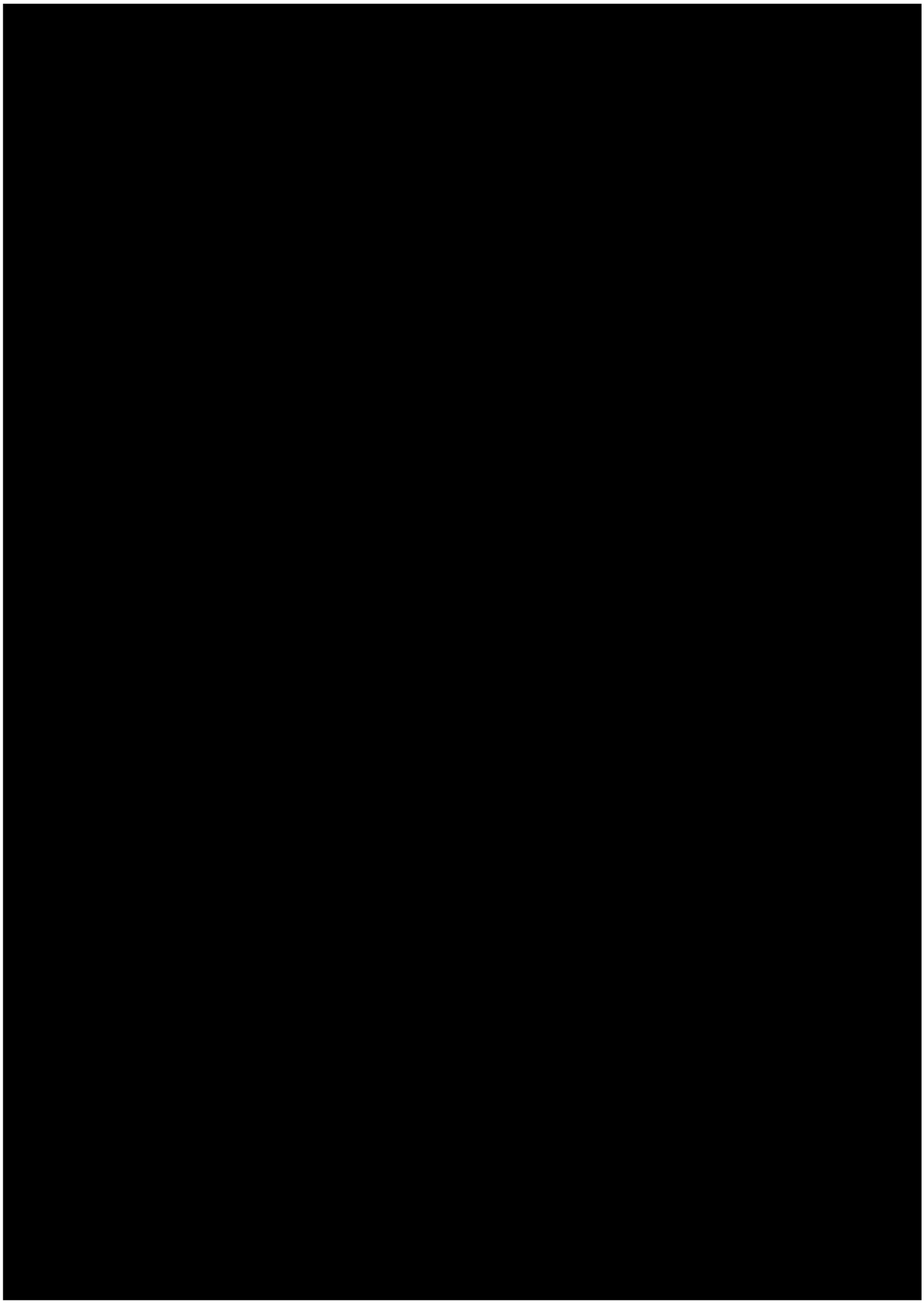


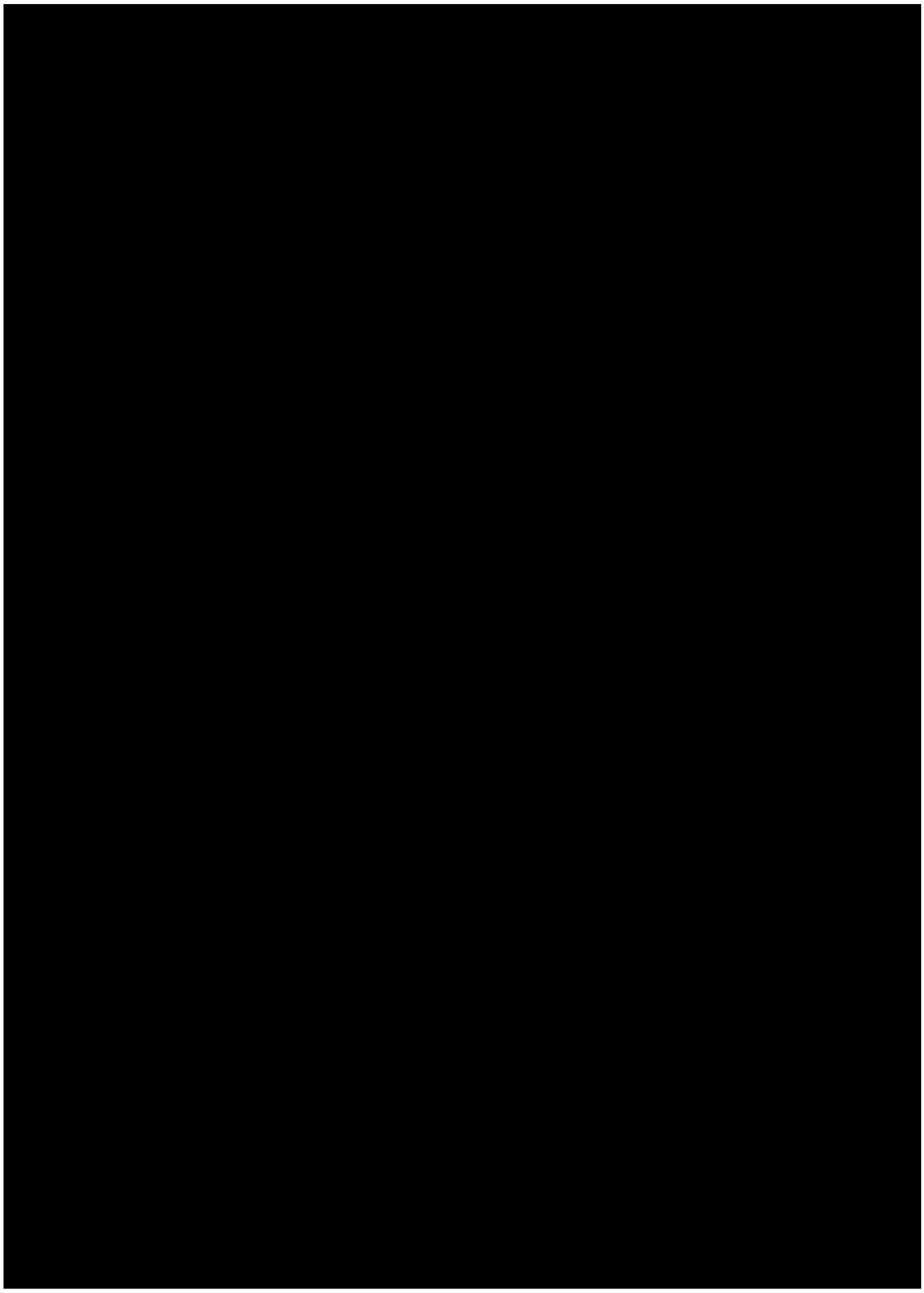




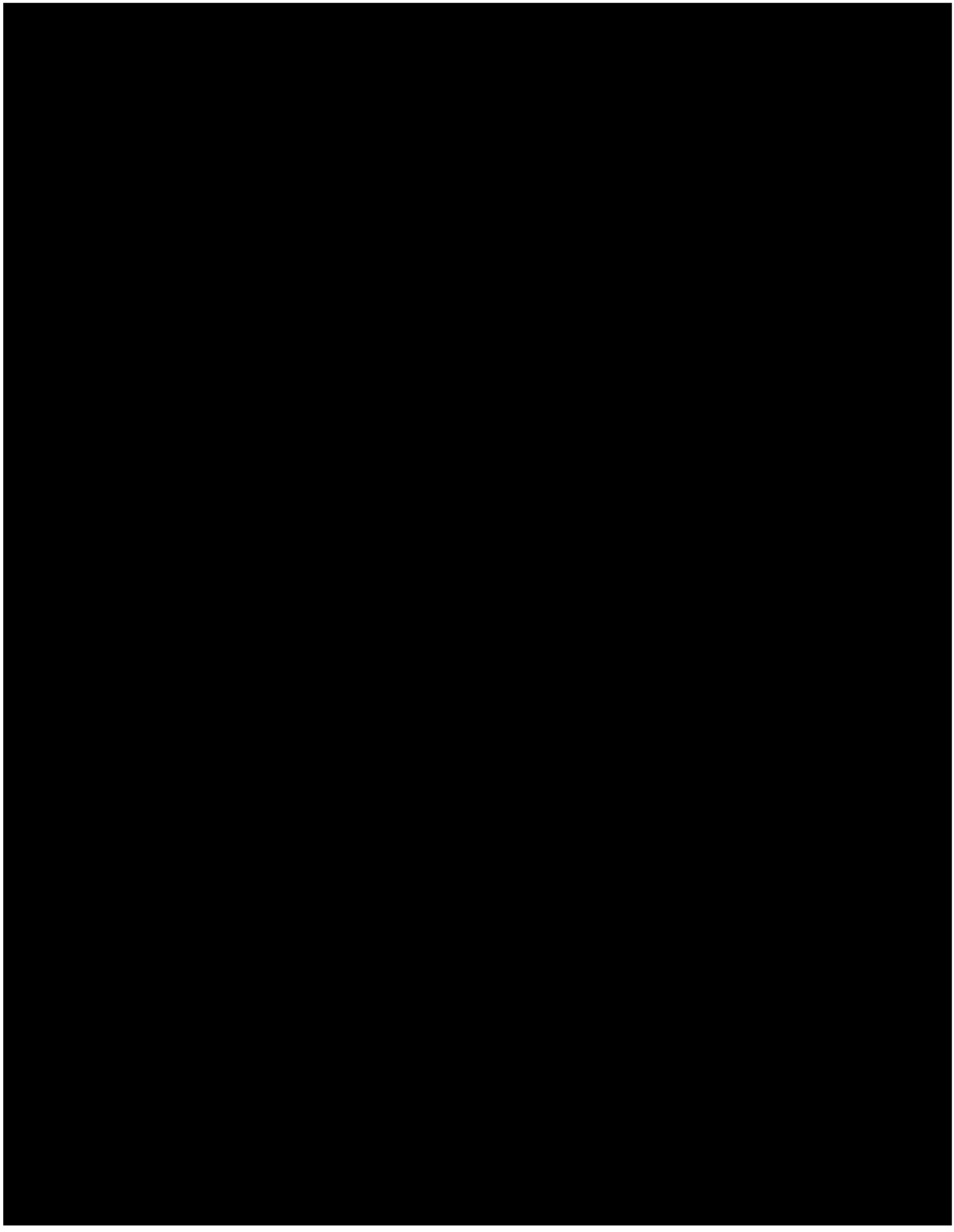




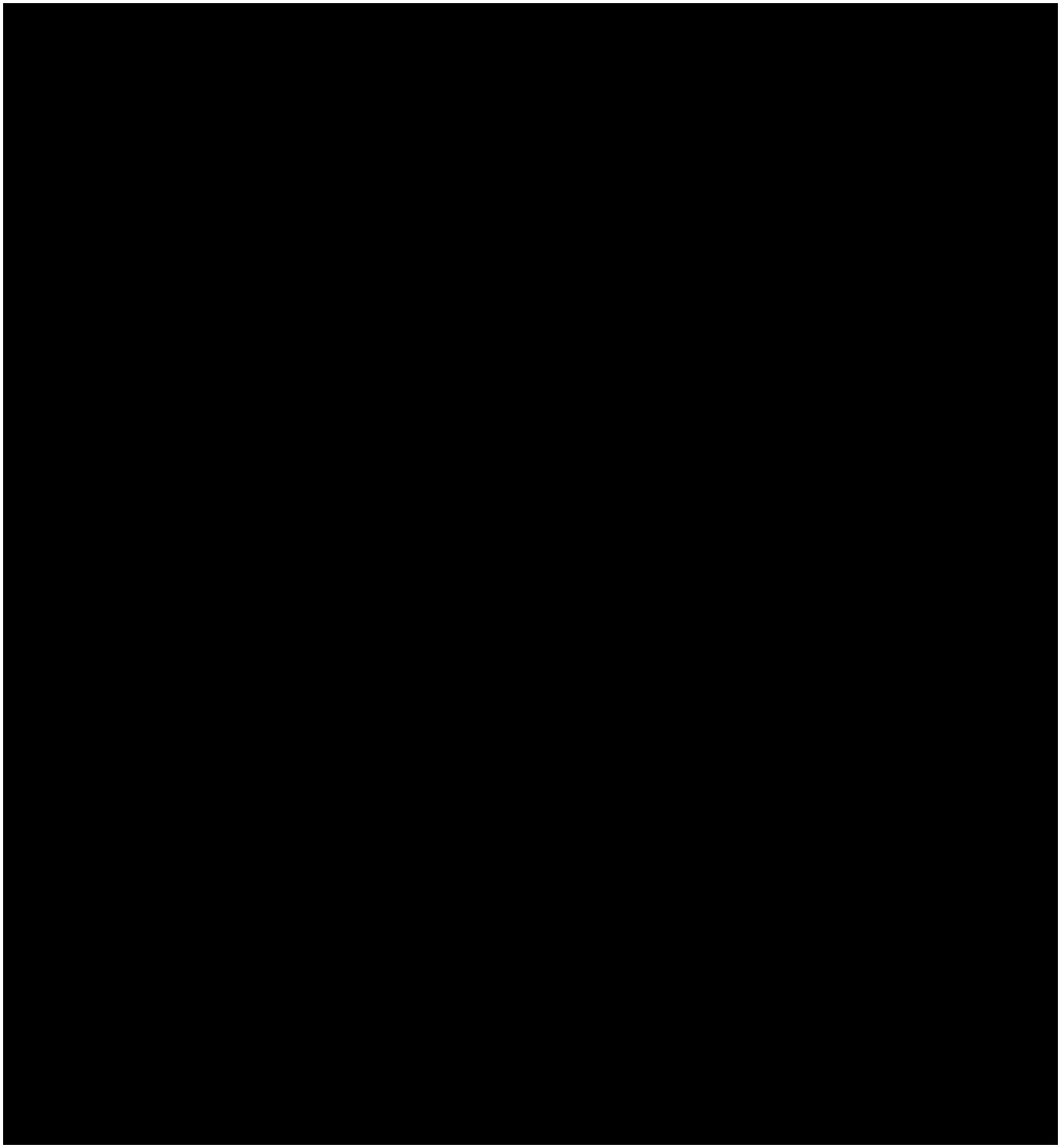




10.11.5.2 Pruritus Numeric Rating Scale (NRS)



10.11.5.3 Investigator's Global Assessment (IGA)



10.12 APPENDIX 11: ABBREVIATIONS AND DEFINITIONS

AD:	atopic dermatitis
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AMP:	antimicrobial peptide
AST:	aspartate aminotransferase
BHRA:	basophil histamine release assay
BID:	twice a day
BTK:	Bruton's tyrosine kinase
CI:	confidence interval, confidence interval
CMH:	Cochran-Mantel-Haenszel
COVID-19:	coronavirus disease 2019
CPK:	creatine kinase
CRF:	case report form
CYP:	cytochrome P450
DTP:	direct to patient
EASI:	Eczema Area and Severity Index
ECG:	electrocardiogram
e-diary:	electronic diary
EOT:	End of Treatment
FcεR:	Fc-epsilon receptor
FDA:	Food and Drug Administration
H2:	Histamine 2
HIV:	human immunodeficiency virus
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig:	immunoglobulin
IGA:	Investigator's Global Assessment
IgG4-RD:	immunoglobin G4-related disease
IL:	interleukin
IMP:	investigational medicinal product
IRT:	interactive response technology
ITP:	immune thrombocytopenia
JAK:	Janus kinase
LAR:	legally authorized representative
LDH:	lactate dehydrogenase
LS:	least squares
NIMP:	noninvestigational medicinal product

