AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A multinational, multicenter, double-blind, placebo-controlled Phase 2 study to evaluate efficacy and safety of SAR444656 in adult participants with moderate to severe atopic dermatitis**
Protocol number:	**ACT17754**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR444656** **Not applicable/Not applicable**
Brief title:	**Phase 2 study of SAR444656 in adult participants with moderate to severe atopic dermatitis**
Acronym:	**ADVANTA**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail** **94250 Gentilly, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	149184
NCT:	NCT06058156
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EUDAMED:	Not applicable
EU trial number:	2023-504346-66
Other:	Not applicable

Date: 17-Jan-2025 Total number of pages: 128

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 02	All	17 January 2025, version 1 (electronic 2.0)
Amended Clinical Trial protocol 01	All	24 July 2024, version 1 (electronic 1.0)
Original Protocol		29 May 2023, version 1 (electronic 2.0)

Amended protocol 02 (17 January 2025)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment is to remove 7-hour post dose pharmacokinetic (PK) and electrocardiogram (ECG) assessments, while retaining pre dose, 2- and 4-hour post dose assessments. Based on Independent Data Monitoring Committee review of unblinded data from 20 participants with 4 weeks of complete data, the recommended removal of 7-hour post dose PK and ECG assessments are expected to pose no safety concerns for the participants, while reducing participant burden.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Updated amended clinical trial protocol number and the amendment number from “01” to “02”, and the acronym to “ADVANTA”.	Updated to reflect the current amendment number and study acronym.
Title page, Section 1.1 Synopsis	Updated the NCT number to NCT06058156	Updated to reflect the correct regulatory agency identifier.
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall design, Section 4.3 Justification for dose, Section 6.1.1 Investigational medicinal product, Section 6.4 Blinding, Section 6.6 Dose modification, Section 9.2.3	Removal of text related to a potential dose reduction to [redacted] mg. Text related to this was removed/modified throughout the document.	After IDMC review of unblinded data, a dose reduction to [redacted]mg was assessed as not required.

Section # and Name	Description of Change	Brief Rationale
Secondary endpoint(s) analyses, Section 9.3 Interim analyses, Section 9.4 Sample size determination, Section 10.1.5.1 Independent data monitoring committee		
Section 1.3 Schedule of activities	Added X's to [redacted], BSA, EASI, vIGA-AD, and [redacted] at Visit 14 (EOS).	Additional end of study (EOS) efficacy assessments serve to characterize clinical outcomes after study drug washout.
Section 1.3 Schedule of activities (footnotes h, I, and s), Section 5.3.1 Meals and dietary restrictions, Section 8.5 Pharmacokinetics	Removed text regarding 7-hour post dose pharmacokinetic and electrocardiogram assessments at Visits 2, 3, 4, 6, and 12 (EOT).	PK and ECG data supports removing 7-hour post dose PK and ECG assessments at Visits 2, 3, 4, 6, and 12 (EOT). Based on Independent Data Monitoring Committee review of unblinded data from 20 participants with 4 weeks of complete data, the recommended removal of 7-hour post dose PK and ECG assessments at these visits are expected to pose no safety concerns for the participants. Notably, the mean baseline- and placebo-adjusted change in corrected QT intervals using Fridericia's correction formulae (ΔΔQTcF) in the ongoing Phase 2 studies is [redacted] between [redacted] at the scheduled study visits, with [redacted]. This is also endorsed by FDA feedback in a type D meeting.
Section 8 Study assessments and procedures	Removed partially remote visits. Modified visits to be done remote and onsite (ie, Visit 3 changed to be done remotely. Visits 4 and 6 changed to be done onsite).	Due to removal of post dose 7-hour PK and ECG assessments, there is no need for partially remote visits. For participant convenience, Visit 3 can now be conducted fully remotely. Visit 4 and 6 will be fully done onsite.
Section 10.8.3 China	Removed "for testing analytical method performance such as comparability and incurred sample reproducibility and"	To reflect the China specific requirements based on local regulations.
Section 10.8.6 South Korea	Added entire section	Added language per request from South Korea's Ministry of Health

In addition, other minor editorial changes (eg, stylistic, grammatical, and typographical modifications/corrections) were implemented in the protocol.

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LIST OF ABBREVIATIONS

AD: atopic dermatitis
AE: adverse event
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BCRP: breast cancer resistance protein
BGLMM: Bayesian generalized linear model
[redacted]
BLMM: Bayesian linear mixed model
BSA: body surface area
BUN: blood urea nitrogen
CFR: code of federal regulations
CIOMS: council for international organizations of medical sciences
COVID-19: coronavirus disease-19
CPK: creatine phosphokinase
CSICF: core study informed consent form
CSR: clinical study report
CYP3A4: cytochrome P450 3A4
[redacted]
EASI: eczema area and severity index
ECG: electrocardiogram
eCRF: electronic case report form
EOS: end of study
EOT: end of treatment
EU: European Union
FIH: first in human
FSH: follicle stimulating hormone
GCP: Good Clinical Practice
GDPR: General Data Protection Regulation
[redacted]
HBcAb: hepatitis B core antibody
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
HIV: human immunodeficiency virus
[redacted]
hsCRP: high sensitive C reactive protein
HV: healthy volunteteer
IB: investigator brochure

IC_{50}:	half maximal inhibitory concentration
ICF:	informed consent form
ICH:	international council for harmonization
IDMC:	independent data monitoring committee
IE:	intercurrent event
IEC:	Independent Ethics Committee
IFN-γ:	interferon gamma
IgE:	immunoglobulin E
IgM:	immunoglobulin M
IGRA:	interferon-gamma release assay
IL-13:	interleukin 13
IL-1R:	interleukin-1 receptor
IL-31:	interleukin 31
IL-4:	interleukin 4
IRAK4:	interleukin-1 receptor associated kinase 4
IRB:	institutional review board
IRT:	interactive response technology
JAK:	janus kinase
LAR:	legally authorized representative
LDH:	lactate dehydrogenase
LLOQ:	lower limit of quantification
MAD:	multiple ascending dose
MoA:	mechanism of action
MYD88:	myeloid differentiation primary response 88
NRS:	numerical rating scale
NYHA:	New York Heart Association
PBMC:	peripheral blood mononuclear cell
PBPK:	preliminary physiologically based pharmacokinetic
PCSA:	potentially clinically significant abnormalities
PD:	pharmacodynamics
PDE4:	topical phosphodiesterase 4
[redacted]	
PK:	pharmacokinetics
PK/PD:	pharmacokinetics/pharmacodynamics
[redacted]	
PP-NRS:	peak pruritus numeric rating scale
[redacted]	
PRO:	patient reported outcome
[redacted]	
QoL:	quality of life
QTL:	quality tollerance limit
RBC:	red blood cell
SAD:	single ascending dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SoA:	schedule of activities

SUSAR:	suspected unexpected serious adverse reaction
TARC:	thymus- and activation-regulation chemokine
TB:	tuberculosis
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroids
TEAE:	treatment-emergent adverse event
Th1:	T helper type 1
Th17:	T helper 17 cell
Th2:	T helper type 2
TLR:	Toll-like receptor
ULN:	upper limit of normal
UPS:	ubiquitin-proteasome system
vIGA:	validated Investigational Global Assessment
WBC:	white blood cell
WOCBP:	woman of childbearing potential
WONCBP:	woman of non childbearing potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A multinational, multicenter, double-blind, placebo-controlled Phase 2 study to evaluate efficacy and safety of SAR444656 in adult participants with moderate to severe atopic dermatitis.

Brief title:

Phase 2 study of SAR444656 in adult participants with moderate to severe atopic dermatitis.

Regulatory agency identifier number(s):

IND:	149184
NCT:	NCT06058156
WHO:	U1111-1287-6919
EUDAMED:	Not applicable
EU trial number:	2023-504346-66
Other:	Not applicable

Rationale:

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases. It is characterized by recurrent, pruritic eczema with the highest disease burden among the various skin diseases. AD patients and their families often experience decreased quality of life, especially in patients with moderate to severe AD. AD can lead to personal dysfunction, psychosocial distress and considerable economic burden.

Key aims of AD management include improving symptoms/functions and establishing long-term disease control. Mild AD usually can be controlled with topical medications, whereas more severe AD often requires systemic immunomodulatory therapy. Conventional systemic immunosuppressants may result in severe side effects. The novel systemic therapies still cannot clear disease in a considerable proportion of patients and safety concerns continue to exist. There are still high unmet medical needs for an effective and convenient novel therapy with acceptable safety profile for patients with moderate to severe AD.

IRAK4 is a key molecule in several inflammatory pathways involved in the pathogenesis and progression of AD. SAR444656 is a potent, highly selective, orally administered small molecule therapeutic targeting IRAK4 to mediate the selective degradation of IRAK4. It has demonstrated robust IRAK4 degradation in healthy subjects, AD and HS patients in the completed Phase 1 study. In the open-label Part C of the completed Phase 1 study, signals of clinical benefit were apparent after 28 days of treatment with SAR444656 [redacted] mg administered (fed state) QD in AD patients. Most patients had reduction in disease activity as measured by EASI score and improvement in symptoms as measured by worst pruritus NRS. The ACT17754 Phase 2 study will further evaluate the efficacy and safety of SAR444656 in moderate to severe AD participants with longer treatment duration in randomized, double-blind and placebo-controlled setting.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of SAR444656 on AD lesions compared with placebo in adult participants with moderate to severe AD.	• Percent change from baseline in EASI at Week 16.
Secondary	
• To assess the efficacy of SAR444656 on additional clinical assessments of AD compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. • Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16. • Absolute change from baseline in EASI at Week 16. • Proportion of participants achieving EASI-50 (reduction of EASI score by ≥50% from baseline) at Week 16. • Proportion of participants achieving EASI-90 (reduction of EASI score by ≥90% from baseline) at Week 16. • Change from baseline in percent BSA affected by AD at Week 16.
• To assess the efficacy of SAR444656 on patients reported outcomes (PRO) compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with reduction of weekly average of daily PP-NRS ≥4 points from baseline at Week 16. • Percent change from baseline in weekly average of daily PP-NRS at Week 16. • Absolute change from baseline in weekly average of daily PP-NRS at Week 16.
• To assess the safety of SAR444656 in adult participants with moderate to severe AD.	• Incidence of TEAEs, SAEs, and AESIs, IMP discontinuation due to TEAEs.
• To assess the pharmacokinetic profile of SAR444656 in adult participants with moderate to severe AD.	• Plasma SAR444656 concentration at Week 0, Week 1, Week 2, Week 4, and Week 16.

Overall design synopsis:

This is a multinational, multicenter, double-blind, placebo-controlled, parallel-group, Phase 2, 4-arm study to evaluate the efficacy and safety of SAR444656 in adult participants with moderate to severe AD who are inadequately controlled with topical therapies or for whom such topical therapies are inadvisable and who are candidates for systemic therapy.

Approximately 200 participants will be randomized to IMP in a targeted 1:1:1:1 allocation ratio to receive SAR444656 with food at the higher dose [redacted] mg [redacted], or SAR444656 medium dose [redacted] mg [redacted], or SAR444656 low dose [redacted] mg [redacted], or matching placebo.

Brief summary:

This is a multinational, multicenter, double-blind, placebo-controlled, parallel-group Phase 2, 4-arm study to evaluate the efficacy and safety of SAR444656 treatment in adult participants with moderate to severe AD who are inadequately controlled with topical therapies or for whom such topical therapies are inadvisable and who are candidates for systemic therapy.

Participants will be randomized to receive SAR444656 with food at [redacted] mg [redacted], or SAR444656 [redacted] mg [redacted], or SAR444656 [redacted] mg [redacted], or matching placebo.

Participants who meet inclusion/exclusion criteria will be stratified for randomization by severity of AD (moderate [baseline EASI score <22] versus severe [baseline EASI score ≥22]).

The total duration of study is approximately 24 weeks, including 1 to 4 weeks (maximum 30 days) for screening, 16 weeks for double-blind study treatment and 4 weeks for follow-up.

An IDMC will perform safety monitoring on an ongoing basis for this study. The IDMC may make a recommendation regarding study continuation based on the safety data of active studies of SAR444656. In the event of a safety signal of concern identified by the IDMC or Sponsor, the study enrollment may be paused or stopped.

Number of participants:

Approximately 200 participants are planned to be randomized to study intervention.

Note:

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

Study arms and duration:

Study interventions

High dose group: SAR444656 [redacted] mg [redacted] with food

Medium dose group: SAR444656 [redacted] mg [redacted] with food

Low dose group: SAR444656 [redacted] mg [redacted] with food

Placebo group: matching placebo [redacted] with food

Investigational medicinal products (IMP): SAR444656 or placebo

SAR444656

- Formulation: tablet of [redacted] mg strength
- Route(s) of administration: oral

- Dose regimen: [redacted] mg [redacted] or [redacted] mg [redacted] or [redacted] mg [redacted]

Placebo

- Formulation: tablet, matching to SAR444656 [redacted] mg strength
- Route(s) of administration: oral
- Dose regimen: [redacted]

Devices

Not applicable.

Post-trial access to study medication

Not applicable.

Duration of study intervention

The study duration will be 1 to 24 weeks, including:

- Screening period: 1 to 4 weeks (maximum 30 days)
- Treatment period: 16 weeks
- Post-treatment follow-up: 4 weeks

Statistical considerations:

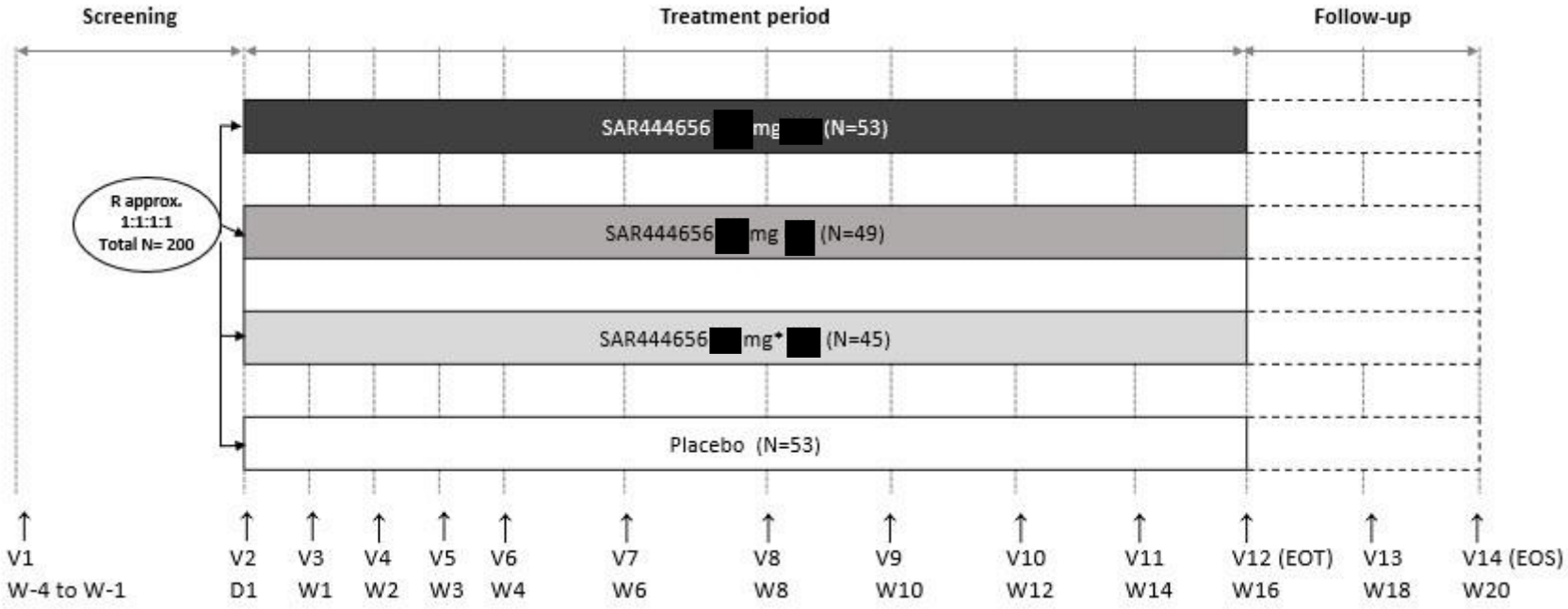
- **Primary endpoint:** The primary efficacy analysis will be the comparison between SAR444656 and placebo in the percent change from baseline in EASI at Week 16, using a BLMM including effects for participant-specific baseline EASI score, visit, treatment group, visit-by-treatment group, and adjusted by randomization stratum (moderate: EASI<22; severe: EASI≥22). Repeated measurements for each visit will be taken within subject. Historical data will be used to amend the prior distribution of the placebo arm.
- **Main secondary endpoints:** Binary secondary endpoints will be analyzed using a logistic BGLMM and adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22).

Data Monitoring/Other committee: Yes

An IDMC will be appointed for this study. The IDMC will monitor the safety and scientific integrity of a human research intervention and make recommendations to the Sponsor regarding the conduct of the study. The composition of the committee will include relevant medical/scientific experts, such as dermatologists and cardiologists.