NRS:	Numerical Rating Scale
PBMC:	peripheral blood mononuclear cell
PCSA:	potentially clinically significant abnormality
PF:	pemphigus foliaceus
PP-NRS:	peak pruritus Numerical Rating Scale
PV:	pemphigus vulgaris
QFT:	Quantiferon test
qRT-PCR:	quantitative reverse transcription polymerase chain reaction
RBC:	red blood cells
SAE:	serious adverse event
SAP:	statistical analysis plan
SoA:	Schedule of Activities
TARC:	thymus- and activation-regulated chemokine
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event
TID:	three times a day
ULN:	upper limit of normal
wAIHA:	warm autoimmune hemolytic anemia
WOCBP:	woman of childbearing potential
WONCBP:	woman of non-childbearing potential

10.13 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 02 (03 January 2022)

This amended protocol 02 (amendment 02) 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 reason for this amendment is to evaluate the efficacy and safety of two dose regimen of rilzabrutinib, the current dose regimen of 400 mg twice a day (BID) and an additional higher regimen of 400 mg three times a day (TID) in two staggered double-blind cohorts for a total number of 120 participants split as follows:

- The total number of participants in the BID cohort is reduced from 70 to 50 (n=30 rilzabrutinib / 20 matching placebo)
- The total number of participants in the TID cohort is 70 (n=42 rilzabrutinib / 28 matching placebo).

Bruton's tyrosine kinase (BTK) appears as an attractive drug target in atopic dermatitis (AD) by inhibiting the dysregulated signaling and activation of the pathogenic cells B-cells, mast cells and basophils implicated in skin inflammation suggesting the presence of both Type 1 and Type 2 inflammation as per the Gell and Coombs classification (Type1 being an immediate hypersensitivity mediated by IgE and Type 2b being mediated by IgG autoantibody). The basophil histamine release assay (BHRA) has been used in assessing endotypes of chronic spontaneous urticaria (CSU). Those with BHRA- results are classified as Type 1 (immediate hypersensitivity mediated by IgE) while those with BHRA+ results are classified as Type 2b (mediated by IgG autoantibody). This endotype classification system has been demonstrated to contribute to clinical responses to BTK inhibitors. BHRA has not been studied extensively in AD. Thus, determining the BHRA status at baseline and end of study will provide epidemiology of BHRA classification in AD and assess if a given endotype has a better response to BTK inhibitor or not.