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: D = day; EOS = end of study; EOT = end of treatment; IDMC = independent data monitoring committee; N = number; R = randomization; [redacted]; V = visit; W = week.
*[redacted] mg arm starts after the protocol amendment 1.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (1-4 weeks)	Intervention Period (16 weeks)											Follow-up (28 days after last IMP dose)		Early discontinuation/ Unscheduled visit (if applicable)[a]
Visit label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12 (EOT)**	**V13**	**V14 (EOS)**	**V100**
Visit week (Wk)	**W-4 to Wk-1**	**Wk0**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk6**	**Wk8**	**Wk10**	**Wk12**	**Wk14**	**WK16**	**WK18**	**W20**	**Unscheduled**
Day (D)	**D-30 to D-7**	**D1**	**D8 ±1d**	**D15 ±1d**	**D22 ±1d**	**D29 ±1d**	**D43 ±3d**	**D57 ±3d**	**D71 ±3d**	**D85 ±3d**	**D99 ±3d**	**D113 ±3d**	**D127 ±5d**	**D141 ±5d**	
Participant eligibility															
Informed consent	X														
Inclusion and exclusion criteria[b]	X	X													
Demography	X														
Medical history and prior medication/procedure[c]	X														
Randomization		X													
Treatment															
IRT call	X	X				X		X		X		X		X	X
Dispense IMP		X				X		X		X					
[redacted]															
Diary training[d]	X	X													
[redacted] diary recording by participants[e]		←==========										==========→			
Diary review		X	X	X	X	X	X	X	X	X	X	X			X

Procedure	Screening (1-4 weeks)	Intervention Period (16 weeks)										Follow-up (28 days after last IMP dose)		Early discontinuation/ Unscheduled visit (if applicable)[a]
Visit label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12 (EOT)**	**V13**	**V14 (EOS)**	**V100**
Visit week (Wk)	**W-4 to Wk-1**	**Wk0**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk6**	**Wk8**	**Wk10**	**Wk12**	**Wk14**	**WK16**	**WK18**	**W20**	**Unscheduled**
Day (D)	**D-30 to D-7**	**D1**	**D8 ±1d**	**D15 ±1d**	**D22 ±1d**	**D29 ±1d**	**D43 ±3d**	**D57 ±3d**	**D71 ±3d**	**D85 ±3d**	**D99 ±3d**	**D113 ±3d**	**D127 ±5d**	**D141 ±5d**	
Concomitant medications/procedures[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments															
Complete physical examination[f]	X											X			X
Targeted physical examination[g]		X						X							
Adverse events (AEs)	←==========													==========→	X
Triplicate 12-lead ECG, Holter monitoring as needed[h]	X	X[i]	X[i]	X[i]	X	X[i]	X	X	X	X	X	X[i]	X	X	X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[k]	X	X		X		X		X		X		X			X
Serum biochemistry[l]	X	X		X		X		X		X		X			X
Urinalysis[m]	X	X				X		X		X		X			X
HIV, Hepatitis B and C[n]	X														
Tuberculosis (TB) testing[o]	X														

Procedure	Screening (1-4 weeks)	Intervention Period (16 weeks)											Follow-up (28 days after last IMP dose)		Early discontinuation/ Unscheduled visit (if applicable)[a]
Visit label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12 (EOT)**	**V13**	**V14 (EOS)**	**V100**
Visit week (Wk)	**W-4 to Wk-1**	**Wk0**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk6**	**Wk8**	**Wk10**	**Wk12**	**Wk14**	**WK16**	**WK18**	**W20**	**Unscheduled**
Day (D)	**D-30 to D-7**	**D1**	**D8 ±1d**	**D15 ±1d**	**D22 ±1d**	**D29 ±1d**	**D43 ±3d**	**D57 ±3d**	**D71 ±3d**	**D85 ±3d**	**D99 ±3d**	**D113 ±3d**	**D127 ±5d**	**D141 ±5d**	
COVID-19 testing[p]	X														
Pregnancy Tests (WOCBP only)[q]	X	X				X		X		X		X		X	X
Follicle stimulating hormone (FSH)[r]	X														
Pharmacokinetics (PK)															
SAR444656 plasma concentration[s]		X	X	X		X						X			X
Pharmacodynamics / Biomarkers/ Skin biopsy															
[redacted]															

Procedure	Screening (1-4 weeks)	Intervention Period (16 weeks)											Follow-up (28 days after last IMP dose)		Early discontinuation/ Unscheduled visit (if applicable)[a]
Visit label (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12 (EOT)**	**V13**	**V14 (EOS)**	**V100**
Visit week (Wk)	**W-4 to Wk-1**	**Wk0**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk6**	**Wk8**	**Wk10**	**Wk12**	**Wk14**	**WK16**	**WK18**	**W20**	**Unscheduled**
Day (D)	**D-30 to D-7**	**D1**	**D8 ±1d**	**D15 ±1d**	**D22 ±1d**	**D29 ±1d**	**D43 ±3d**	**D57 ±3d**	**D71 ±3d**	**D85 ±3d**	**D99 ±3d**	**D113 ±3d**	**D127 ±5d**	**D141 ±5d**	
[redacted]															
Efficacy assessments															
PP-NRS daily diary[z]	←==========											==========→			X
[redacted]															
BSA	X	X		X		X		X		X		X		X	X
EASI	X	X		X		X		X		X		X		X	X
vIGA-AD	X	X		X		X		X		X		X		X	X
[redacted]															

Abbreviations: AD = atopic dermatitis; AE = adverse event; BSA = body surface area; COVID-19 = coronavirus disease-19; [redacted]; EASI = eczema area and skin severity index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FSH = follicle stimulating hormone; [redacted]; HIV = human immunodeficiency virus; IgE = Immunoglobulin E; IMP = investigational medical product; PP-NRS = peak pruritus numeric rating scale; [redacted]; PBMC = peripheral blood mononuclear cell; [redacted]; PP-NRS = peak pruritus numeric rating scale; [redacted]; TB = tuberculosis; vIGA = validated Investigator global assessment; WOCBP = women of childbearing potential.

a Unscheduled visit may be used for early discontinuation (ED) of study treatment or when participant needs a rescue medication for atopic dermatitis (AD), or for safety reason, or for dose modification. When this visit is used for ED, all scheduled EOT assessments should be performed. Procedures for unscheduled visit for reasons other than ED will be selected as needed.

b To qualify for enrollment and IMP administration, all inclusion criteria and none of the exclusion criteria are met by the participant.

c Medical history and prior medications include AD history and prior treatments for AD. Particular attention should be given to any prior/current use of prohibited medication.

d Each participant will receive training and an observed practice session for using the diary for data entry. After screening visit/V1 participants will be expected to use the diary every day until the end of the treatment. On the first day of IMP administration, the study staff will train the participant how to record information on IMP administration in the participant diary.

e Participants will record peak pruritus Numerical Rating Scale (PP-NRS) scores and topical treatment (ie, moisturizers/emollients) in the diary every day from screening visit up to the EOT. Participants will record IMP dosing compliance in the diary [redacted] during the study intervention period. Participants should also record all temporary intervention discontinuations in the diary [redacted] (when applicable) during the study intervention period.

f Complete physical examination includes, at a minimum, examination of the skin, assessments of the cardiovascular, respiratory, gastrointestinal (including palpation of liver and spleen), neurological, lymphatic, and musculoskeletal systems, height (only at Visit 1) and weight.

g Targeted physical examination includes, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and weight. Symptom-directed physical examination may be performed as clinically indicated at visits when complete or targeted physical examination is not specified.

h On-site pre-dose ECG could be substituted by ECG at home. For further information about remote visits, refer to Section 8. Additional ECG will be performed 2 hours (±30 minutes) and 4 hours (±30 minutes) post-dose at Visit 2 (Week 0) and Visit 4 (Week 2), just before time of PK sampling. Twenty-four hour Holter monitoring is considered in case of symptoms or signs of arrhythmia and/or ECG abnormalities.

i On the days of PK sampling at Week 0,1, 2, 4, and 16, triplicate ECG will be done pre-dose, just before the time of PK sampling. The post-dose ECG should be performed just before the venipuncture of the post-dose PK sampling at Visit 2 (Week 0) and Visit 4 (Week 2). For other visits, triplicate ECG will be done pre-dose.

j Vital signs include systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and body temperature (°C). Vital signs could also be collected during the remote visit. For further information about remote visits, refer to Section 8.

k Hematology 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 and monocytes).

l Serum biochemistry panel includes sodium, potassium, calcium, magnesium, chloride, phosphate, glucose (fasting or non-fasting), high sensitivity C reactive protein (hsCRP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-GT (GGT), direct and indirect bilirubin, alkaline phosphatase (ALP), creatinine, blood urea nitrogen (BUN), total protein, albumin and bicarbonate.

m 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.

n HIV testing (anti-HIV-1 and anti-HIV-2 antibodies); Hepatitis testing covering hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HbsAb), immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM HBcAb), total antibody to hepatitis B core antigen (HBcAb total) and hepatitis C total antibodies (HCV Ab). In case of results showing anti-HBc positivity, HBV-DNA testing will be performed and confirmed negative prior to enrollment. In case of results showing HCV Ab positivity, HCV RNA testing will be performed and should be confirmed negative prior to enrollment. For Japanese participant: in case of results showing anti-HBc and/or anti-HBs positivity, an HBV-DNA testing will be performed and confirmed negative prior to enrollment. If participants have HBsAb (positive) but are confirmed to have no detectable HBV-DNA, they are required to undergo HBV-DNA testing at Week 4, Week 8 and Week 12 (refer Section 10.8.5 for Japan specific requirements).

o QuantiFERON® TB Gold Interferon-Gamma Release Assay (IGRA) is required to rule out active/latent TB and can be done locally. If this TB tests are not locally available, a blood sample for QuantiFERON-TB Gold IGRA testing should be sent to the Central Laboratory.

p COVID-19 testing at screening or baseline before randomization. The type of COVID-19 test performed should comply with local requirements. The test will be performed in local laboratory.

q Only for woman of childbearing potential (WOCBP): serum pregnancy test (β-HCG test, as required by local regulations) at screening visit and urine pregnancy test at baseline/Week 0/Day 1, Weeks 4, 8, 12, 16 and 20. A negative result must be obtained at screening visit and baseline/Week 0/Day 1 prior to randomization. From randomization onwards, only urine pregnancy test will be performed at pre-specified timepoints, and before IMP administration. 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.

r FSH only if needed to confirm post-menopausal status.

s Blood sample for PK to be collected pre-dose at Week 0, 1, 2, 4 and 16. Additional PK samples will be collected 2 hours (±30 minutes) and 4 hours (±30 minutes) post-dose at Visit 2 (Week 0) and Visit 4 (Week 2). On these days, participants will take IMP at clinical site. The date and clock time for PK sample and date and clock time of last dose and current dose should be accurately recorded. In addition, date and clock time of meal taken before dosing on the day of PK sampling is recommended to be recorded. Additional PK sample may be collected during the treatment period in case of AE/SAE/lab abnormalities if needed. This PK sample is recommended to be collected at a time as close as possible to the AE/SAE, eg, at a time as close as possible to symptoms/signs of arrhythmia, or ECG abnormalities, or other AE/SAE and lab abnormalities. The date and clock time for PK sample and date and clock time of last dose should be accurately recorded for the additional PK sample. On-site PK sampling could also be substituted by PK sampling at home. For further information about remote visits, refer to Section 8.

[redacted]

u Baseline samples should be collected prior to IMP administration.

[redacted]

y Optional sample collected for potential retrospective safety follow-up and/or additional exploratory analysis in participants who provide a specific consent.

z PP-NRS will be recorded daily by the participants, ideally in the evening, with the aim to consistently complete it at approximately the same time of the day, based on the previous 24 hours, with worst (maximum) itch intensity recorded. Beginning at baseline/Week 0/Day1, investigators will review participant diary entries from the previous visit to assess compliance and need for additional instructions.

[redacted]

2 INTRODUCTION

Atopic dermatitis, also known as atopic eczema, is one of the most common inflammatory skin diseases. It is characterized by recurrent, pruritic eczema. It usually developed from childhood and may persist into adulthood. The global prevalence of AD is estimated to be 15% to 20% among children and up to 10% among adults (1). The Global Burden of Disease study demonstrated AD has the highest disease burden among skin diseases as measured by disability-adjusted life-years (2). AD patients and their families often experience decreased quality of life due to chronic and relapsing eczema, severe itch, sleep disturbance, coexisting medical conditions and dermatologic complications, as well as personal dysfunction, psychosocial distress and considerable economic burden, especially in patients with moderate to severe AD.

The pathogenesis of AD involves a complex interaction among genetic, environmental factors, microbial imbalance, skin barrier, and immune dysfunction. The initial inflammation is thought to be driven by damaged skin barrier and activation of epidermal inflammatory dendritic and innate lymphoid cells, which attract and interact with TH2 cells. Activated T cells release cytokines, mainly IL-4, IL-13 and IL-31, which promote inflammation, pruritus and production of IgE (1). Lesional AD skin shows dysregulated expression of a wide range of genes, especially TH2-associated and TH22-associated genes. An activation of Th1-mediated and Th17-mediated responses has been reported in chronic skin lesions, in particular children and people of Asian descent (3, 4).

Key aims of AD management include improving symptoms and establishing long-term disease control. Basic treatments include avoidance of trigger factors, skin barrier restoration with moisturizer and step-up and step-down approach to reduce inflammation based on severity of the disease (3). Mild AD usually can be controlled with topical medications, whereas more severe AD might require systemic immunomodulatory therapy. When eczema occurs, the use of topical immunosuppressive therapies (eg, TCS, TCI and topical PDE4 inhibitor) is recommended as first approach. Phototherapy may be used in moderate eczema. However, it is not used in children and young adults due to potential risk of skin cancer with long term use. For moderate to severe AD, several conventional systemic immunosuppressants eg, glucocorticoids, cyclosporine, methotrexate and azathioprine have been used. However, these agents are all non-selective and may result in severe side effects, including severe infections, liver and kidney dysfunction (1). In recent years, several novel systemic therapies for AD have been approved for moderate to severe AD, such as anti-IL-4/IL-13 monoclonal antibody (dupilumab), anti-IL-13 monoclonal antibody (tralokinumab) and small molecule JAK inhibitors (eg, baricitinib, abrocitinib and upadacitinib). However, based on data from clinical trials of these agents, there are still around 40% to 60% of AD patients who have not achieved clearance or almost clearance of AD lesions (5, 6, 7, 8). Further, there are significant safety concerns associated with some of these novel therapies, for example, black-box warnings for JAK inhibitors related to increased risks of serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis. Therefore, there is still high unmet medical needs for an effective, convenient oral novel therapy with acceptable safety profile for patients with moderate to severe AD.

2.1 STUDY RATIONALE

SAR444656 is a potent, highly selective, orally administered heterobifunctional small molecule therapeutic targeting IRAK4 and the E3 ligase cereblon to mediate the selective degradation of IRAK4 via the ubiquitin-proteasome system. It is being developed for the treatment of moderate to severe AD to address the significant unmet medical need.

IRAK4 is a key component of the myddosome, a multiprotein complex involved in innate immunity that mediates signaling through TLR and IL-1Rs (9). IRAK4 protein is ubiquitously expressed across multiple different tissue types, including skin, lymphoid tissue, bone marrow, gastrointestinal tract, and lung. The function of IRAK4 is dependent both on its kinase activity and on its scaffolding properties, which is required for the assembly of the myddosome complex following TLR or IL-1R engagement and MyD88 activation (10, 11, 12). Data from SAR444656 FIH Phase 1 study (KT474-HV-101) showed that the IRAK4 level in skin of AD patients were nearly 2-fold higher compared with healthy subjects, suggesting activation of IRAK4 in AD patients.

IL-1 family cytokines, including IL-1 α , IL-1 β , IL-18, IL-36, and IL-33, have been implicated in a variety of different immunology and inflammatory diseases, such as HS and AD (13). As both TLRs and IL-1Rs are involved in the production and/or response to all of these IL-1 family cytokines (13), the clinical hypothesis is that targeting IRAK4 with a single small molecule degrader, SAR444656, could have pleiotropic effects on multiple different cytokines and chemokines and thereby provide a transformative approach to the treatment of TLR/IL-1R-driven diseases.

There is evidence that both IL-33 and IL-1 are involved in the generation of Th2 cell mediated inflammation in both AD and other allergic diseases (eg, eosinophilic asthma and chronic rhinosinusitis), and monoclonal antibodies against IL-33 (etokimab) has shown preliminary activity in AD (14). The ability of an IRAK4 degrader to impact the production of IL-33 and IL-1 (through TLR inhibition) and the cellular response to both cytokines (through IL-1R inhibition) provides a compelling mechanistic rationale for development in AD that has been de-risked through early clinical validation of the pathway and is differentiated from the targeting of single cytokines. As TLR/IL-1R signaling also modulates Th1 and Th17 inflammation (15) and there is Th1 and Th17 activation in chronic AD, especially in some racial/ethnic groups. Therefore, IRAK4 degradation may provide a novel target that [redacted] in AD patients and should be further evaluated in clinical studies.

The completed Phase 1 study of SAR444656 enrolled healthy participants in SAD cohorts (Part A) and MAD cohorts (Part B); as well as 21 participants with HS or AD in an open-label repeated dose study in a single cohort (Part C).

Pharmacokinetic assessments in HV demonstrated less than dose proportional increase in exposure following SAD and MAD, about 3-to-4-fold accumulation and steady state achieved following 7 days of QD dosing and about 2.5-fold and 1.3-fold increase in exposure following single dose administration with food at 600 mg and 50 mg respectively. The PK in AD and HS patients was generally similar to that of HV.

In Part C of the completed Phase 1 study, participants were dosed 75 mg SAR444656 once daily in a fed state for 28 days. In PBMCs from participants with AD in Part C, IRAK4 protein expression in blood decreased by up to 87%. In skin, IRAK4 protein decreased by 63% at Day 28. In addition, SAR444656 treatment caused decrease of multiple cytokines released from cells in ex-vivo whole blood assays stimulated with TLR ligands. Although the study was open label and not designed nor powered to show clinical efficacy, most AD patients experienced disease improvement. The mean EASI score in AD patients decreased by 37% at Day 28 with associated decreases in pruritus scores. These data indicate SAR444656 may have [redacted] for AD patients. Therefore, a Phase 2 randomized, double-blind, placebo-controlled study is warranted to evaluate the efficacy and safety of SAR444656 in participants with moderate to severe AD with longer treatment duration. Three dose levels of SAR444656 will be tested, [redacted] mg [redacted], [redacted] mg [redacted], and [redacted] mg [redacted] administered with food (see Section 4.3).

2.2 BACKGROUND

SAR444656 (KT-474) is a potent, highly selective, orally administered heterobifunctional small molecule therapeutic targeting IRAK4 and the E3 ligase cereblon to mediate the selective degradation of IRAK4 via the ubiquitin-proteasome system. It has been developed for the treatment of moderate to severe HS and AD.

Chemistry:

The molecular structure of SAR444656 contains three chiral centers, including two fixed/stable centers around the morpholine ring (R,R) and one epimerizable chiral center (R/S) resulting in the two diastereomers, [redacted]

Pre-clinical experience:

A series of in vitro and in vivo studies were performed to evaluate and confirm the ability of KT-474 to degrade its intended target, IRAK4, and to inhibit downstream production of disease relevant pro-inflammatory cytokines and chemokines.

In in vivo PK studies conducted in rats, dogs, and monkeys, KT-474 PK was characterized by moderate to high clearance, high volume of distribution at steady state, a moderate terminal half-life, and low to moderate bioavailability. KT-474 exhibited low solubility, moderate permeability, and was identified as a substrate of [redacted] in vitro.

Repeat-dose toxicity studies were conducted in Sprague Dawley rat and Beagle dog via BID dosing for 14 days in rats and QD dosing for 14 days in dogs and 28 days in rats and dogs. In the dose range finding studies of 14 days duration conducted in rat and dog, no adverse effects were noted up to 600 and 100 mg/kg/day, respectively, the highest dose tested in each study. Please refer to the IB for more details.

Clinical experience:

A total of 153 participants were included in Phase 1 FIH clinical study, Part A & B with HVs (SAD/MAD) and Part C with HS and AD participants. A total of 122 participants were exposed to SAR444656:

- Part A: a double-blind, randomized, placebo-controlled, SAD, sequential group study included 72 adult HVs (56 IMP/16 placebo). Nine single oral doses were tested: fasted: 25 mg, 75 mg, 150 mg, 300 mg, 600 mg, 1000 mg, and 1600 mg; fed: 600 mg, and 50 mg.
- Part B: a double-blind, randomized, placebo-controlled, MAD, sequential group study in approximately 60 adult HVs (45 IMP/15 placebo). Five dose regimens were tested: 25 mg QD, 50 mg QD, 100 mg QD, 200 mg QD, 200 mg BIW for 14 days, all taken in fasted state.
- Part C: an open-label, multiple dose study of SAR444656 administered daily for 28 days in a single cohort of patients with active AD or HS. Part C was conducted on an outpatient basis and patients were followed for safety through Day 42. Thirteen HS patients and 8 AD patients were enrolled to receive 75 mg QD in fed state.

A detailed description of the chemistry, pharmacology, efficacy and safety of SAR444656 is provided in the Investigator's brochure.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SAR444656 may be found in the IB.