In addition, clarifications and corrections have been made based on feedback from study sites.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	NCT identifier updated.	Administrative change.
Section 1.1 Synopsis; Section 1.2 Schema; Section 4.1 Overall Design;	Added additional TID cohort (42 participants receiving rilzabrutinib / 28 participants receiving placebo) which will begin enrolling after participants enrolled in BID cohort. Adjusted BID cohort sample size from 42 in rilzabrutinib arm and 28 in placebo arm to 30 in rilzabrutinib and 20 in placebo. Thus, the total number of participants was adjusted to "**approximately 120**".	Dose regimen reconsidered to ensure sufficient inhibition in mast cells and basophils activation that play an important role in Type 2-predominant inflammatory diseases such as atopic dermatitis.
Section 1.1 Synopsis; Section 6 Study Intervention(s) and Concomitant Therapy	The frequency for IMP dosing was revised to "**Consecutive doses should ideally be administered 12 hours apart (and not less than 8 hours apart) for BID dosing, and ideally at least 6 hours apart (and not less than 4 hours apart) for TID dosing**".	Clarification to align with the amended study design.
Section 1.3 Schedule of Activities (SoA)	Added footnote "**y**" to clarify last dose is taken in the morning of Visit 7 (Week 16). The legend "Serum and plasma soluble biomarker assays" has been replaced with "**Sampling for soluble biomarker assays**". Added "**for future use**" in the legend of "Whole blood sample for RNA extraction (optional)".	Clarification.
Section 1.3 Schedule of Activities (SoA); Section 4.1 Overall Design	In the SoA, changed "skin prick testing (RAST)" to "skin prick testing / RAST". In Section 4.1, added "**or skin prick testing when RAST testing is not feasible**" for Screening Skin testing.	To allow alternative test for RAST as skin testing is more commonly used in some countries.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA) Section 3 Objectives and Endpoints; Section 9.3.4 Exploratory Endpoint (s) Section 8.6 Biomarkers	In the SoA, added basophil histamine release assay (BHRA) as a biomarker assessment to be tested at baseline (Week 0) and end of study (Week 17). In Section 3 and Section 9.3.4, added "histamine release factors including functional autoantibodies against FceRI" to the exploratory endpoint to assess the effect of rilzabrutinib on biomarkers. In Section 8.6, included BHRA cellular assay to biomarker tests.	To add BHRA to help characterize the disease endotypes of responders.
Section 1.3 Schedule of Activities (SoA): footnote "**e**" Section 4.1 Overall Design	Changed from "background treatment" to "background **topical** treatment".	Clarification.
Section 1.3 Schedule of Activities (SoA): footnote "**e**" Section 7.1.3 Temporary Discontinuation	In the SoA, footnote "**e**", added "**Participants should also record all temporary intervention discontinuations in the e-diary everyday (when applicable) during the study intervention period**". In Section 7.1.3, revised to state that all temporary intervention discontinuations should be recorded "**by the participant in the e-diary**".	To align with the fact that the information of temporary intervention discontinuation is recorded by the participants in the e-diary.
Section 2.1 Study Rationale Section 2.2 Background	Updated information of systemic therapies approved for AD. Updated "Clinical Experience" based on the new version of Investigator's Brochure (IB).	Update.
Section 4.1 Overall Design	Included "cats" into the query on personal and family history of allergy during Screening.	Consistency.
Section 4.3 Justification for Dose	Revised to include the scientific rationale for the TID dose regimen.	Changes to align with amended study design.
Section 5.1 Inclusion Criteria	I 06. Added a note ***BSA estimated using the method described in Section 8.1.2.**" to clarify the method for BSA estimation.	Clarification.
Section 5.2 Exclusion Criteria	"E 04" and "E 13" were revised to: "E 04. History of serious infections requiring intravenous therapy with the potential for recurrence (**as judged by the Site Investigator and the Sponsor Medical Monitor), 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)." "E 13. Use of TCS, **topical** calcineurin (tacrolimus, and/or pimecrolimus) or topical phosphodiesterase 4 inhibitor within 1 week prior to baseline and as concomitant medication."	Clarification.
Section 6.1 Study Intervention(s) Administered	Added footnote "**a**" in Table 3 for IMP "Dose Formulation": [redacted]	Clarification of the non-drug component within IMP formulations and consistency.

Section # and Name	Description of Change	Brief Rationale
	[redacted] Table 3 and Table 4 were updated with addition of information related to the TID cohort.	
Section 6.4 Study Intervention Compliance	Removed "~~The Investigator records the dosing information on the appropriate page(s) of the eCRF~~"; the term "Intervention Log Form" has been revised to "**Accountability Log Form**" in last 2 bullet points; and the term "eCRF data" has been updated to "**compliance data**" in last bullet point.	To align with the fact that the dosing information is recorded in the e-diary and not in the eCRF, and the number of tablets remaining in the returned kits is recorded in the Accountability Log Form.
Section 6.8 Concomitant Therapy Section 10.10.3 Non-exhaustive list of prohibited medications and therapies	Added a non-exhaustive list of prohibited medications and therapies in the Section 10.10.3 Appendix 10 and referred to this list from Section 6.8. In Section 6.8, added "**Prescription moisturizers (with or without additives such as ceramide, hyaluronic acid, urea, or filaggrin), topical anesthetics or antihistamines that have been initiated prior to the screening period are allowed to be continued if the doses are stable**".	Clarification and consistency.
Section 6.8.1 Rescue Medicine	Added "**The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded**".	Clarification.
Section 8 Study Assessments and Procedures	Revised the maximum amount of blood collected from "400 mL" to "450 mL".	Updated total sampled blood volume to include the additional sample taken for BHRA test.
	Added "**Section 10.10.5 provides representative examples of the EASI scoring system, estimation of BSA of EASI, NRS and IGA that will be used in this study**"	Clarification.
Section 8.1.2 Estimation of Body Surface Area (BSA) of EASI	Adapted the text on BSA to the palm method provided in the Section 10.10.5.1 Appendix 10.	Consistency with Section 10.10.5.1 Appendix 10.
Section 8.3.1 Time period and frequency for collecting AE and SAE information	Removed duplicated sentence "~~All AE will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3)~~".	Correction.
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 refer to section 10.3.1 for definition of disease-related events NOT meeting the AE definition.	Consistency with Section 10.3 Appendix 3.
Section 8.9 Use of Biological Samples and Data for Future Research	Revised to align with updated common language provided by Sponsor protocol template.	Template language update.
Section 1.1 Synopsis; Section 9.1 Sample Size Determination;	Revised to adjust the sample size for participants receiving rilzabrutinib 400 mg BID or matching placebo and added the sample size justification for participants receiving rilzabrutinib 400 mg TID or matching placebo.	Consistency with updated study design and clarification.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1 General Considerations; Section 9.3.2 Primary Endpoint(s); Section 9.3.3.1 The main secondary endpoints	Revised the summary of primary estimand for primary endpoint and the analysis of the main secondary endpoints to clarify the planned statistical analyses.	
Section 10.10.2 Non-exhaustive list of live (attenuated) vaccines	Added footnote "**Sringrix is allowed for Shingles as a non-live Varicella vaccine**".	Clarification.