2.3.1 Risk assessment

Based on the nonclinical data and preliminary clinical data available for SAR444656, the following are considered as potential risks:

- Serious infections
- QTc interval prolongation

Detailed information on the risk assessment is provided in Table 1.

Table 1 - Risk assessment/mitigation

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Serious infection	Based on immunomodulatory MoA and human loss of function mutations reported in literature. During infancy and early childhood, patients with either IRAK4 or MyD88 deficiency are susceptible to serious streptococcus, staphylococcus and pseudomonas bacterial infections but not to mycobacterial, viral, fungal or parasitic infections. After adolescence, there is no increased risk of infection, suggesting that adaptive immunity and/or further maturation of innate immunity has eliminated the dependency on MyD88-IRAK4 signaling for protection against these bacterial pathogens in adults(16, 17).	• Exclude participants with active or chronic infection requiring systemic treatment within 4 weeks prior to baseline. • Exclude participants known history of, or suspected, significant current immunosuppression. • Use of other systemic immunomodulators is prohibited within a certain period prior to baseline visit and during the study treatment. • Screen and exclude active HIV, HCV, HBV, COVID-19 infections and active/latent TB. • Routine monitoring of serious infection via indicative clinical signs and symptoms. • Serious infection is listed as AESI. • IDMC is set up to provide continual safety monitoring.
QTc interval prolongation	Signal of transient QTc prolongation observed early in treatment period in the FIH study and decline toward baseline by D28 in the Phase 1 clinical study in patients. Preclinical data showed delayed QTc prolongation detected in cynomolgus monkey repeat dose cardiovascular safety study.	• Exclude participants with QTcF interval >440 msec or QRS interval >110 msec during screening. • Exclude participants with medical conditions prone to QTc interval prolongation and arrhythmia. • Exclude participants who need to use concomitant medications known to prolong QTc interval, moderate and strong CYP3A4 inhibitors 30 days or 5 half-lives (whichever is longer) prior to baseline visit and during study treatment. • Close EGC monitoring: triplicate 12-lead ECG every week in the first 4 weeks of treatment and then biweekly afterward. Holter monitoring is arranged in case of symptoms or signs of arrhythmia and/or ECG abnormalities. • Set cardiac AESI. • IDMC is set up to monitor general/cardiac safety. Central ECG reading panel is set up to monitor any potential ECG abnormalities on an ongoing basis. • Individual stopping rules are defined to ensure patient safety.

Abbreviations: AESI = adverse event of special interest; COVID-19 = coronavirus disease; D = day; ECG = electrocardiogram; FIH = first in human; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRAK4 = interleukin-1 receptor-associated kinase 4; MoA = mechanism of action; MYD88 = myeloid differentiation primary response 88; TB = tuberculosis.

2.3.2 Benefit assessment

Based on the data from the AD patient cohort with active disease evaluated in the completed Phase 1 study, SAR444656 dosed at [redacted] in fed state for 28 days led to a favorable signal of clinical benefit. There was clinically meaningful reduction in disease activities as reflected in improvement of skin lesions as measured by EASI score and the pruritus NRS. Given the limitations of available therapies and unmet need, SAR444656 may become an alternative novel treatment for patients with active AD. It also may provide patients with the convenience of an orally administered therapeutic option.

2.3.3 Overall benefit/risk conclusion

With the safety monitoring and management measures implemented for this study, the potential risk associated with SAR444656 are appropriately mitigated. Aggregated data available for SAR444656 suggest [redacted] for patients with moderate to severe AD. Thus, the benefit-risk assessment is favorable for these patients who will be treated in ACT17754 study.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of SAR444656 on AD lesions compared with placebo in adult participants with moderate to severe AD.	• Percent change from baseline in EASI at Week 16.
Secondary	
• To assess the efficacy of SAR444656 on additional clinical assessments of AD compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points at Week 16. • Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16. • Absolute change from baseline in EASI at Week 16. • Proportion of participants achieving EASI-50 (reduction of EASI score by ≥50% from baseline) at Week 16. • Proportion of participants achieving EASI-90 (reduction of EASI score by ≥90% from baseline) at Week 16. • Change from baseline in percent BSA affected by AD at Week 16.
• To assess the efficacy of SAR444656 on patients reported outcomes (PRO) compared with placebo in adult participants with moderate to severe AD.	• Proportion of participants with reduction of weekly average of daily PP-NRS ≥4 points from baseline at Week 16. • Percent change from baseline in weekly average of daily PP-NRS at Week 16. • Absolute change from baseline in weekly average of daily PP-NRS at Week 16.
• To assess the safety of SAR444656 in adult participants with moderate to severe AD.	• Incidence of TEAEs, SAEs, and AESIs, IMP discontinuation due to TEAEs.
• To assess the pharmacokinetic profile of SAR444656 in adult participants with moderate to severe AD.	• Plasma SAR444656 concentration at Week 0, Week 1, Week 2, Week 4 and Week 16.
Tertiary/Exploratory	
• [redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Primary estimands defined for primary and key secondary efficacy endpoints are summarized in Table 3 below. More details are provided in Section 9.2.

For all these estimands, the comparison of interest will be the comparison of SAR444656 versus placebo.

Table 3 - Summary of primary estimands for main endpoints

Endpoint			Estimands	
Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To assess the efficacy of SAR444656 on AD lesions compared with placebo in adult participants with moderate to severe AD.				
Primary endpoint	Percent change from baseline in EASI at Week 16.	Efficacy	The IEs will be handled with the following strategies; only measurements assessed up to the IE will be considered, data collected after start of IE will be set to missing: • Intake of rescue/prohibited medications will be handled with the while before rescue/prohibited medications strategy. • Misallocation of treatment will be handled with the while on randomized treatment strategy.	BLMM will include effects for participant specific baseline EASI score, visit, treatment group, and visit-by-treatment group interaction. Repeated measurements for each visit will be taken within participant. Historical data will be used to amend the prior distribution of the placebo arm.

Endpoint			Estimands	
Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: To assess the efficacy of SAR444656 on additional clinician assessments of AD compared with placebo in participants with moderate to severe AD.				
Secondary endpoint	Proportion of participants with vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points at Week 16.	Efficacy	• Same as primary endpoint	Logistic BGLMM will adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group.
Secondary endpoint	Proportion of participants achieving EASI-75 (reduction of EASI score by ≥75% from baseline) at Week 16.	Efficacy	• Same as primary endpoint	Logistic BGLMM will adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group.

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy assessment tools, EASI and vIGA-AD completed by Investigators and PP-NRS completed by participants have been validated in AD. They are extensively used and widely accepted by health authorities. BSA affected by AD is a validated clinician completed tools to assess disease severity of AD. [redacted] Overall, these clinician-reported and patient-reported outcomes provide essential evaluation of the therapeutic effect of SAR444656 on AD lesions and major symptoms.

See Section 8.2 for more details.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multinational, multicenter, double-blind, placebo-controlled, parallel-group, Phase 2, 4-arm study to evaluate the efficacy and safety of SAR444656 in adult participants with moderate to severe AD who are inadequately controlled with topical therapies or for whom such topical therapies are inadvisable and who are candidates for systemic therapy.

Participants will be randomized to receive SAR444656 with food at [redacted] mg [redacted], or SAR444656 [redacted] mg [redacted], or SAR444656 [redacted] mg [redacted], or matching placebo.

Participants who meet inclusion/exclusion criteria will be stratified for randomization by severity of AD (moderate [baseline EASI score <22] versus severe [baseline EASI score ≥22]).

The total duration of study is approximately 24 weeks, including 1 to 4 weeks for screening, 16 weeks for double-blind study treatment and 4 weeks for follow-up.

There will be visit every week for the initial 4 weeks of treatment, followed by visit every other week until the end of the study. Between the planned visits, if deemed necessary, unscheduled remote or clinic visits could be performed.

An IDMC (Section 10.1.5.1) will perform safety monitoring on an ongoing basis for this study. The IDMC may make recommendation regarding study continuation based on the safety data of active studies of SAR444656. In the event of a safety signal of concern identified by the IDMC or Sponsor, the study enrollment may be paused or stopped. After IDMC review of unblinded data, a dose reduction to [redacted] mg was assessed as not required and removed from the protocol.

Approximately 200 participants will be randomized to IMP in a targeted 1:1:1:1 allocation ratio to receive SAR444656 with food at higher dose [redacted] mg [redacted], or SAR444656 medium dose [redacted] mg [redacted], or SAR444656 lower dose [redacted] mg [redacted] or matching placebo with food.

If medically necessary, rescue therapy for AD is allowed at the discretion of the Investigator. If possible, Investigators should attempt to limit the first step of rescue therapy to topical medications, eg, low to medium potency TCS, TCI and topical PDE4 inhibitor. 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. If a participant receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs, study intervention will be immediately interrupted. 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.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study eligibility criteria will ensure participants meet the diagnosis of moderate to severe AD as defined by the American Academy of Dermatology Consensus Criteria for at least 1 year before the baseline. Participants will be required to have an EASI score of ≥12, a vIGA-AD score ≥3 (out of 5), AD involvement ≥10% of BSA at screening and baseline visits. Additionally, participants will need to have baseline weekly average of PP-NRS ≥4 and documented history within 6 months prior to baseline visit, of either inadequate response or inadvisability to topical medications.

The primary objective is to assess the efficacy of SAR444656 on AD lesions compared with placebo and the primary endpoint is percent change from baseline in EASI score at Week 16. EASI scoring is one of the frequently used measurements of AD severity in clinical studies. As a physician-reported outcome, it assesses both intensity and extent of AD typical lesions. EASI was validated in previous AD clinical trials and is suitable to follow up in drug-effect studies of AD for research purposes. As a continuous outcome, percent change over placebo provides a more sensitive way to detect the effect of SAR444656. A placebo control is included to assess the net treatment effect of SAR444656.

Secondary efficacy endpoints include but are not limited to proportion of participants with vIGA of 0 or 1 and reduction from baseline of ≥2 points, proportion of participants achieving EASI-75, EASI-50, EASI-90, change from baseline in percent BSA and pruritus NRS. These clinical assessments and patients reported outcome are widely used and well validated in previous AD clinical trials and will provide additional evidence of potential therapeutic effect of SAR444656 on AD lesions and major symptoms.

The total study duration per participant is expected to be approximately 24 weeks, including 1 to 4 weeks for screening, a 16-week on-treatment double-blind period and a 4-week post-treatment follow-up. The 16-week treatment duration is selected to ensure adequate time for the onset of optimal treatment benefit and is comparable with the typical double-blind, controlled study treatment period of usual AD trials assessing the efficacy of an intervention. The completed Phase 1 study patient cohort data showed the plasma SAR444656 concentration returned to 0 by 14 days after EOT and the concentration in skin may sustained longer. Therefore, there will be 4-week safety follow-up.

4.3 JUSTIFICATION FOR DOSE

Three dose levels of SAR444656 will be tested in this study, over a 16-week treatment period. These doses are selected based on the observed IRAK4 degradation, which is a potential biomarker of therapeutic response, from the completed Phase 1 study.

The dose of SAR444656 [redacted] mg [redacted], administered with food, is planned to be evaluated as the high dose. Based on a preliminary PBPK, population PK and PK/PD model developed using data from Phase 1 Study KT474-HV-101, this dose and dosing regimen is predicted to provide SAR444656 systemic exposures comparable to the [redacted] dose level that was administered to healthy subjects in the MAD part of the completed Phase 1 study (ie, [redacted], fasted)

and was well tolerated. Further, the steady state SAR444656 exposure (median C_{trough}) following this dose and dose regimen are predicted to be about [redacted]-fold higher than skin IRAK4 IC_{50}. This dose and dose regimen, therefore, allows to determine if exposure/dose greater than the dose evaluated in AD participants in the Phase 1 study (ie, [redacted], fed) can further augment IRAK4 degradation and clinical activity.

Additional dose levels of SAR444656 [redacted] mg [redacted], and SAR444656 [redacted] mg [redacted], administered with food, are planned to evaluate exposure/dose-response relationships for PD and efficacy to guide future development. The steady state SAR444656 exposure (median C_{trough}) following [redacted] mg dose is predicted to be about [redacted]-fold higher and with [redacted] mg dose is predicted to be roughly similar to the skin IRAK4 IC_{50}. Therefore, the additional doses are expected to provide differentiation from the PK/PD predicted at the high dose ([redacted] mg [redacted], fed), where the (median C_{trough}) following this dose and dose regimen is predicted to be about [redacted]-fold higher than skin IRAK4 IC_{50}.

4.4 END-OF-STUDY DEFINITION

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

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

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

Type of participant and disease characteristics

I 02. Participants with AD as defined by the American Academy of Dermatology Consensus Criteria (16) for at least 1 year before the baseline visit.

I 03. EASI ≥12 at screening and at baseline visit.

I 04. vIGA (17) score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening and baseline visit.

I 05. AD involvement ≥10% of BSA at screening and baseline visit.

I 06. Baseline PP-NRS ≥4

NOTE:

The baseline weekly average of daily PP-NRS will be calculated from the 7 consecutive days immediately preceding the baseline visit. A minimum of 4 daily scores out of the 7 will be required. Randomization should be postponed until this requirement is met, but without exceeding the 30-day maximum duration for screening.

I 07. Participant must have documented history within 6 months prior to baseline visit, of either inadequate response or inadvisability to topical medications.

NOTE:

- Acceptable documentation includes contemporaneous chart notes that recorded topicals prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician.
- Inadequate response to topical medications is defined as failure to achieve or maintain remission or a low disease activity state (IGA ≤2) despite treatment with a daily regimen of TCS of medium to higher potency [± TCI as appropriate], applied for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.

- Participants who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil will be also considered as surrogate for having inadequate response to topical therapy.
- Inadvisability is defined as important side effects or safety risks as those that outweighed 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. Participants must have applied daily topical emollient (moisturizer) for at least the 7 consecutive days immediately before the baseline visit. Participants should continue using daily emollient (moisturizer) during the study.

I 09. Participant must be willing and able to complete the electronic diary for the duration of the study as required by the study protocol.

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 10. 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 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 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 4 weeks before the first administration of study intervention, see Section 8.3.5 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 11. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Presence of other skin conditions 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, severe renal conditions (eg, participants on dialysis), immunosuppression conditions, 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 active or chronic infection requiring systemic treatment (eg, antibiotics, antivirals, antifungals, anthelminthics) within 4 weeks prior to baseline (1 week in the event of superficial infections).

E 04. Known history of, or suspected, significant current immunosuppression, including history of invasive opportunistic or helminth infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration.

E 05. History of solid organ or stem cell transplant.

E 06. Participant with history of splenectomy.

E 07. Participant with history of any malignancy or lymphoproliferative disease, except if the participant has been free from disease for ≥5 years. Successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma, or localized carcinoma in situ of the cervix are allowed.

E 08. History (within last 2 years prior to baseline) of prescription drug or substance abuse, including alcohol, considered significant by the Investigator.

E 09. Family history of sudden death or long QT syndrome.

E 10. History of congenital or drug-induced long QT syndrome.

E 11. Congestive heart failure (NYHA Class 2-4), greater than Class 1 angina pectoris, acute coronary syndrome within prior 6 months, known structural heart disease.

E 12. History of any major cardiovascular events (eg, myocardial infarction, unstable angina pectoris, coronary revascularization, stroke, or transient ischemic attack) at any time prior to screening.

E 13. History of ventricular fibrillation, ventricular tachycardia, Torsades de Pointes, atrial fibrillation, syncope not explained by non-cardiac etiology.

E 14. Uncontrolled hypertension defined as consistent systolic blood pressure ≥150 mm Hg or consistent diastolic blood pressure ≥90 mm Hg despite antihypertensive medication.

E 15. Bradycardia with heart rate <50 beats per minute during screening.

E 16. Supine 12-lead triplicate ECG demonstrating a mean QTcF interval >440 msec or QRS interval >110 msec in ECG obtained during screening.

E 17. Serum potassium, magnesium, or calcium below lower limit of normal during screening.

Prior/concomitant therapy

E 18. Participants had major surgery within 4 weeks prior to the screening or have planned any elective major surgery during the study.

E 19. Live (attenuated) vaccine 12 weeks prior to Day 1 or plan to receive one during the trial.

E 20. Non-live vaccines (eg, non-live seasonal influenza, COVID-19) within 14 days prior to study Day 1.

E 21. Having received any of the following therapy within the specified timeframe(s) prior to the baseline visit (unless otherwise specified):

Table 4 - Prohibited therapy prior to baseline

Therapy	Time frame
Topical treatments	
TCS, TCI, topical PDE4 inhibitor, topical delgocitinib	within 1 week
Topical ruxolitinib	within 4 weeks
Systemic treatments	
Depleting agents/therapies such as rituximab or ofatumumab or other long-acting biologics	6 months
Biologic therapies such as abatacept, adalimumab, anakinra, certolizumab, dupilumab, etanercept, golimumab, infliximab, tocilizumab, sarilumab, secukinumab, tralokinumab	12 weeks or 5 half-lives (whichever is longer)
Omalizumab	130 days
JAK inhibitors such as ruxolitinib, tofacitinib, baricitinib, upadacitinib, abrocitinib	4 weeks or 5 half-lives (whichever is longer)
Immunosuppressants/immunomodulators such as corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, cyclophosphamide, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ	4 weeks or 5 half-lives (whichever is longer)
Leukotriene receptor antagonists/modifiers such as montelukast or zafirlukast (unless used as a continuous treatment for at least 4 weeks before the baseline visit)	4 weeks
Specific or non-specific desensitization therapy/immunotherapy	4 weeks
Herbal supplements (including St. John's Wort)	4 weeks
Phototherapy or regular use (more than 2 visits per week) of a tanning booth/parlor	4 weeks
Medications known to prolong QTc interval (See Section 10.11.1)	30 days or 5 half-lives (whichever is longer)
Moderate and strong CYP3A4 inhibitors or inducers (See Appendix 11, Section 10.11.2)	30 days or 5 half-lives (whichever is longer)
Investigational product	4 weeks or 5 half-lives (whichever is longer)

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

Prior/concurrent clinical study experience

E 22. Previous use of a IRAK4 inhibitor or degrader.

Diagnostic assessments

E 23. History of HIV infection or positive HIV serology at screening.

E 24. Presence of HBsAg or positive HBcAb at screening.

- For Japanese participant only: Positive HBcAb or positive antibody to hepatitis B surface antigen, associated with positive (or detectable) HBV-DNA at screening (refer Section 10.8.5 for Japan specific requirements).

E 25. Presence of positive HCV antibody test result at screening.

E 26. Any of the following laboratory abnormalities at the screening visit:

- Hemoglobin <9 g/dl
- Absolute neutrophil count $<1.5 \times 10^9$/L
- AST or ALT >2 × ULN
- Total bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%)
- A platelet count $<100 \times 10^9$/L (<100,000/µl)

E 27. Evidence of active or latent TB as documented by medical history (eg, chest X-rays), examination and TB testing: a positive or 2 indeterminate QuantiFERON® TB Gold IGRA testing at screening (regardless of prior treatment status).

Other exclusion criteria

E 28. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 29. 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 30. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).

E 31. 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 32. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 of the protocol (country-specific requirements) (Section 10.8).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Refrain from consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, and Seville orange juice or other products containing grapefruit or Seville oranges 72 hours before the start of study intervention until after the final dose.

For pre-dose ECGs assessments, the participant must be fasting (except water), and a breakfast/snack will be provided by site following assessment completion.

For specific visits (Visit 2 and Visit 4), a standardized light meal should be provided to the participant. There should be no food intake within 2 hours prior to the ECG.

5.3.2 Caffeine, alcohol, and tobacco

No restriction is required during the study. However, no caffeine containing beverage or food can be consumed at least 2 hours prior to ECG assessment.

5.3.3 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. For ECG assessments, participant should be in a supine position followed by at least 10 minutes rest in that position in a quiet environment.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. Participants who are rescreened are required to sign a new ICF, and should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the screening visit pages. In case the participant is a temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered in the additional pages.

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

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9) should be considered for screening, enrollment, randomization, and administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

6.1.1 Investigational medicinal product

For a description of study interventions administered see Table 5.

Table 5 - Study intervention(s) administered

Intervention label	SAR444656	Placebo
Intervention name	SAR444656	Placebo
Intervention description	SAR444656 [redacted] mg or SAR444656 [redacted] mg or SAR444656 [redacted] mg [redacted]	SAR444656 matching placebo [redacted]
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strength(s)	[redacted]mg/tablet	N/A
Dosage level(s)	[redacted] mg [redacted] or [redacted] mg [redacted] or [redacted] mg [redacted]	[redacted] mg [redacted]
Route of administration	Oral	Oral
Use	Experimental	Placebo-comparator
IMP and AxMP	IMP	IMP
Packaging and labeling	IMP will be provided in a double-blind kit (wallet) labeled as required per country requirement.	Placebo will be provided in a double-blind kit (wallet) labeled as required per country requirement.
[Current/former name(s) or alias(es)]	SAR444656	N/A

Table 6 - Study arm(s)

Arm title	SAR444656	Placebo
Arm type	Experimental	Placebo
Arm description	Participants will receive SAR444656 [redacted] mg or [redacted] mg or [redacted]mg orally [redacted]	Participants will receive placebo orally [redacted].
Associated intervention labels	SAR444656	Placebo

Participants will be instructed to take their dose of study intervention with food [redacted] within [redacted] of starting breakfast.

The SAR444656/placebo may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

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

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) 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, prepare, or administer study intervention.
3. 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.
4. The Investigator, or authorized site staff 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 8.4.8).

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 IMP to a third party (except for 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 ASSIGNMENT TO STUDY INTERVENTION

At Visit 2 (Week 0), after all baseline evaluations have been completed, participants will be randomly assigned to study intervention (SAR444656 or matching placebo).

The list of randomized intervention kit numbers is generated centrally by Sanofi. The IMPs (SAR444656 and placebo) are packaged in accordance with this list.

The randomization and intervention allocation are performed centrally by an IRT. Before the study is initiated, the telephone number and call-in directions and/or the log in information, and directions for the IRT will be provided to each site.

The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.

Participant's randomization list will be stratified by severity of AD (moderate [baseline EASI score <22] versus severe [baseline EASI score ≥22]).

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants. Details of the IRT procedure will be provided in the IRT site manual.

During the treatment period, several intervention kit numbers will be allocated to participants by the IRT across visits, in the same arm as assigned at randomization.

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

Time of randomization for a participant is defined as the time recorded by IRT.

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

6.4 BLINDING

This is a double-blind study in which the participants and Investigators are blinded to study intervention.

Investigators will not have access to the randomization (treatment) codes except under exceptional medical circumstances.

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 the Investigator's 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 of this occurrence. The date and reason for the unblinding must be recorded in the source documentation and eCRF, as applicable.

At the assay institutions (bioanalytical labs) responsible for PK measurements, only samples collected from participants on active drug may be analyzed leading to unblinding of responsible bioanalysts prior to the data base lock. Bioanalysts are excluded from the clinical study operational team and a process will be set up to prevent any potential unblinding, ie, no unblinded data will be shared with the clinical study operational team prior to database lock.

The Investigator will be blinded to PK data. Population PK analysis may be conducted prior to data base lock leading to unblinding of personnel in charge of dataset creation for the analysis. These personnel are excluded from the clinical study operational team.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE for the purpose of expedited regulatory reporting (see Section 8.4.4). Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

Methods of blinding

- The placebo tablet will be identical to the SAR444656 [redacted] mg tablet in appearance, quantity, taste, odor, packaging, and labeling. SAR444656 [redacted] mg,[redacted] mg, [redacted] mg, and placebo will be provided in indistinguishable wallets, in identical kits labeled with a treatment kit number.
- The IDMC will have access to unblinded data if deemed necessary by the IDMC. No unblinding information will be shared by the IDMC with the study team members. Details about the distribution of unblinding data to the IDMC while protecting the blind are described in the IDMC charter and Appendix 1 (Section 10.1.5.1).
- In case of an interim analysis, a designated Statisticians and Programmers will be unblinded for the analyses and work independently from the study team to ensure maintenance of the blind. Their ability to access such unblinded data will be documented. They will keep the randomization schedule in a locked area, which is not accessible to the Sponsor's clinical study operational team and will not disclose the randomization or the individual unblinded data before the official opening of the randomization.
- Laboratory assessments listed as PD markers and biomarkers in the SoA (Section 1.3) will be blinded from baseline/Day 1 throughout the study, except for those which are needed for screening (see Table 8) or are used for an Interim Analysis. Their ability to access such unblinded data will be documented. In case of a safety concern, unblinding can be performed by the Investigator and/or Sponsor for the PD marker.

6.5 STUDY INTERVENTION COMPLIANCE

A participant diary will be provided to participants receiving oral therapy during treatment.

Participant compliance will be assessed via the participant diary during each visit.

On the day of screening, while the participant is in the clinic, the diary will be dispensed. On the first day of IMP administration, the study staff will train the participant how to record information on IMP administration in the participant diary. Participants will note [redacted] the information related to IMP compliance.

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. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

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

The Investigator or designee will keep an accurate record of all IMP that is received, dispensed, and returned on a per participant basis using an IMP accountability log. Refer to pharmacy manual for details. Measures taken to ensure and document treatment compliance and IMP accountability include:

- The Investigator will record accurately the IMP information as required on appropriate eCRF page.
- All treatment kits (whether empty or unused) are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
- The monitor in charge of the study then checks the eCRF data by comparing them with the IMP that has been retrieved and the participant treatment log form.

A record of the quantity of IMP 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.

6.6 DOSE MODIFICATION

Not applicable.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

No study intervention will be provided after the end of the study.

6.8 TREATMENT OF OVERDOSE

- An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as a higher [redacted] dose than specified in the protocol within the intended therapeutic interval, adjusted according to the tested drug.

Sponsor does not recommend specific treatment for an overdose other than supportive care.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Evaluate the participant to determine, if possible, whether study intervention should be interrupted.

- Obtain a plasma sample for PK analysis and perform ECG, if possible.
- Document appropriately in the e-CRF.
- Contact the Sponsor as soon as possible.

6.9 PRIOR AND CONCOMITANT THERAPY

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

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

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

Medications that have not been listed as prohibited therapies may be permitted for use during the study if the medication will not interfere with the study. They include the following:

- Daily emollients (moisturizers) will be continued during the study.
- Oral corticosteroid rinses (mouth washes), ocular or inhaled corticosteroids are allowed.
- Oral or topical antibiotics for up to 2 weeks for AD-associated superficial skin infections are allowed.
- 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 that modify or that suppress their immune response, is not yet established. While vaccination with an approved COVID-19 vaccine is widely recommended, 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.

6.9.1 Prohibited concomitant therapies

The following medications/procedures are prohibited during the study treatment period:

- Topical or systemic immunosuppressive or immunomodulating drugs (eg, TCS, TCI, PDE4 inhibitor, biologics, JAK inhibitors, corticosteroids (except allowed concomitant therapy, see Section 6.9.2), mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, etc), unless allowed as AD rescue therapy (see Section 6.9.2).

- Depleting agents/therapies such as: rituximab or ofatumumab or other long-acting biologics
- Live (attenuated) vaccines.
- Phototherapy, or regular use (more than 2 visits per week) tanning booth/parlor.
- Medications known to prolong QTc interval (See Section 10.11.1) during the study period, including the follow-up period.
- Herbal supplements (including St. John's Wort).
- Moderate and strong CYP3A4 inhibitors or inducers (See Appendix 11, Section 10.11.2).
- Drugs where BCRP-mediated efflux (eg, rosuvastatin) is the major limiting factor of oral absorption.
- Long-acting gastric acid-reducing agents (ARA), ie, proton pump inhibitors, are not recommended (may reduce exposure of SAR444656 based on in vitro data suggesting low solubility at high pH). Participants who are on proton pump inhibitors should be switched to an alternative ARA like histamine (H2) receptor antagonists, if possible.
- Other investigational products.

6.9.2 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 to topical medications, eg, low to medium potency TCS, TCI and topical PDE4 inhibitor.

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, azathioprine, etc).

If a participant receives rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc), study intervention will be immediately temporarily 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 systemic medications. An unscheduled visit may be used for this purpose if necessary.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for all assessments indicated in the SoA unless participant withdraws consent. 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.

Under the following circumstances participant should permanently discontinue the study intervention:

- Participant's request.
- The Investigator has the right to remove any participant from study intervention (eg, due to intercurrent illness that prevents further administration of study intervention).
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Administration of the study intervention will be discontinued in the event of a TEAE that persists despite appropriate measures or any other AE that, in the opinion of the Investigator, warrants discontinuation (Section 8.4) or in the event of AESI as described in the following:
  - Symptomatic or asymptomatic confirmed QT/QTcF of >500 msec.
  - Confirmed QTcF prolongation >60 msec from baseline.
  - Occurrence of any AESI assessed as cardiac-related.
  - Pregnancy occurring in a female participant who entered the clinical trial or in a female partner of a male participant who entered the clinical trial.
  - Symptomatic overdose (serious or nonserious) with IMP.

In case of any abnormal laboratory value, the assessment should be repeated as soon as possible and when applicable, after 24 hours to confirm the abnormalities and before making a decision of permanent discontinuation of the IMP for the concerned participant. A guidance for actions and follow-up assessments are provided in Appendix 6 (Section 10.6).

In case of ECG findings, the ECG should be repeated immediately and if possible after 24 hours, before it is used to support a decision to discontinue IMP.

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 PK sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF 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 Cardiac stopping criteria

Administration of study drug should be permanently discontinued if a participant meets either bulleted criterion:

- Symptomatic or asymptomatic confirmed QT/QTcF >500 msec
- Increase of QTcF >60 msec from baseline
- Occurrence of any AESI assessed as cardiac-related

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using the Fridericia formula QTcF after enrollment), the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

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

Dosing of IMP should be temporarily interrupted for the following reasons:

- Clinically important laboratory abnormalities, such as:
  - Absolute neutrophil count $\leq 1.5\times10^9$/L but $>0.5\times10^9$/L
  - Platelet count $\leq 100\times10^9$/L but $>50\times10^9$/L
  - Creatine phosphokinase >10×ULN

- AE or other intercurrent illness when temporary discontinuation is deemed clinically appropriate by the Investigator.
- Participants receive systemic rescue therapy for AD.
- An infection requiring systemic treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requiring oral treatment with such agents for more than 2 weeks.
- Where elective surgery is required, this must be communicated in writing with the medical monitor regarding temporary discontinuation of IMP prior to any planned surgical intervention. IMP must not be re-started without communication with the medical monitor.

Temporary intervention discontinuation may be considered by the Investigator because of disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or e-CRF.

Reinitiation of the IMP after temporary discontinuation should be discussed with the Sponsor.

7.1.5 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 5.1 and Section 5.2).

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) 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 from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).

- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

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

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

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

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF 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/reallocated (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 the participant 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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.

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.

Assessment/procedures at a visit may be performed in the following order:

1. Patient questionnaires
2. ECG with 10 minutes of rest before ECG
3. PK and blood sampling
4. Investigator Assessments
5. IMP administration

- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 timeframe defined in the SoA (Section 1.3).
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 9 [Section 10.9]).
- Safety/laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If remote visits (for Visits 3, 5, 7, 9, 11, and 13) are preferred, the implementation of remote visits (eg, home nurses, etc) may be planned for study assessment. Visits 1, 2, 4, 6, 8, 10, 12, and 14 must be done on site. The following conditions must be met at a site level before such visits can be authorized.

- The visit must be performed by appropriately delegated study site staff or a home healthcare service.
- The correct equipment necessary to perform the required assessments must be taken to the visits.
- Home visits must be permitted by the site, local regulations, relevant ethics committee, relevant regulatory authority.
- The participant must have given consent via informed consent.

- Prior to implementing remote visits for participants, notification to the Sponsor (or its designee) must be provided. The notification should include justification and expected participants and visits that may be impacted.

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.

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

For each participant, the follow-up period is defined from EOT to up to 28 days from the last IMP intake except in case of premature study termination due to one of the following reasons: withdrawal of consent, loss to follow up, or death.

8.1 ADMINISTRATIVE AND GENERAL/BASELINE PROCEDURES

8.1.1 Inclusion and exclusion criteria

Participants will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at the screening and baseline visits.

8.1.2 Informed consent

An IEC/IRB approved, study specific informed consent will be reviewed, signed, and dated by the participant before any study procedures are undertaken in order to participate in this study.

8.1.3 Informed consent for optional skin biopsy, photography and additional blood samples

Participants will be asked to review, sign and date an additional consent to participate in the optional assessment. Participants will not be excluded from the study if they do not consent to optional skin biopsy, photography and additional blood samples. Participants have the right to withdraw consent to skin biopsy, photography and additional blood samples at any time.

8.1.4 Demographics

Demographic information will be collected at the screening visit as follows:

- Age
- Gender
- Race/Ethnicity (refer to Section 10.1.4)

8.1.5 Atopic dermatitis and other medical history

Detailed information of each participant's AD and other medical history will be collected at the screening visit and will include, but will not be limited to, the following:

- The date of initial onset of AD.
- The date, onset, and duration of past treatments for AD.

8.2 EFFICACY ASSESSMENTS

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

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

8.2.1 Clinician reported outcome measures (ClinROs)

Investigator assessments will be performed only by adequately trained Investigators or qualified designee. The same Investigator (or qualified designee) shall perform the clinician reported outcomes (ClinROs) for the same participant throughout the study as much as.

8.2.1.1 Eczema area severity index (EASI)

The EASI is an Investigator-assessed validated tool used to measure the extent (area) and severity of AD (18). The Investigator will assess the severity of 4 disease characteristics (erythema [E], induration/papulation [I], excoriation (X) and lichenification [L]) present in four different body areas using a 4-point scale; 0 (absent) to 3 (severe). In addition, the extent of involvement of AD in 4 body regions; head/neck, trunk, upper extremities, and lower extremities will be assessed. The possible highest score for extent of involvement in each region is 100%. For each region, the percentage of BSA will be converted to an area score; 0 = No eruption (in that region), 1 = 1%-9%, 2 = 10%-29%, 3 = 30%-49%, 4 = 50%-69%, 5 = 70%-89% and 6 = 90%-100% for each major region of the body (head, upper extremities, trunk and lower extremities), EASI score = (E + I + X + L) × Area Score. The total EASI score is the weighted total of the region EASI using the weights 10% (head), 20% (upper extremities), 30% (trunk) and 40% (lower extremities). Total score ranges from 0 to 72 with a higher score indicating increased extent and severity of AD. This assessment will be completed using an internet-enabled device (See Section 10.11.4).

8.2.1.2 Validated investigator global assessment - atopic dermatitis (vIGA-AD)

The vIGA-AD is an Investigator-lead assessment scale used to determine severity of AD and clinical response to treatment. The vIGA-AD was developed based on clinician consensus and endorsed for utilization by FDA (19). The vIGA-AD is based on a 5-point scale, ranging from 0 (clear) to 4 (severe). This assessment will be completed using an internet-enabled device (See Section 10.11.5).

8.2.1.3 Body surface area (BSA)

The BSA affected by AD will be assessed by the Investigator for each section of the body (each body region is weighted using the 'rule of nines': head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. (See Section 10.11.6).

8.2.2 Patient reported outcome measures (PROs)

8.2.2.1 Peak pruritus (PP-NRS)

The PP-NRS is a validated single item 0-10 numeric rating scale assessing peak pruritus (itch) associated with AD during the past 24 hours. The participant is asked about the severity of his/her pruritus with 0 = no itch and 10 = worst itch imaginable. The PP-NRS will be completed daily as a daily diary, ideally at the same time each day (evening). The content of the PP-NRS was validated using in-depth qualitative interviews with participants and the psychometric properties have been assessed using data from Phase IIb and Phase III dupilumab clinical trials.
The threshold for interpreting clinically meaningful within-patient change is ≥2-4-point change in the PP-NRS (20). The PP-NRS will be completed using an internet-enabled device. Participants will be asked to complete the PP-NRS for 7 consecutive days leading up to the baseline visit with a minimum requirement of 4 completions (See Section 10.11.7).

8.2.2.2 [redacted]

[redacted]

8.2.2.3 [redacted]

[redacted]

8.2.2.4 [redacted]

[redacted]

8.2.2.5 [redacted]

[redacted]

8.2.3 [redacted]

[redacted]

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in the SoA Section 1.3.

8.3.1 Physical examinations

- A complete physical examination will include, at a minimum, examination of the skin, assessments of the cardiovascular system, pulmonary system, gastrointestinal system (including palpation of liver and spleen), neurological, lymphatic, and musculoskeletal systems. Height will be measured and recorded at the screening visit and weight will be measured and recorded at screening and EOT visit. Investigators should pay special attention to clinical signs related to previous serious illnesses. The complete physical examination has to be performed at the screening and at EOT visit.
- A targeted physical examination will include, at a minimum assessment of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and weight and will be performed at baseline and at Visit 8.
- Symptom-directed physical examination may be performed as clinically indicated at visits when complete or targeted physical examination is not specified.

8.3.2 Vital signs

- Oral/forehead/temporal artery/other temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mm Hg) will be recorded (before blood collection for laboratory tests) at baseline and at each visit during the treatment period.
- Blood pressure and pulse measurements will be assessed in seated and supine positions with a completely automated device and should be preceded by at least 5 minutes of rest for the participant in a quiet setting. Manual techniques will be used only if an automated device is not available.

8.3.3 Electrocardiograms

- Standard digital 12-lead ECGs (safety ECGs) are recorded using a digital electrocardiographic device after the participant has been resting in supine position for at least 10 minutes in a quiet environment. The electrodes should be positioned as much as possible at the same place for each ECG recording throughout the study.
- Triplicate ECG will consist of 3 ECGs and will be recorded within 5 minutes with at least 1 Minute between 2 replicates (refer to SoA [Section 1.3]).
- Each replicate ECG consists of a 10-second recording of the 12 leads simultaneously, leading to a single 12-lead ECG (25 mm/s, 10mm/mV) printout with heart rate, PR, QRS, QT, QTcF automatic correction evaluation (by the ECG device), including date, time, and participant study identification, signature of the research physician, and at least 3 complexes for each lead. The Investigator's medical opinion and automatic values will be recorded in the e-CRF. Each replicate printout will be retained at the site.
- Further ECG reading by an ECG core lab will be performed. The following parameters will be assessed: RR, HR, PR, QRS, QT, J-Tpeak intervals; the calculation/derivation of HR-corrected QT intervals (QTcB and QTcF) and JT peak (J-Tpeak c); the morphological analysis of ECG waveforms.