In addition, other minor editorial changes were implemented throughout the protocol.

Amended protocol 01 (08 July 2021)

This amended protocol 01 (amendment 01) 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

To incorporate feedback from health authorities 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
Section 1.3 Schedule of Activities	Added IMP dispense for unscheduled visit with a footnote "x": "**x. if needed, according to Investigator (eg, end of temporary discontinuation, etc).**"	Correction since dispensing IMP may occur during unscheduled visit
[redacted]	[redacted]	[redacted]
Section 1.3 Schedule of Activities, footnote "j" and Section 10.2 Appendix 2 Clinical Laboratory Tests	"urea" was clarified as "blood urea nitrogen"	Clarification.
Section 5.1 Inclusion Criteria	Inclusion Criterion I09, for female participants, "… • Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate	Correction for consistency with the wording in Appendix 4 where a period of at least 4 weeks after the last administration of study intervention is

Section # and Name	Description of Change	Brief Rationale
	of < 1% per year), **preferably** with low user dependency, as described in Appendix 4 Contraceptive and barrier guidance (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."	requested (and not 1 week). Contraceptive methods with low user dependency are preferred, but methods that are user dependent are nevertheless allowed during the study.
Section 8.3.5 Pregnancy	In the first bullet point, the follow-up period for collection of details of all pregnancies was extended from "1 week" to "**4 weeks**" to align with the required time period for post-intervention contraception determined in inclusion criterion I09. The following text were removed: "~~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~~."	Consistency to align with the updated post-intervention contraception follow up period of 4 weeks. Correction as pregnancy will lead to permanent intervention discontinuation in all cases, so study intervention continuation is not applicable for this study.

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

11 REFERENCES

1. Bieber T. Atopic dermatitis. Ann Dermatol. 2010;22(2):125-37.

2. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70(2):338-51.

3. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schäppi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? J Allergy Clin Immunol. 2017;139(4S):S58-S64.

4. Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies. J Allergy Clin Immunol Pract. 2017;5(6):1519-31.

5. Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatol Clin. 2017;35(3):283-9.

6. Moyle M, Cevikbas F, Harden JL, Guttman-Yassky E. Understanding the immune landscape in atopic dermatitis: The era of biologics and emerging therapeutic approaches. Exp Dermatol. 2019;28(7):756-68.

7. Schmitt J, Schwarz K, Baurecht H, Hotze M, Fölster-Holst R, Rodríguez E, et al. Atopic dermatitis is associated with an increased risk for rheumatoid arthritis and inflammatory bowel disease, and a decreased risk for type 1 diabetes. J Allergy Clin Immunol. 2016;137(1):130-6.

8. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. J Allergy Clin Immunol. 2016;138(2):336-49.

9. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1.