- Each digital file will be identified by theoretical time (day and time, actual date and time [recorder time], Sponsor study code, participant number [ie, 3 digits], site and country numbers, if relevant). The digital recording, data storage, and transmission need to comply with all applicable regulatory requirements (ie, FDA 21 CFR, Part 11).
- Warning: when vital signs, physical examination, ECG, and blood samples are scheduled at the same time as the IMP administration and/or a meal, they should be done prior to IMP intake and/or meal. In order to respect exact timing of PK samples (refer Section 1.3 for window allowance of PK samples), the other measurements will be done ahead of the scheduled time.
- Refer to SoA (Section 1.3) for the frequency and Section 7.1.3 for cardiac withdrawal criteria and any additional QTc readings that may be necessary.
- Additional triplicate ECG can be performed as clinically indicated at any time during the study.
- On-site ECG could be substituted by ECG at home. Baseline triplicate ECGs must be performed on-site.

Twenty-four-hour Holter:

- Unscheduled Holter ECG may be decided based on safety findings (symptoms/signs of arrhythmia and/or in case of abnormalities in ECG). Holter will be recorded over approximately 24 hours using an internationally recognized device with adequate resolution to allow ECG extractions.
- The digitized recording, data storage, and transmission need to comply with all applicable regulatory requirements (eg, FDA 21 CFR).
- Holter recordings will be transferred by the study site to the ECG core laboratory for further analysis. ECG strips extraction and interval measurements of the digital ECG waveforms will be performed by the ECG core laboratory using a standardized methodology (in accordance with the Sanofi ECG central reading master statement of services, and after checking interobserver reproducibility and repeatability). The following ECG intervals will be measured or derived from the centrally read ECGs: RR, HR, PR, QRS, QT, QTcB, QTcF, J-Tpeak, J-Tpeak c, T-wave morphology metrics.
- For each extracted ECG, a morphological analysis will also be performed, independently of the quantitative measurement of the ECG parameters, and according to the coded list used by the ECG core laboratory. At a minimum, the following main categories should be described: rhythm analysis, ST segment morphology characterization, T wave morphology characterization, and U wave morphology characterization.

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator:
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.
  - A guidance for actions and follow-up assessments are provided in Appendix 6 (Section 10.6) in case of abnormal laboratory results such as an increase in ALT, CPK and in case of acute renal impairment.

Precaution to be taken: When vital signs, ECG, and blood samples are scheduled at the same time as the IMP administration and/or a meal, they should be done prior to IMP intake and/or meal. In order to respect exact timing of PK samples (refer to Section 1.3 for window allowance of PK samples), the other measurements will be done ahead of the scheduled time.

8.3.5 Pregnancy testing

Refer to Section 5.1 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 woman with an early undetected pregnancy:

- Serum pregnancy testing (β-hCG) should be done (as required by local regulations) within 4 weeks before the first administration of study intervention and urine pregnancy test (dipstick) to be done for WOCBP every month until EOT visit and for at least 4 weeks after the last administration of study intervention according to the SoA (Section 1.3).
- 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.

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

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.6.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR) 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 study.

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).

8.4.1 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 EOS visit at the timepoints 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 the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of detecting AEs and SAEs

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

8.4.3 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 AESIs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.4.4 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.
- SAEs that are considered expected will be specified in the reference safety information (see IB).
- Investigator safety reports must be prepared for 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.
- For the European Union, safety reporting to the agency is described in Section 10.8.2.1.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 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 pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- 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. Follow-up of offspring for 6 months is desirable.
- Any post-study pregnancy-related SAE considered reasonably related to the IMP by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former participant/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 IMP or be withdrawn from the study.

8.4.6 Adverse events of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. AESI may be added, modified, or removed during a study by protocol amendment.

All reported AESIs will be reviewed by an IDMC.

For AESIs, the Sponsor is to be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Appendix 3 (Section 10.3), even if a seriousness criterion is not met, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF:

- 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 Section 8.4.5).
- Symptomatic overdose (serious or nonserious) with IMP (see definition of an overdose in Section 6.8).
- Increase in alanine transaminase (ALT) >3×ULN (please refer to Appendix 6 [Section 10.6]).
- Other project specific AESI(s):
  - Serious infections
  - QT/QTc >500 msec
  - Change in QTcF from baseline >60 msec
  - Torsade de pointes
  - Sudden cardiac death
  - Ventricular tachycardia
  - Ventricular fibrillation and flutter
  - Unexplained or presumptive cardiac syncope
  - Seizures

8.4.7 Medication errors or misuses of medicinal product

All reports of medication error or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant. This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.4.8 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.

8.5 PHARMACOKINETICS

- PK sampling time: Whole blood samples will be collected from all participants for measurement of plasma concentrations of SAR444656 as specified in the SoA (Section 1.3).
- PK sample handling procedure: Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded.
- Bioanalytical method: SAR444656 plasma concentrations will be determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (KT47HPP; achiral analyte) with a lower limit of quantification (LLOQ) of 0.15 ng/mL under the responsibility of Sponsor or Sponsor's designee.
- PK parameters: PK variables will include plasma SAR444656 concentrations determined at each time point described in the SoA (Section 1.3). Depending on the timing of the PK sample collection versus the previous dose, SAR444656 PK parameters will be defined as follows:
  - C2h: SAR444656 concentration in PK sample taken 2 hours after IMP administration.
  - C4h: SAR444656 concentration in PK sample taken 4 hours after IMP administration.
  - C_{trough}: SAR444656 concentration in PK sample taken just prior to IMP administration (pre-dose).

PK samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

Please refer to Section 10.8.3 for China specific requirements.

8.6 PHARMACODYNAMICS

Blood samples will be collected for measurement of IRAK4 levels in WBCs, as specified in the SoA (Section 1.3). Changes in IRAK4 levels will be used as a measurement of the selective degradation of IRAK4 by SAR444656 via the UPS. The reduction of IRAK4 levels will be used to confirm in vivo action of SAR444656 (ie, target engagement and degradation). Additional pharmacodynamic biomarkers are described in Section 8.8.

8.7 GENETICS



8.8 [redacted]

[redacted]

8.9 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) collected as a part of study will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded study data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection - Processing of coded study data

The study participant will be provided will all mandatory details of the data processing in Part 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, EOS 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.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Part 2 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes. Biological samples for future use will be stored for up to 25 years after the end of the study unless local regulations require a different retention period. 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.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 7 - 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 is received.
Efficacy	All randomized participants who have taken at least one dose of study intervention. Participants will be analyzed according to the intervention allocated by randomization.
Intent-to-treat (ITT)	All randomized participants who have taken at least one dose of study intervention. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All participants from the safety population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamics (PD)	All participants from the safety population with at least one post-baseline PD parameter assessed.

Abbreviations: ICF = informed consent form; IRT = interactive response technology; PK = pharmacokinetics; PD = pharmacodynamics.

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 (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

9.2 STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.2.1 General considerations

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/enrollment.

Unless otherwise specified, analyses will be performed by dose level (and overall for baseline and demographics characteristics).

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent** (TE) **period** is defined as the period from the first IMP administration up to EOS (EOS included). The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +15 days.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period starting after the end of the treatment-emergent period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Definition of endpoint(s)

The primary endpoint is the percent change of EASI from baseline at Week 16.

9.2.2.2 Main analytical approach

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Percent change from baseline in EASI at Week 16.
- Treatment condition: SAR444656 will be compared to placebo.
- Analysis population: Efficacy population.

- Intercurrent events:
  - Intake of rescue/prohibited medications will be handled with the while before rescue/prohibited medications strategy. Data collected after this IE will be set to missing.
  - Misallocation of treatment will be handled with the while on randomized treatment strategy. Data collected on or after misallocation of treatment will be set to missing.
- Population-level summary: estimated difference between interventions from a BLMM, based on all participants who received matching placebo or SAR444656 at each dose level. The model will be adjusted for randomization stratum (EASI<22) and will include effects for participant specific baseline EASI score, visit, treatment group, and visit-by-treatment group interaction. Historical data will be used to amend the prior distribution of the placebo arm by an equivalent of 5 participants. Repeated measurements for each visit will be taken within participant. [redacted]

9.2.2.3 [redacted]

[redacted]

9.2.2.4 [redacted]

[redacted]

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are:

- Proportion of participants with vIGA-AD of 0 or 1 and reduction from baseline of ≥2 points at Week 16.
- Proportion of participants with at least a 75% reduction from baseline in EASI (EASI-75) at Week 16.

Analyses of endpoints related to adverse events are defined in Section 9.2.6.1.

Analysis of the Proportion of participants with vIGA-AD of 0 or 1 and reduction from baseline of ≥2 points:

Analysis will be based on the Efficacy population.

A logistic BGLMM will be applied, including all participants who received matching placebo or SAR444656 at each dose level, based on response data for Week 16. The model will be adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) and will include effect for treatment group. [redacted]

Analysis Proportion of participants with at least a 75% reduction from baseline in EASI-75:

Analysis will be based on the Efficacy population.

A logistic BGLMM will be applied, including all participants who received matching placebo or SAR444656 at each dose level, based on response data for Week 16. The model will be adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22) will include effect for treatment group. [redacted]

9.2.4 [redacted]

[redacted].

9.2.5 Multiplicity adjustment

No multiplicity adjustment will be applied.

9.2.6 Safety analyses

All safety analyses will be performed on the safety population. The summary of safety results will be presented by treatment group.

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment 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 AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

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

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit, during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

In addition, for ECG parameters including QTc variables, mean of raw data and changes from baseline with the corresponding standard error will be tabulated and plotted over time.

Analyses according to PCSA

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

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either 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.

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

- Normal/missing.
- Abnormal.

9.2.7 Other analyses

Plasma SAR444656 concentrations will be summarized using descriptive stats, by visit and will be described in the SAP.

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

If applicable, the impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety may be detailed in the SAP.

9.3 INTERIM ANALYSES

No formal interim analyses are planned. However, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted.

9.4 SAMPLE SIZE DETERMINATION

This study includes a total of 200 participants overall, with 53, 49, 45 and 53 participants randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo, respectively. The randomization ratio varies during the study: The initial 95 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 2:1:2 ratio. The remaining 105 participants will be randomized to SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted], SAR444656 [redacted] mg/[redacted] or matching placebo at a 1:2:3:1 ratio, targeting an overall allocation of 1:1:1:1.

Data from historical studies which have similar target population may be used as prior information supplementing the placebo arm, using a Bayesian approach.

The conditional prior distribution for the reduction in placebo has been chosen as a normal distribution with mean 35, standard deviation 40, and assuming that historical information takes a weight of 5 additional patients treated with placebo, while a non-informative prior is used for the active arm.

With 53 and 53 participants randomized to SAR444656 [redacted]mg and placebo, and applying the above Bayesian framework, the half-width for the 2-sided [redacted] CI of the mean % change in EASI score from baseline to Week 16 of SAR444656 group as compared to the placebo group will be [redacted]. Similarly, with 45 and 53 participants randomized to SAR444656 [redacted] mg and placebo, respectively, the corresponding CI will have a half-width of [redacted]

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 CIOMS international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
  - The GDPR and any other applicable data protection laws.
  - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator 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, as applicable:
  - 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.
  - 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, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.
  - 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 concerned 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.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, 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.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

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 ICF will be provided to the study participant in paper version. When feasible, an eConsent process may be used at global level and/or locally if permitted by country regulations.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participants when their participation ends.
- Potential participants must be informed that their participation is voluntary. They 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 General Data Protection Regulation (GDPR) and of the French law, 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 address the use for future 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 CSICF Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in CSICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research, and consent for performance of genetic analyses

on biological samples. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

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

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 trial participants, 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 personal 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 expected to modify the drug response/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, when applicable, 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.
- Participants must be informed that their 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.
- Participants must be informed that their 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.

- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- 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 personal 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 twenty five (25) 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 - 46 avenue de la Grande Armée – 75017 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

10.1.5.1 Independent data monitoring committee

- An IDMC with members independent from the Sponsor and the Investigators will be implemented to make appropriate recommendations on the conduct of the clinical trial to ensure the protection and the safety of the enrolled participants on the study. The IDMC reviews and analyses, on a regular basis, blinded safety and, if requested by the IDMC, efficacy data throughout the study (and unblinded data if deemed necessary by the IDMC).
- Details regarding membership, scope, and logistics (including meeting intervals) of the IDMC are addressed in the IDMC charter.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

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, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

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 vivli.org.

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

Professionals involved in the study or in the drug development program

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 different 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 e-CRF 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 or monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring 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 first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

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

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

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

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

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

10.1.10 Publication policy

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

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 8 will be performed by the central laboratory unless specified otherwise.
- For tests which are required to be performed by 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 8 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Hemoglobin
	Hematocrit
Clinical chemistry[a]	Blood urea nitrogen (BUN)
	Potassium
	Creatinine
	Glucose (fasting, or nonfasting)
	Sodium
	Calcium
	Magnesium
	chloride
	phosphate

Laboratory tests	Parameters
	bicarbonate
	high sensitivity C reactive protein (hsCRP)
	creatine phosphokinase (CPK)
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[b]
	LDH
	Total and direct bilirubin
	Total protein
	Albumin
	GGT
Routine urinalysis	Specific gravity
	pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte] by dipstick
	Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	[Serum or highly sensitive urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only)
	HIV testing (anti-HIV-1 and anti-HIV-2 antibodies); Hepatitis testing covering hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HbsAb), immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM HBcAb), total antibody to hepatitis B core antigen (HBcAb total) and hepatitis C total antibodies (HCV Ab). In case of results showing HBsAg negative and anti-HBc positive, hepatitis B virus (HBV)-DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. In case of results showing HCV Ab positive, HCV RNA testing will be performed to rule out a false positive.
	The type of COVID-19 test performed should comply with local requirements. The test will be performed in local laboratory.
	QuantiFERON TB Gold Interferon-Gamma Release Assay (IGRA) can be done locally. If this TB tests are not locally available, a blood sample for QuantiFERON-TB Gold IGRA testing should be sent to the Central Laboratory.
	Refer Section 10.8.5 for Japan specific requirements.

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 6 (Section 10.6) [Liver and other safety. Suggested actions and follow-up assessments].

b If alkaline phosphatase 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 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.

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, or more severe than expected for the participant's condition), 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 condition 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.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- 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 abnormal laboratory findings or other abnormal safety assessments that 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 untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Is a medically important event:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

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 one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- 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.
- 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.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem 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 offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in Investigator site file.

SAE reporting to the Sponsor via paper data collection tool

- 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 timeframes.
- 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.

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 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), Investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>ULN as defined by central laboratory readout) is required.
   - 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 randomization.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner (Vasectomized partner 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. Spermatogenesis cycle is approximately 90 days)

Highly Effective Methods[b] That Are User Dependent
• 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 If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

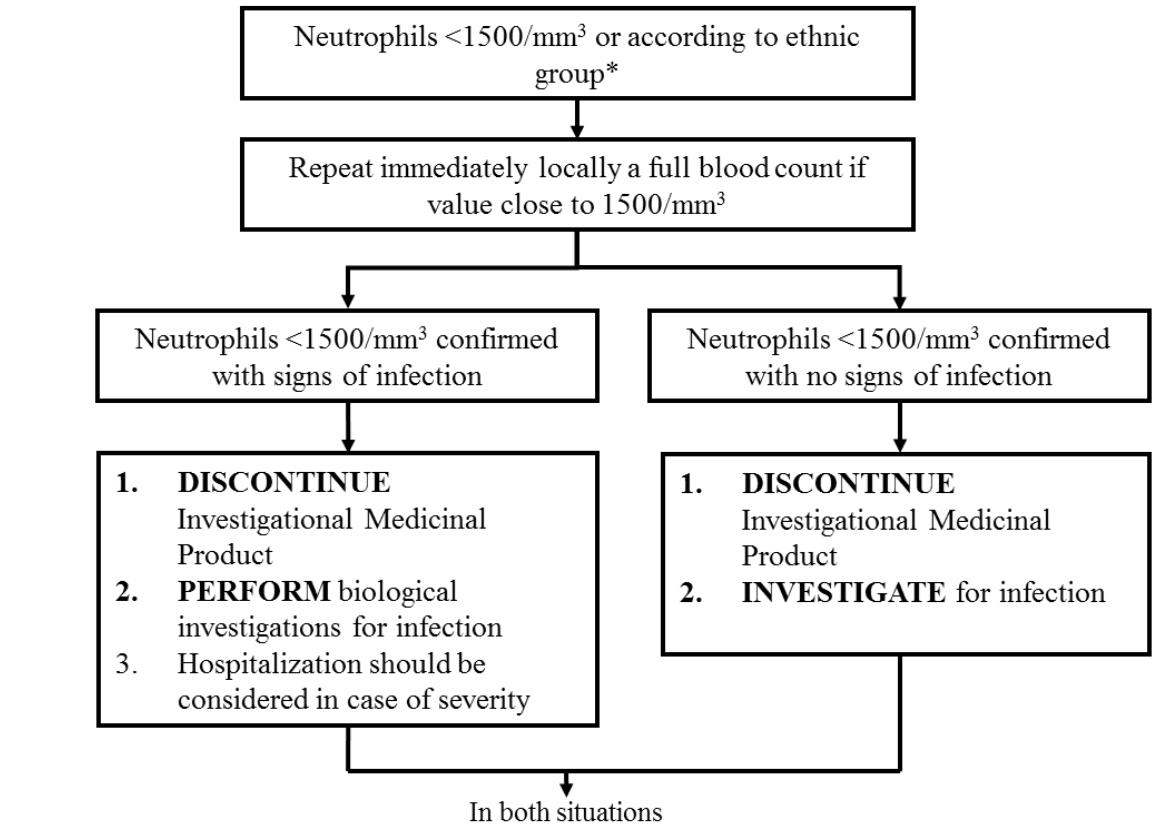
10.5 APPENDIX 5: GENETICS





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

NEUTROPENIA

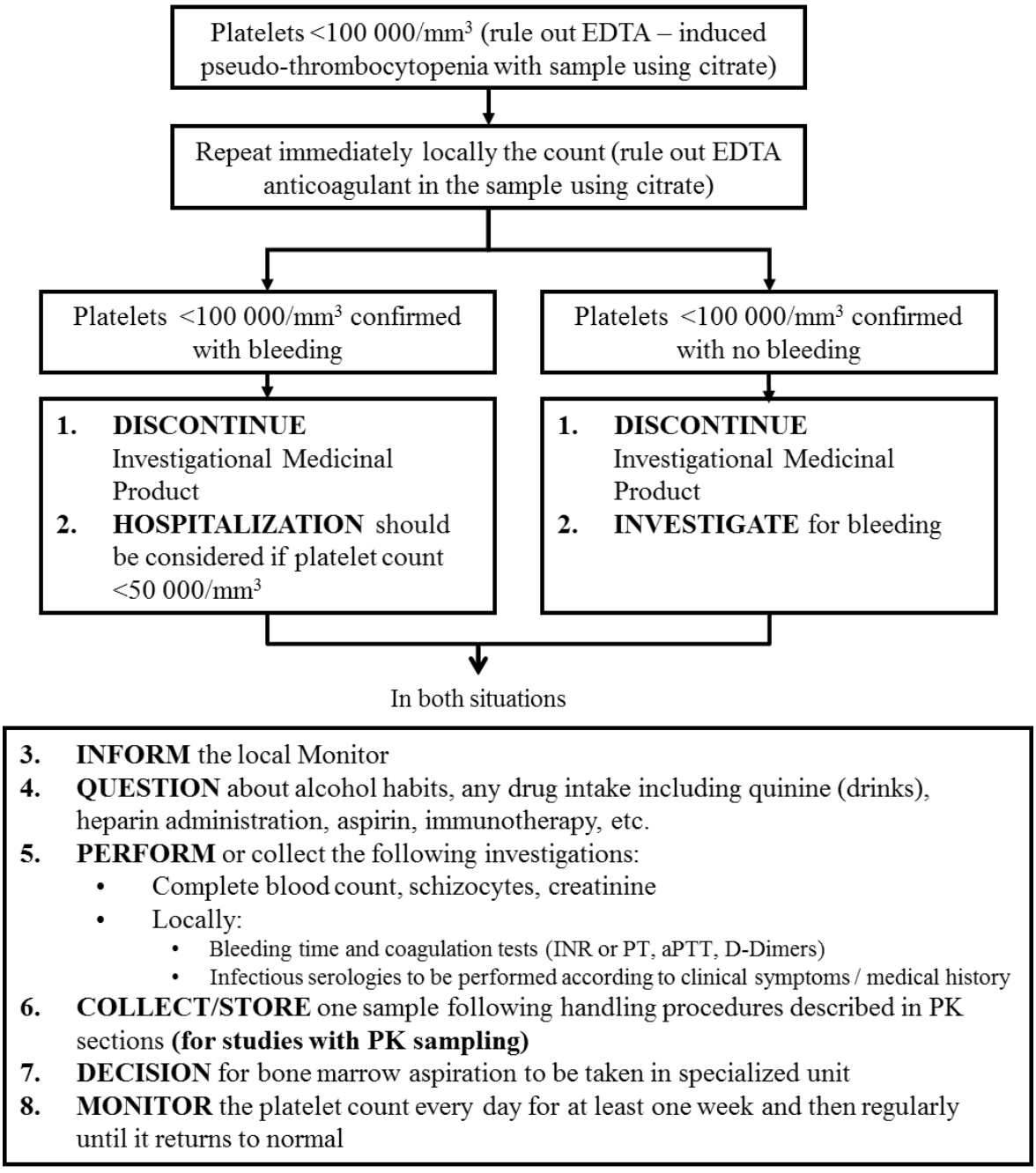


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - 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