10. Kataoka Y. Thymus and activation-regulated chemokine as a clinical biomarker in atopic dermatitis. J Dermatol. 2014;41(3):221-9.

11. Sugita K, Akdis C. Recent developments and advances in atopic dermatitis and food allergy. Allergol. Intern. 2020;69(2):204-14.

12. Badloe FMS, De Vriese S, Coolens K, Schmidt-Weber CB, Ring J, Gutermuth J, et al. IgE autoantibodies and autoreactive T cells and their role in children and adults with atopic dermatitis. Clin Transl Allergy 2020;10:34.

13. Ahmed A, Solman L, Williams HC. Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal. Br J Dermatol 2018;178(3):659-62.

14. Mohamed AJ, Yu L, Backesjo CM, Vargas L, Faryal R, Aints A, et al. Bruton's tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. Immunol Rev. 2009;228(1):58-73.

15. Rip J, Van der Ploeg EK, Hendriks RW, Corneth O. The role of Bruton's Tyrosine Kinase in immune cell signaling and systemic autoimmunity. Crit Rev Immunol. 2018;38(1):17-62.

16. Futatani T, Watanabe C, Baba Y, Tsukada S, Ochs HD. Brutons tyrosine kinase is present in normal platelets and its absence identifies patients with X-linked agammaglobulinaemia and carrier females. Br J Hematol. 2001;114(1):141-9.

17. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2013;369(1):32-42.

18. Zarrin AA, Bao K, Lupardus P, Vucic D. Kinase inhibition in autoimmunity and inflammation. Nat Rev Drug Discov. 2021;20(1):39-63.

19. Chang BY, Huang MM, Francesco M, Chen J, Sokolove J, Magadala P, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis Res Ther. 2011;13(4):R115.

20. Xu D, Kim Y, Postelnek J, Vu MD, Hu DQ, Liao C, et al. RN486, a selective Bruton's tyrosine kinase inhibitor, abrogates immune hypersensitivity responses and arthritis in rodents. J Pharmacol Exp Ther. 2012;341(1):90-103.

21. Di Paolo JA, Huang T, Balazs M, Barbosa J, Barck KH, Bravo BJ, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nat Chem Biol. 2011;7(1):41-50.

22. Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B cell activation and is efficacious in models of autoimmune disease and B cell malignancy. Proc Natl Acad Sci USA. 2010;107(29):13075-80.

23. Kim KH, Maderna A, Schnute ME, Hegen M, Mohan S, Miyashiro J, et al. Imidazo[1,5-a]quinoxalines as irreversible BTK inhibitors for the treatment of rheumatoid arthritis. Bioorg Med Chem Lett. 2011;21(21):6258-63.

24. Crofford LJ, Nyhoff LE, Sheehan JH, Kendall PL. The role of Bruton's tyrosine kinase in autoimmunity and implications for therapy. Expert Rev Clin Immunol. 2016;12(7):763-73.

25. Hutcheson J, Vanarsa K, Bashmakov A, Grewal S, Sajitharan D, Chang BY, et al. Modulating proximal cell signaling by targeting Btk ameliorates humoral autoimmunity and end-organ disease in murine lupus. Arthritis Res Ther. 2012;14(6):R243.

26. American College of Rheumatology; ACR COVID-19 Vaccine Clinical Guidance Task Force. COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. Downloaded Apr 2021: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf.

27. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. Hematology Am Soc Hematol Educ Program. 2020;(1):336-45.

28. Langrish CL, Bradshaw JM, Francesco MR, Owens TD, Xing Y, Shu J, et al. Preclinical Efficacy and Anti-Inflammatory Mechanisms of Action of the Bruton Tyrosine Kinase Inhibitor Rilzabrutinib for Immune-Mediated Disease. J Immunol. 2021;206(7):1454-68.

29. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11-8.

30. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761-9.

31. He H, Bissonnette R, Wu J, Diaz A, Saint-Cyr Proulx E, Maari C, et al.Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis. J Allergy Clin Immunol. 2021;147(1):199-212.

32. Paller AS, Mancini AJ. Chapter 3: Eczematous eruptions in childhood. In: Paller AS, Mancini AJ, eds. Hurwitz clinical pediatric dermatology. St Louis (MO): Elsevier Inc; 2011.p.49.

33. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116-32.

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