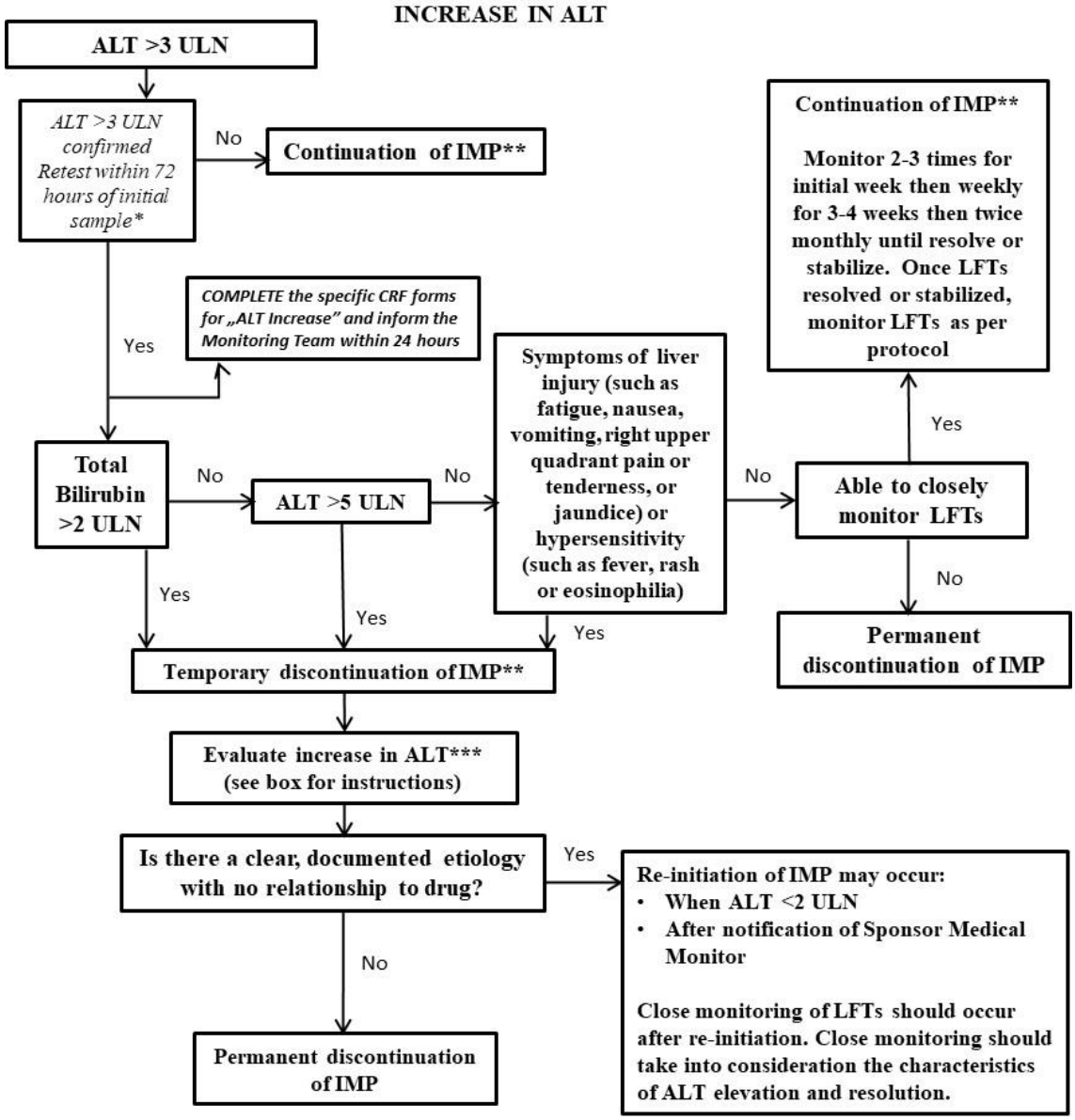
***** For individuals of African descent, the relevant value of concern is <1000/mm3

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.

THROMBOCYTOPENIA



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.



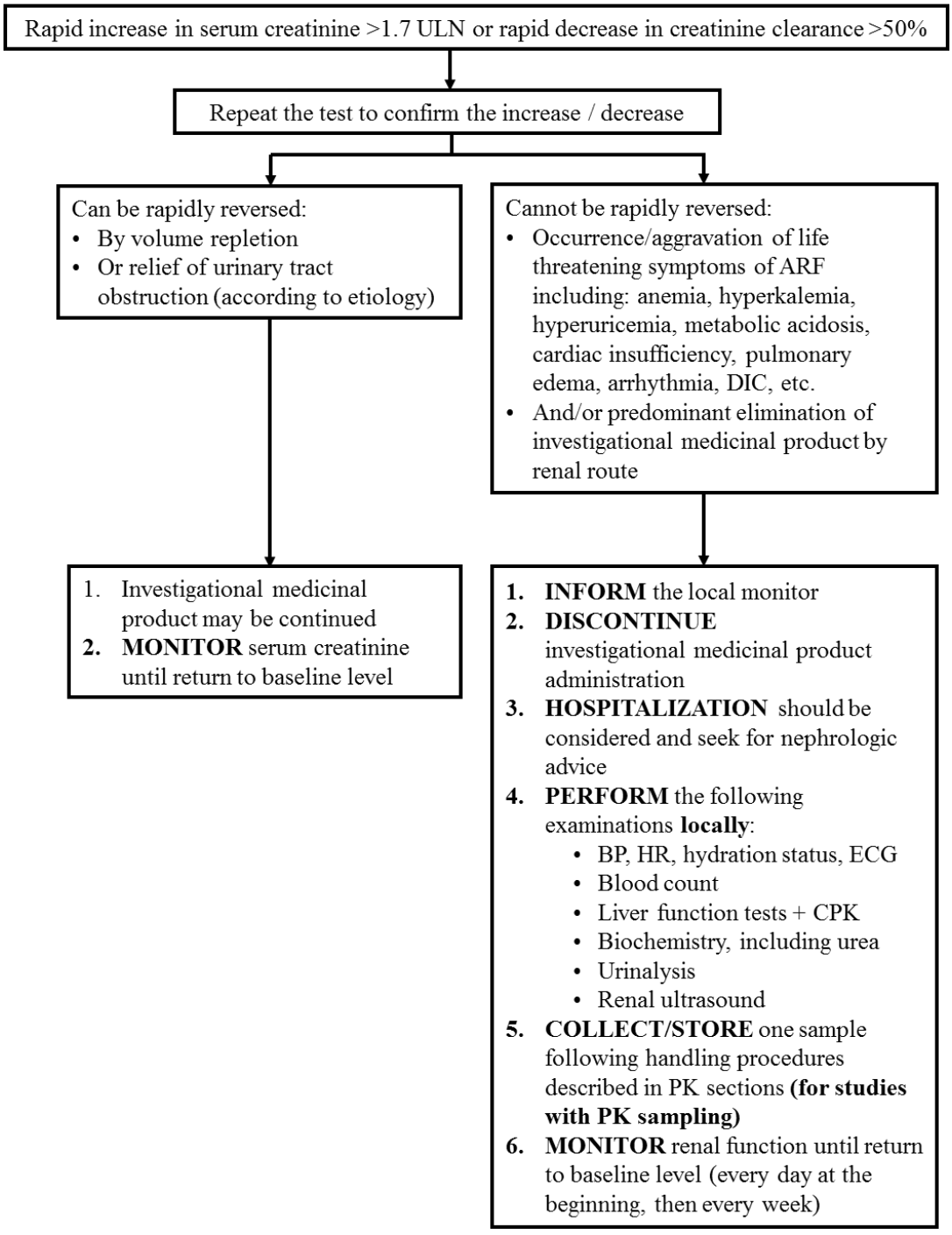
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met
*** See box below
Note:

- "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.

Evaluate Increase in ALT***

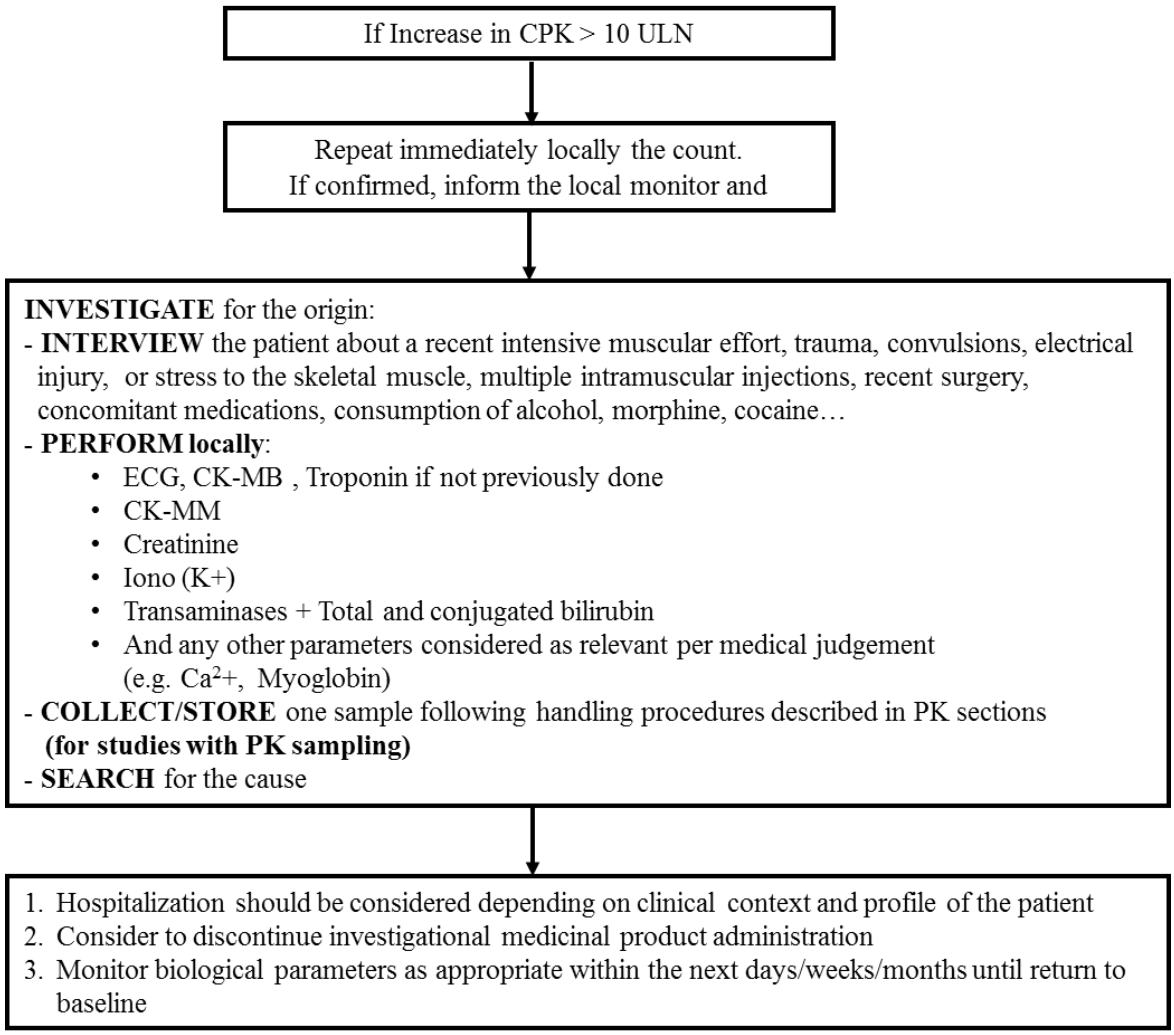
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine 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.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



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

10.7 APPENDIX 7: MEDICAL DEVICES 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/REGION REQUIREMENTS

10.8.1 Germany

Informed consent process: All references to “legally authorized representative” are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to “legally authorized representative” are found in Section 5.1, Section 8.4, and Section 10.1.3.

10.8.2 European Union

10.8.2.1 Safety reporting to the agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

10.8.3 China

Section 8.5 Pharmacokinetics

PK samples collected in Chinese participants will not be used for possible exploratory analysis of drug metabolites.

Section 8.8 Biomarkers

Plasma biomarkers collected for additional and/or future pharmacodynamic and safety assessments (see Section 8.8 biomarker) are not applicable for participants in China.

10.8.4 France

10.8.4.1 Exclusion criteria specific to France

- The participant is not affiliated to a social security scheme.
- The participant is under tutorship or curatorship; the participant is under safeguard of justice or deprived of his/her liberty by an administrative or court decision.

10.8.5 Japan

Section 1.3 Schedule of Activities (SoA)

For Japan, footnote n, HIV testing (anti-HIV-1 and anti-HIV-2 antibodies); Hepatitis testing covering hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HbsAb), immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM HBcAb), total antibody to hepatitis B core antigen (HBcAb total) and hepatitis C total antibodies (HCV Ab). In case of

results showing anti-HBc and/or anti-HBs positivity, HBV-DNA testing will be performed and confirmed negative prior to enrollment. If participants have HBsAb (positive) but are confirmed to have no detectable HBV-DNA, they are required to undergo HBV-DNA testing at Week 4, Week 8 and Week 12.

Section 5.2 Exclusion criteria

For Japan, E 24, Presence of HBsAg or positive HBcAb at screening. In addition, Japanese patients with positive HBcAb or positive antibody to hepatitis B surface antigen, associated with positive (or detectable) HBV-DNA at screening.

Section 10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

For Japan, the description “Other screening tests” is replaced to the following description.

Laboratory tests	Parameters
Other screening tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only)
	HIV testing (anti-HIV-1 and anti-HIV-2 antibodies); Hepatitis testing covering hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HbsAb), immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM HBcAb), total antibody to hepatitis B core antigen (HBcAb total) and hepatitis C total antibodies (HCV Ab). In case of results showing HBsAg negative and anti-HBc positive, hepatitis B virus (HBV)-DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. If participants have HBsAb (positive) but are confirmed to have no detectable HBV-DNA, they are required to undergo HBV-DNA testing at Week 4, Week 8 and Week 12.
	The type of COVID-19 test performed should comply with local requirements. The test will be performed in local laboratory.
	QuantiFERON TB Gold Interferon-Gamma Release Assay (IGRA) can be done locally. If this TB tests are not locally available, a blood sample for QuantiFERON-TB Gold IGRA testing should be sent to the Central Laboratory.

10.8.6 South Korea

Participants must be ≥18 of age inclusive, at the time of signing the informed consent. Only subjects ≥19 years of age at the time of signing the informed consent may be enrolled in South Korea.

10.9 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 GCP 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.

Informed consent

In exceptional circumstances, such as a regional or national emergency declared by a governmental agency, consent may be collected through a remote solution if allowed through country and site regulations and following approval by the IEC/IRB. Implementation must have prior approval from the Sponsor (or its designee). Contingency procedures may be implemented for the duration of the emergency.

The participant or their LAR 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).

Study drug administration

During the treatment period of the study, study drug must be administered in accordance with Section 6. At all other times, consideration may be given to administration of study drug at home if all conditions in the pharmacy manual are adhered to and prior Sponsor agreement is obtained.

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

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

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 a government declared regional or national 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 laboratory tests analyses cannot be performed due to a government-declared regional or national emergency. These local laboratory results will only be performed to ensure participant safety and will not be used for the purpose of statistical analyses.

If remote visits are preferred, the implementation of remote visits (eg, phone call, virtual consultation, televisit, etc) or home visits (eg, home nurses, etc) may be planned for the collection of possible safety and/or efficacy data.

A televisit is defined as a videoconference, video call, or telephone call.

The following conditions must be met at a site level before such visits can be authorised:

- The visit must be performed by appropriately delegated study site staff or a home healthcare service.
- The correct equipment necessary to perform the required assessments must be taken to the visits.
- Home visits or televisits must be permitted by the site, local regulations, relevant ethics committee, relevant regulatory authority.
- The participant must have given consent via informed consent.
- Prior to implementing remote study visits for participants, notification to the Sponsor (or its designee) must be provided. The notification should include justification and expected participants and visits that may be impacted.

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.

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 conducted 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.

For Germany contingency measures are currently only applicable for the COVID-19 pandemic.

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.11 APPENDIX 11: ADDITIONAL APPENDICES

10.11.1 Non-exhaustive list of medications known to prolong QTc interval

This list is not intended to be exhaustive and may be out of date. For more detailed and updated information, please refer to www.crediblemeds.org or product labeling:

Aclarubicin
Amiodarone
Anagrelide
Arsenic trioxide
Astemizole
Azithromycin
Bepridil
Cesium Chloride
Chloroquine
Chlorpromazine
Chlorprothixene
Cilostazol
Ciprofloxacin
Cisapride
Citalopram
Clarithromycin
Cocaine
Disopyramide
Dofetilide
Domperidone
Donepezil
Dronedarone
Droperidol
Erythromycin
Escitalopram

Flecainide
Fluconazole
Gatifloxacin
Grepafloxacin
Halofantrine
Haloperidol
Hydroquinidine (Dihydroquinidine)
Hydroxychloroquine
Ibogaine
Ibutilide
Levofloxacin
Levomepromazine (Methotrimeprazine)
Levomethadyl acetate
Levosulpiride
Meglumine antimoniate
Mesoridazine
Methadone
Mobocertinib
Moxifloxacin
Nifekalant
Ondansetron
Oxaliplatin
Papaverine HCl (Intra-coronary)
Pentamidine
Pimozide
Probucol
Procainamide
Propofol
Quinidine
Roxithromycin
Sertindole
Sevoflurane
Sotalol
Sparfloxacin
Sulpiride
Sultopride
Terfenadine
Terlipressin
Terodiline
Thioridazine
Vandetanib

10.11.2 List of moderate and strong CYP3A4 inhibitors

	Strong	Moderate
CYP3A4 inducers	apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, St. John's wort	bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib
CYP3A4 inhibitors	ceritinib, clarithromycin, idelalisib, nefazodone, nelfinavir cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir (and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, 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 Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA or product labeling.

10.11.3 Non-exhaustive list of live (attenuated) vaccines

This list is indicative and not exhaustive:

Chickenpox (Varicella)

Intranasal influenza,

Measles (Rubeola),

Measles-mumps-rubella (MMR) combination,

Mumps,

Oral polio (Sabin),

Oral typhoid, Rubella,

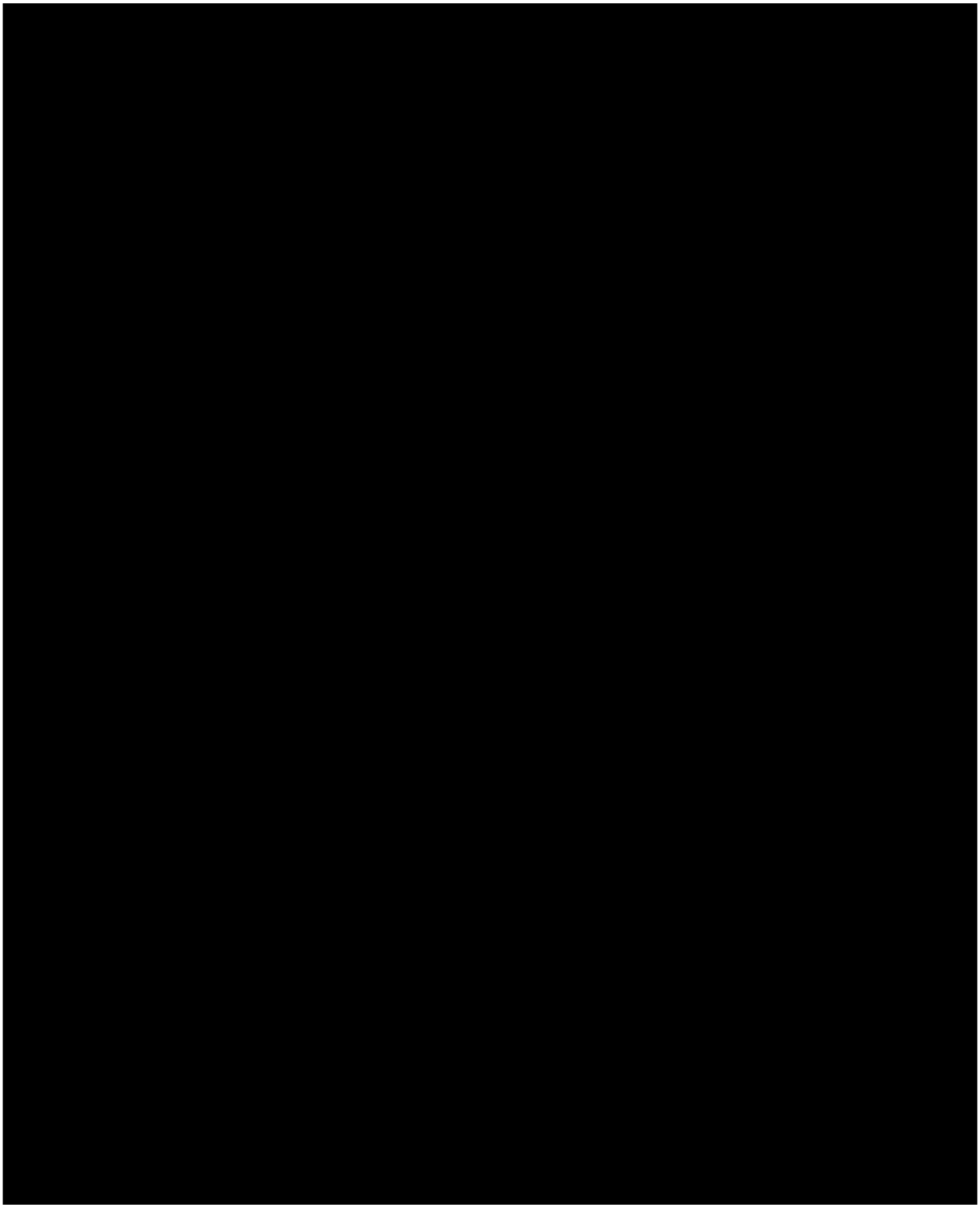
Smallpox (Vaccinia),

Shingles (Herpes zoster),

Bacille Calmette-Guerin,

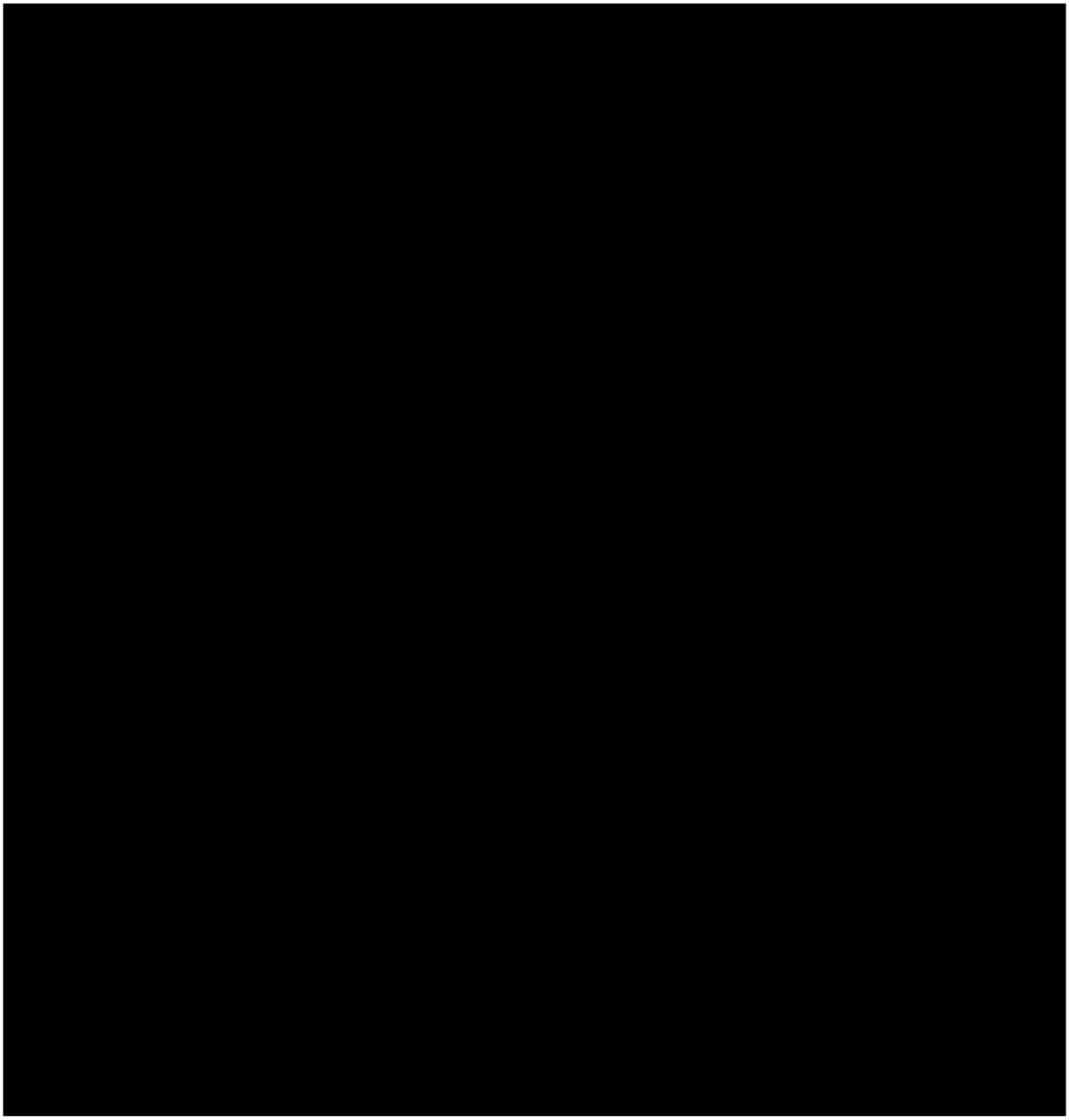
Yellow fever

10.11.4 Eczema area and severity index (EASI)



EASI © Munksgaard 2001, managed by Wiley
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 Feb;10(1):11-8

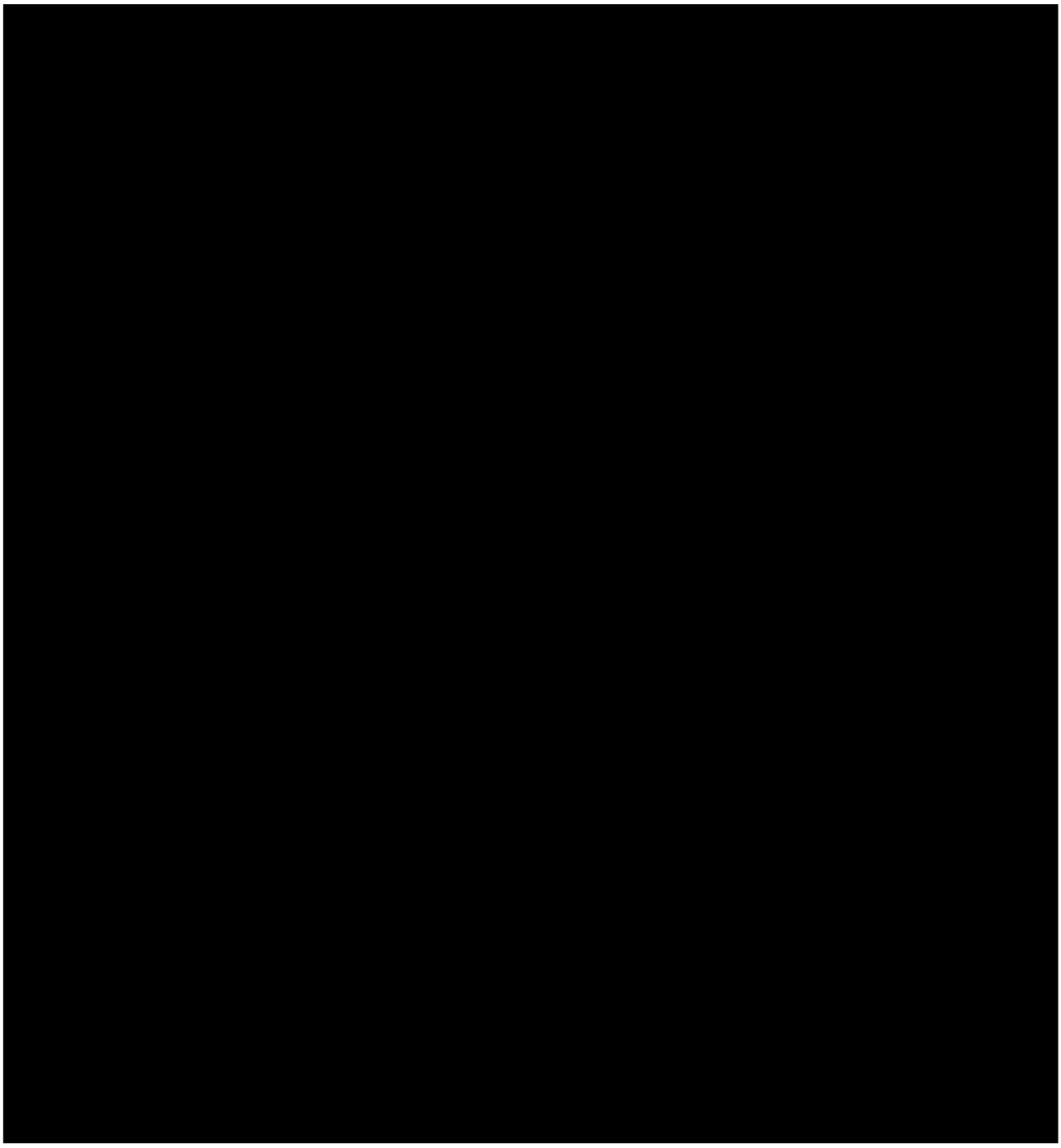
EASI - United States/English
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EASI © Munksgaard 2001, managed by Wiley
Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USori.doc

10.11.5 Validated investigator global assessment scale (vIGA)



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10.11.6 Body surface area (BSA)

Body Surface Area (BSA) Affected by AD

Instructions:

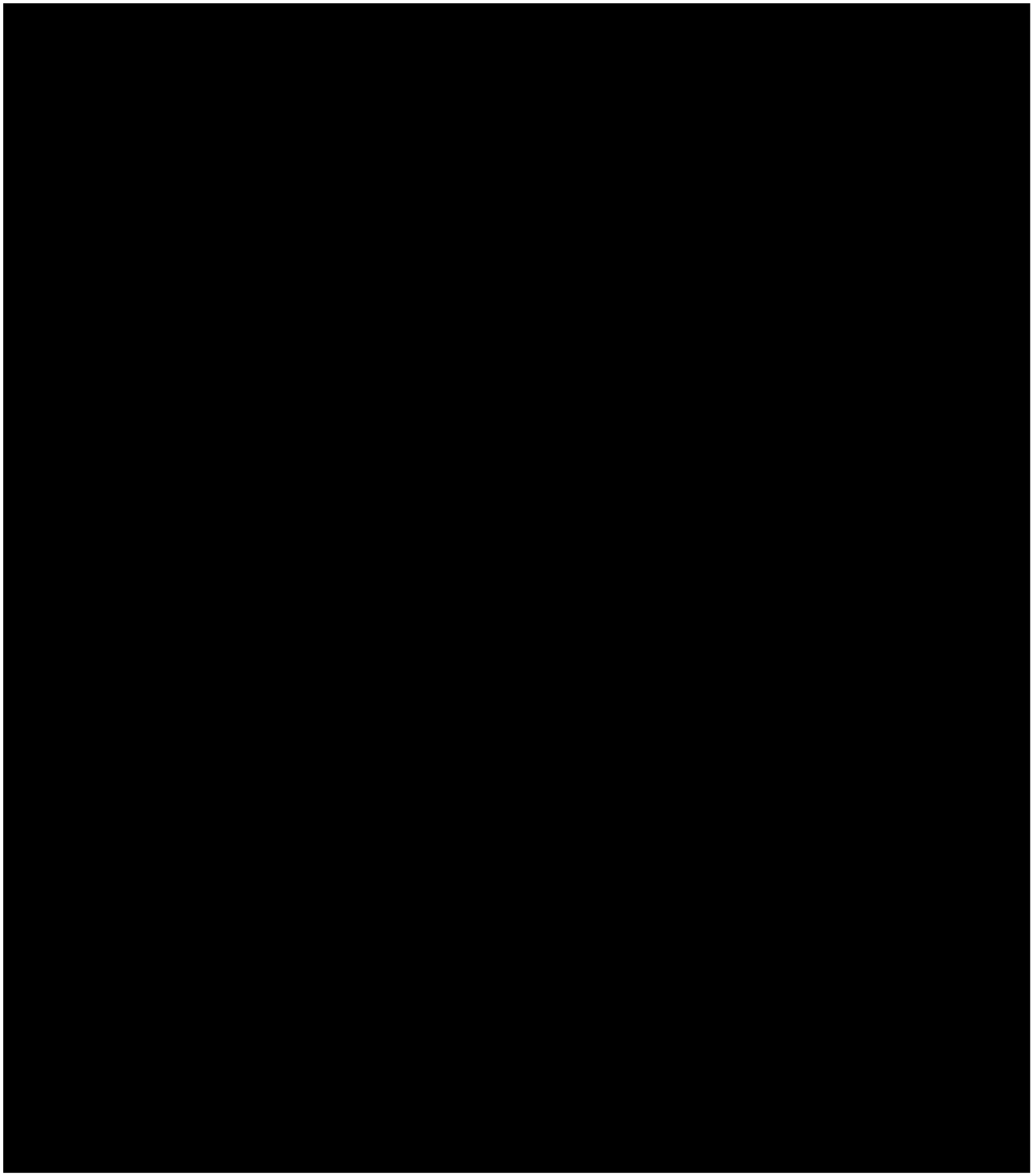
Body surface area (BSA) affected by atopic dermatitis will be assessed for each major section of the body (head, trunk, arms, and legs). Use the 'palm method' (the surface of one patient's palm, equals 1%).

Please provide the BSA affected by atopic dermatitis for each of the following body regions:

HEAD	
• Anterior Head (0-4.5%)	%
• Posterior Head (0-4.5%)	%
TORSO	
• Anterior Torso (0-18%)	%
• Posterior Torso (0-18%)	%
LOWER EXTREMITIES	
• Left Anterior Leg (0-9%)	%
• Right Anterior Leg (0-9%)	%
• Left Posterior Leg (0-9%)	%
• Right Posterior Leg (0-9%)	%
UPPER EXTREMITIES	
• Left Anterior Arm (0-4.5%)	%
• Right Anterior Arm (0-4.5%)	%
• Left Posterior Arm (0-4.5%)	%
• Right Posterior Arm (0-4.5%)	%
GENITALIA/PERINEUM (0-1%)	%
TOTAL body surface area affected by AD (0-100)*	%

* Total BSA must be the sum of all individual body areas

10.11.7 Peak pruritus numeric rating scale (PP-NRS)

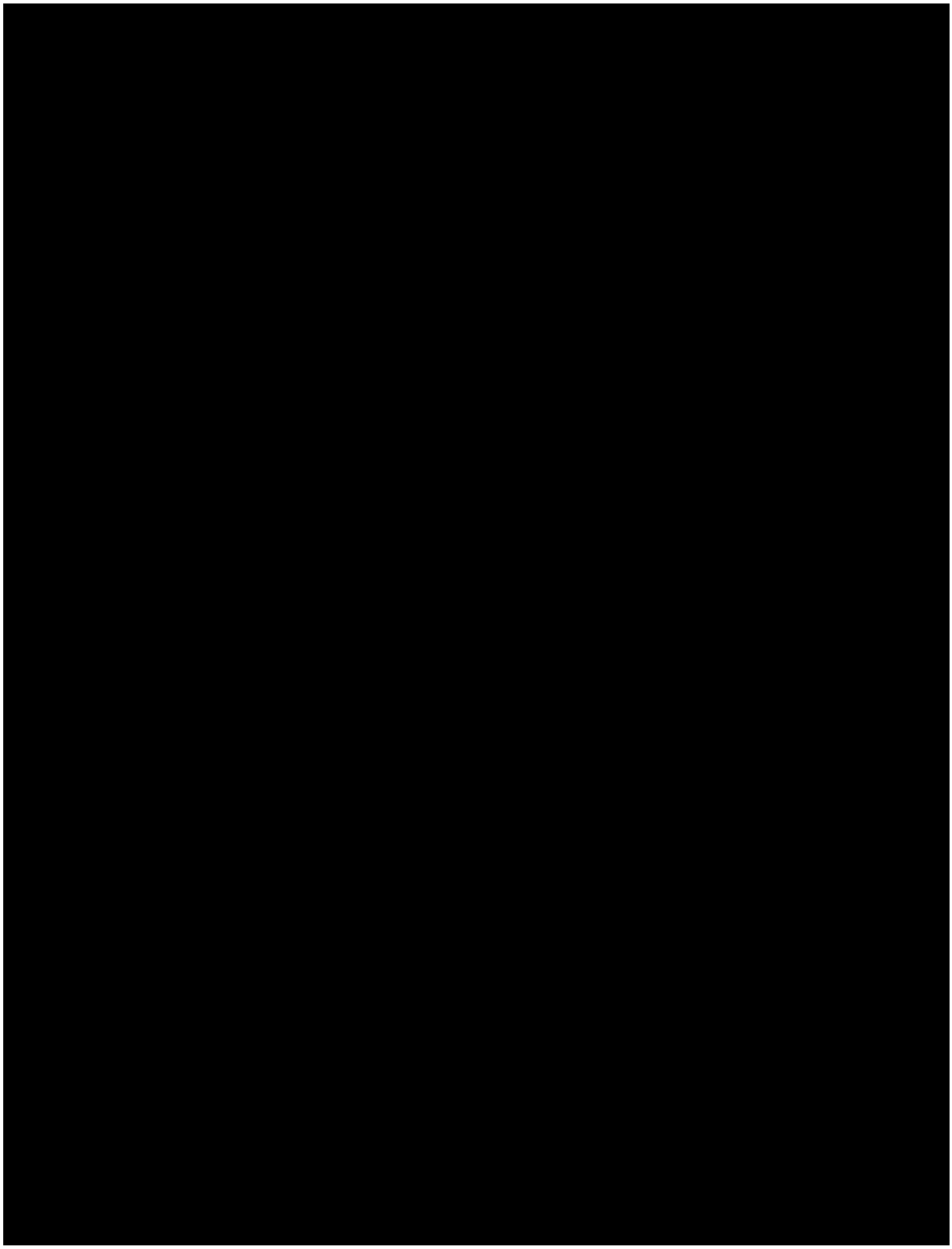


PP-NRS © 2019 Regeneron Pharmaceuticals, Inc. and SAR&D. All rights reserved. Used with permission of Regeneron Pharmaceuticals, Inc. and SAR&D

PP-NRS_AU1.1_eng-USori.docx

10.11.8 [redacted]

[redacted]



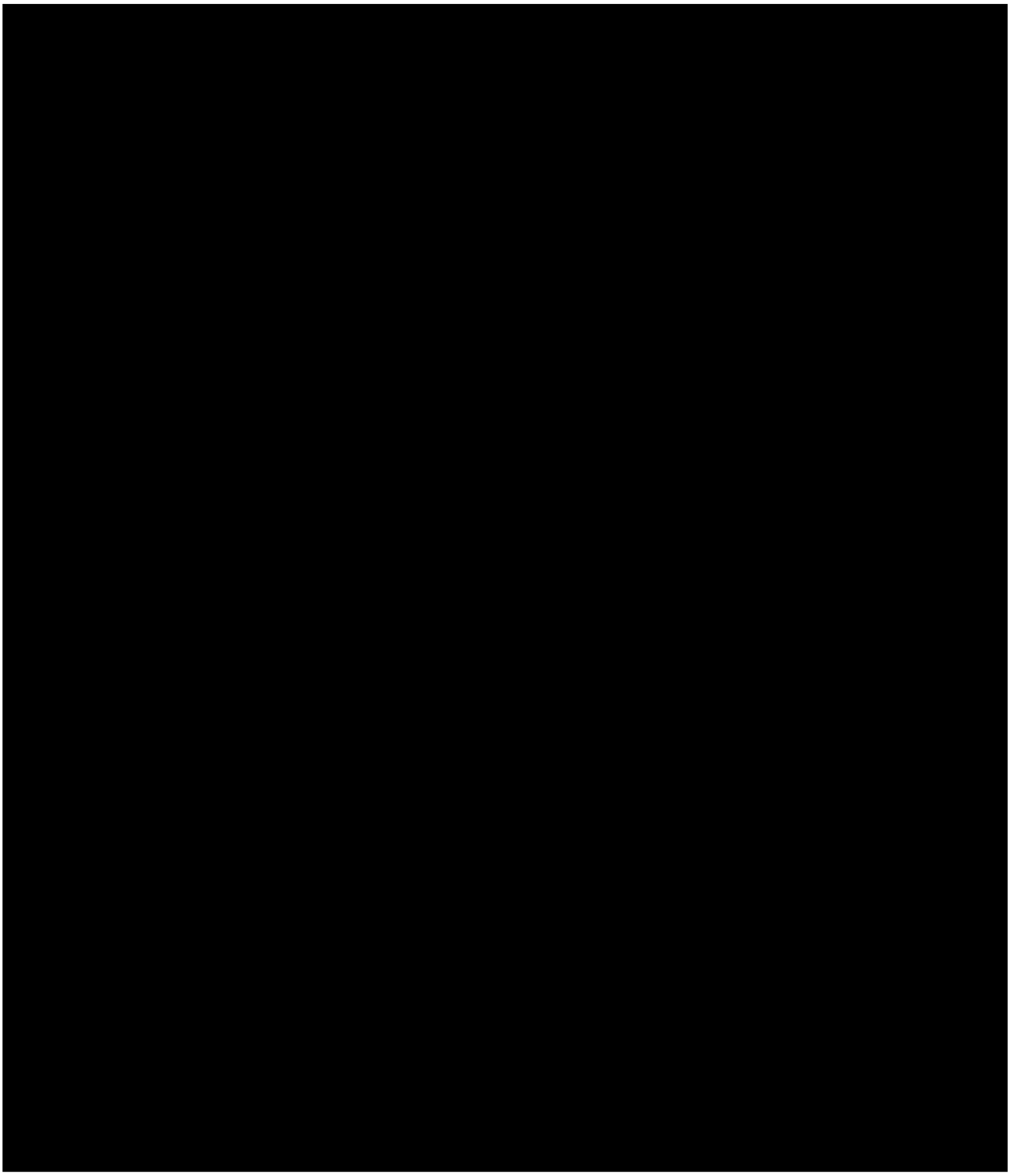
10.11.9 [redacted]

[redacted]

10.11.10 [redacted]

[redacted]

10.11.11 [redacted]



10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

Amended protocol 01 (24 July 2024)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Based on the IDMC review of 21 patients treated (19 treated for 4 weeks), no safety concern has been identified and the IDMC assessed that the benefit-risk balance remains favorable for the study to continue without the need for dose reduction and modification of the existing safety measures. The Sponsor is proposing to add a [redacted] dose group ([redacted] mg/[redacted]) to ACT17754 to further characterize the dose/exposure-response relationship of SAR444656 and guide future development.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the Sponsor address.	To reflect the current Sponsor address.
Section 1.1 Synopsis, Section 4.1 Overall design	Added, additional arm participants to achieve a targeted overall ratio of 1:1:1:1 ([redacted] or [redacted] mg or [redacted] mg of SAR444656 or Placebo). In total approximately 200 participants will be included in the study.	To further characterize the dose/exposure-response relationship of SAR444656 and guide future development. The allocation ratio was adjusted to accommodate for the additional patients included with the added dose group.
	Added the text on additional arm of SAR444656 [redacted] mg [redacted] with food. Updated text as in case of safety concerns, participants in the [redacted] mg dose group will switch to lower dose of [redacted] mg.	IRAK4 degradation is a potential biomarker of therapeutic response and clinical data from the first in human studies was used to choose doses for the Phase 2 study. Based on the preliminary PK/PD analysis conducted using Phase 1 data, dose dependent increase in IRAK4 degradation in PBMCs is expected with [redacted] mg, [redacted] mg, and [redacted] mg doses. In order to characterize sufficiently dose/exposure-response relationship to inform dose selection for future studies, a [redacted] mg dose group is added to this Phase 2 study.
	Replaced “3-arm” with “4 arm” in sentence describing study design.	To reflect the addition of new arm.
Section 1.1 Synopsis	Removed the information on allocation ratio, and number of participants in each individual arm from “number of participants” and added the same paragraph with updated number of participants and allocation ratio to “overall design synopsis”.	To provide protocol clarification and minimize duplication given this is mentioned in the statistical section of the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall design	Removed the sentences on additional number of participants in case of dose reduction.	To reflect the occurrence /absence of dose reduction.
	Added that in the event of a safety signal of concern identified by the IDMC or Sponsor, the study enrollment may be paused or stopped.	To clarify that the study enrollment may be paused or stopped if any safety signals are identified by IDMC or Sponsor.
Section 1.1 Synopsis	Updated the statistical consideration for main secondary endpoints to add “adjusted for randomization stratum (moderate: EASI<22; severe: EASI≥22)”.	To provide protocol clarification.
Section 1.2 Schema	Updated new study schema. Updated text as in case of safety concerns, participants in the [redacted] mg dose group will switch to lower dose of [redacted] mg.	To reflect the new change of the study design.
Section 1.3 Schedule of activities	Removed screening collection timepoint for blood sample for IRAK4 levels and optional plasma sample for protein biomarkers for PD analysis.	Removed screening collection timepoint of blood sample for IRAK4 levels and optional plasma sample for protein biomarkers due to redundancy with baseline sample.
	Updated footnote “e”, to replace “study” with “study intervention period” in sentence describing record of IMP dosing compliance in the diary.	To clarify that participants will record of IMP dosing compliance in the diary during the study “intervention period” only.
	Revised the text to clarify the circumstances where on-site ECG/PK sampling could be substituted by ECG/PK sampling at home/remotely and added text on visits that could be performed remotely/at home.	To clarify that ECG/PK sampling could be substituted by ECG/PK sampling at home/remotely.
	Added the text to clarify the circumstances where on-site vital signs collection could be substituted by vital signs collection at home/remotely.	To clarify that vital signs collection could be substituted by vital signs collection at home/remotely and to specify remote visits.
	Updated footnote “n” to add “In case of results showing anti-HBc positivity, an HBV-DNA testing will be performed and confirmed negative prior to enrollment. In case of results showing HCV Ab positivity, HCV-RNA testing will be performed and should be confirmed negative prior to enrollment.”	To specify that participants with positive HBcAb and negative HBV-DNA testing can be enrolled and keep consistency across all studies for SAR444656. To reflect the PMDA specific requirements for the Japanese participants as study plans to enroll participants from Japan.
	Added Japanese specific requirements on the positive antibody to hepatitis B surface antigen and positive (or detectable) HBV-DNA to footnote “n”.	

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities, Section 5.2 Exclusion criteria and Section 10.2 Appendix 2: Clinical Laboratory tests	Added a cross reference to Japan specific requirements.	To locate the positive antibody to hepatitis B surface antigen and positive (or detectable) HBV-DNA specific requirement in Japan within the document.
Section 1.3 Schedule of activities, Section 3 Objectives, endpoints and estimands, Section 3.1 Appropriateness of measurements	Added the additional tertiary/exploratory endpoints [redacted]	To add the endpoints ([redacted]) commonly reported in other clinical studies.
Section 2.1 Study Rationale	Added text as, "or[redacted] mg [redacted]" for SAR444656 additional dose.	To align with updated study design of the study.
Section 4.3 Justification for dose	Revised the justification for dose to include 3 dose groups of SAR444656.	To specify that an additional dose group is added for further dose exploration to improve dose selection for subsequent trials.
Section 5.2 Exclusion criteria	Exclusion criteria # 24 modified to add the Japan specific requirement on positive antibody to hepatitis B surface antigen and positive (or detectable) HBV-DNA.	To reflect the PMDA specific requirements for the Japanese participants as study plans to enroll participants from Japan.
Section 6.1 Study intervention(s) administered	Added a sub-heading "6.1.1. Investigational medicinal product".	To reflect the current protocol template update.
	Added details of [redacted] mg dose for study intervention, dosage level and study arm.	To reflect the[redacted] mg dose group added to this Phase 2 study.
Section 6.4 Blinding	Text on blinding approach was updated.	To provide clarification on access to unblinded data.
	Added the additional dose, [redacted] mg in Methods of blinding along with other SAR444656 doses.	To reflect the addition of new [redacted] mg arm.
Section 7.1.1 Permanent discontinuation	Revised the permanent discontinuation criteria.	To provide protocol simplification.
Section 8 Study assessments and procedures	Revised the suggested order of assessments to 1. Patient questionnaires; 2. ECG with 10 minutes of rest before ECG; 3. PK and blood sampling; 4. Investigator Assessments; 5. IMP administration.	To provide clarification requested by study sites; the suggested order of assessments was adjusted.
	Added the list of conditions that need to be met for remote visits.	To provide clarification on the conditions for remote visits.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.2 Patient reported outcome measures (PROs)	Added sub-sections 8.2.2.4 [redacted] and 8.2.2.5 [redacted]	To add the details of endpoints [redacted] commonly reported in other clinical studies.
Section 8.3.2 Vital Signs	Added "other" temperature for the temperature parameter in vital signs.	Clarification on temperature parameter.
Section 8.3.3 Electrocardiograms	Removed the sentence "Whenever measurements of ECG, vital signs, physical examination and blood samples for PK or safety coincide, the following order will be respected: physical examination, vital signs, ECG, PK, and then safety samples and other blood samples."	This is duplicative and removed to simplify the protocol. The information is provided in Section 8.
	Removed the sentence "On the days of PK sampling (Visit 2, 3, 4, 6 and 12), triplicate ECG will be done pre-dose and 7 ±1 hours post-dose. At Visit 2 and Visit 4, additional ECG should be performed at 2 hours (±30 minutes) and 4 hours (±30 minutes) post-dose, The ECG should be performed just before the venipuncture of the post-dose PK sampling. For other visits, triplicate ECG will be done pre-dose".	To provide protocol simplification.
	Revised the text to clarify the circumstances where on-site ECG sampling could be substituted by ECG sampling at home/remotely.	To clarify that ECG sampling could be substituted by ECG sampling at home/remotely.
Section 8.3.4 Clinical safety laboratory tests	Removed the sentence "Whenever measurements of vital signs, ECG, and blood samples for PK or safety coincide, the following order will be respected: vital signs, ECG, PK, and then safety samples."	This is duplicative and removed to simplify the protocol. The information is provided in Section 8.
Section 8.4.4 Regulatory reporting requirements for SAEs	Updated cross reference to the section 10.8.2.1 to locate the European Union, safety reporting to the agency.	To locate the safety reporting in European Union.
Section 8.5 Pharmacokinetics	Added a cross reference to China specific requirements.	To locate the PK specific requirement in China within the document.
[redacted]		
Section 8.8 Biomarkers	Added the word "optional" for [redacted] blood samples.	To align with the schedule of activities table.

Section # and Name	Description of Change	Brief Rationale
Section 8.11 Use of biological samples and data for future research	Minor editorial updates.	To reflect the current protocol template update.
Section 9.2 Statistical analyses	Updated the level of credibility intervals.	To reflect presence of multiple dose arms. To adjust level of credibility intervals to a more commonly used value.
Section 9.2.2.2 Main analytical approach	Updated the statistical consideration for primary endpoints to add “adjusted for randomization stratum (EASI<22).”	To provide protocol clarification.
Section 9.3 Interim analyses	Modified the text on interim analyses to be performed related to project planning.	To provide protocol simplification.
Section 9.4 Sample Size Determination	Added details on updated sample size and allocation jointly with the newly achieved half-width of CI.	To justify new sample size.
Section 10.1.4 Data protection	Updated the duration of retention of personal data of professionals and address of Sanofi DPO.	To reflect the current protocol template update and updated address of the Sanofi DPO.
Section 10.2 Appendix 2: clinical laboratory tests	Added “In case of results showing HBsAg negative and anti-HBc positive, hepatitis B virus (HBV)-DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. In case of results showing HCV Ab positive, HCV RNA testing will be performed to rule out a false positive.” to the list of protocol-required laboratory tests	To specify that participants with positive HBcAb and negative HBV-DNA testing can be enrolled and keep consistency across all studies for SAR444656.
Section 10.6 Appendix 6: liver and other safety: suggested actions and follow-up assessments	Updated the section title.	To reflect the current protocol template update.
Section 10.8.2 European Union and Section 10.8.2.1 Safety reporting to the agency	New section added on safety reporting to the agency to include the text on safety reporting in European Union. Safety reporting in European Union to comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014 and reporting of all SUSARs to IMP to the EudraVigilance database within required regulatory timelines.	To reflect the EU CTR updates in a current version of the protocol template.
Section 10.8.3 China	Created a new subsection to add the China specific requirements on PK and biomarkers.	To add the China specific requirements based on local regulations as study plans to enroll participants from China.

Section # and Name	Description of Change	Brief Rationale
Section 10.8.4 France and Section 10.8.4.1. Exclusion criteria specific to France	New section added on exclusion criteria specific to France to include two exclusion criteria.	To reflect the current protocol template update.
Section 10.8.5 Japan	Created a new subsection to add the Japan specific requirements on the positive HBsAb and positive (or detectable) HBV-DNA.	To reflect the PMDA specific requirements for the Japanese participants as study plans to enroll participants from Japan.
Section 10.9 Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency	Removed the European countries and added Germany to the applicable contingency measures for the COVID-19 pandemic.	To reflect the current protocol template update.
Section 10.11 Appendix 11: Additional appendices	Added sub-sections 10.11.10 [redacted] and 10.11.12 [redacted].	To add the questionnaires for endpoints [redacted] commonly reported in other clinical studies.
Throughout the protocol	Minor changes to grammar and punctuation throughout the document.	Minor editorial update for clarity.

Abbreviations: CI = credibility interval; COVID-19 = coronavirus disease; [redacted] DPO = data protections officer; EASI = eczema area and severity index; ECG = electrocardiogram; EU = European Union; EU CTR = European Union clinical trial register; [redacted]; HBsAb = antibody to hepatitis B surface antigen; HBcAb = antibody to hepatitis B core antigen; HBV = hepatitis B virus; HCV Ab = hepatitis C total antibodies; HCV = hepatitis C virus; IDMC = independent data monitoring committee; IMP = investigational medicinal product; IRAK4 = interleukin-1 receptor associated kinase 4; N = number of participants; PBMCs = peripheral blood mononuclear cells; PD = pharmacodynamic; PK = pharmacokinetic; PMDA = Pharmaceuticals and Medical Devices Agency; [redacted] SAEs = serious adverse events; and SUSAR = suspected unexpected serious adverse reaction.

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