AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A Phase 2, International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging study of Efficacy and Safety of SAR441566 in Adults with Moderate to Severe Plaque Psoriasis**
Protocol number:	**DRI17849**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR441566** **Not applicable/Not applicable**
Brief title:	**A study to evaluate efficacy and safety of SAR441566 in adults with plaque psoriasis**
Study name:	**SPECIFI-PSO**
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:	166996
NCT:	NCT06073119
WHO:	U1111-1290-5787
EUDAMED:	Not applicable yet
EU trial number:	2023-503911-14

Date: 25-Apr-2024 Total number of pages: 127

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial protocol 04	All	25-Apr-2024, version 1 (electronic 4.0)
Amended Clinical Trial protocol 03	Czech Republic	04-Dec-2023, version 1 (electronic 3.0)
Amended Clinical Trial protocol 02	EU	22-Nov-2023, version 1 (electronic 2.0)
Amended Clinical Trial protocol 01	Japan	19-Oct-2023, version 1 (electronic 1.0)
Original Protocol	Not applicable	08-Jun-2023, version 1 (electronic 2.0)

Amended protocol 04 (25 April 2024)

This amended protocol (amendment 04) 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

This amendment is implemented to unify at a global level (where possible) local country amendments made at the request of Health Authorities and to add further clarifications to the protocol.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Legal registered address	The legal registered address of Sanofi-Aventis Recherche & Développement has been changed to 82 Avenue Raspail, 94250 Gentilly, France.	From February 1st, 2024, headquarter office location for the Sponsor "Sanofi-Aventis Recherche & Développement" has moved from Chilly-Mazarin to Gentilly, France.
1.1 Synopsis 3 Objectives, Endpoints and Estimands	PASI secondary endpoint clarified as "percent change from baseline" and not "change from baseline" as previously described.	The intended wording was "percent change", the word "percent" was omitted in error.
	sPGA secondary timepoint clarified as Week 12 and not "from baseline to Week 12".	sPGA is not a response/change assessment, therefore analysis only required at Week 12 and not in comparison to baseline.
	sPGA exploratory timepoint clarified at Week 4 and 8 and not "from baseline to Week 4 and 8.	sPGA is not a response/change assessment, therefore analysis only required at Week 4 and 8 and not in comparison to baseline.
1.3 Schedule of activities (SoA) – footnote *a* 7.1 IMP Discontinuation	Clarified the assessments required when patients prematurely discontinue treatment. Further distinguished between patients who	The requirement for patients to undergo all assessments once withdrawn from treatment is deemed not necessary especially with regards to assessments directly linked with

Section # and Name	Description of Change	Brief Rationale
7.1.1 Permanent discontinuation	withdraw from IMP and those who withdraw from the study ie, consent withdrawal.	the administration of IMP such as PK, bloods etc.
3 Objectives, Endpoints and Estimands – Table 2 9.2.2.2 Main analytical approach	The word "prohibited medication" has been replaced by "concomitant medication which could have an impact on the efficacy of the IMP " to include all possible prohibited, permitted, and rescue medications.	Clarification.
5.2 Exclusion Criteria	[redacted]	[redacted]
5.2 Exclusion Criteria 6.9.2 Prohibited concomitant medication	E18: Clarified that the use of 1,25-dihydroxy vitamin D3 and analogues is prohibited only when administered at high doses with the intent to treat psoriasis. Oral intake for the treatment of other indications is not restricted.	Restrictions around the intake of Vitamin D was too broad.
	[redacted]	[redacted]
5.5 Re-testing Laboratory Inclusion/Exclusion criteria	Clarified that only those assessments that did not meet eligibility criteria at the initial assessment, or were performed earlier than 28 days before randomization (outside screening timelines), must be repeated at re-screening. Removed the restriction of laboratory assessments that can be repeated ie, those that are not of explicit exclusionary laboratory testing.	Repeating all screening assessments would be an inconvenience for patients and site staff and there is no clinical justification to support this.
	Removed repeated text that required consultation with the medical monitor.	Repetition.
6.5 Study IMP compliance	Clarified in the first paragraph that “When participants are dosed at the site, the Investigator or the designee will provide IMP to the participant from a new IMP kit, and not from a previous IMP kit”.	Clarification.
	Clarified that participants would be determined compliant if they received 80% or more of their scheduled IMP during the treatment period.	Guidance provided to investigators on compliance estimations in line with Sanofi procedures.
6.9.3 Permitted concomitant therapy	Clarification of the text for better linguistic understanding.	Clarification of the text.
7.1.1 Permanent discontinuation	Provided recommended wash out period for SAR441566 before starting another treatment.	Additional guidance given to investigators in case they want to start another treatment in patients who discontinue SAR441566.
7.1.3 [redacted]	Clarified that the [redacted] will be used for the assessment of [redacted]. This is in line with other sections of the protocol.	Aligning text throughout the protocol.

Section # and Name	Description of Change	Brief Rationale
7.1.4 Temporary discontinuation	Clarified that temporary IMP discontinuations correspond to ≥2 consecutive IMP doses not being administered.	Provide clear guidance to investigators.
8 Study Assessments and Procedures	Corrected previous wording that allowed the use of local laboratory results to determine eligibility as long as these fell within protocol required timelines. Eligibility should be determined based on central laboratory results with specific exceptions for TB and pregnancy testing.	Incorrect process included in error.
[redacted]	[redacted]	[redacted]
8.4.8 Adverse events of special interest	Removed AESI relating to drug abuse with IMP. This was in error copied from the protocol template and not applicable to this study and IMP.	Included in error.
8.8 Biomarkers	This section of the study protocol stated in error that the proteomics blood sample was an optional sample. This was not in line with other sections of the protocol and ICF, which stated that the proteomics sample is mandatory.	Protocol wording inconsistency.
9.3 Interim Analysis	[redacted]	EoS is the last visit for these patients.
10.3.2 Definition of an SAE	Typographical error, for clarification the word “intervention” was added to the following sentence: “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”.	Definition error.
[redacted]	[redacted]	[redacted]
10.13.3 Amended protocol 03 (04 December 2023)	This section has been added to the protocol amendment history.	Keeping track of previous amendments.
Throughout	Minor editorial, typographical error corrections and document formatting revisions.	Minor, therefore, have not been summarized.

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LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC:	area under the curve
AxMP:	auxiliary medicinal product
BCG:	Bacillus-Calmette-Guérin
BID:	bis in die - twice a day
BMI:	body mass index
BSA:	body surface area
BUN:	blood urea nitrogen
CASP8:	caspase-8
CBC:	complete blood count
CIOMS:	Council for International Organizations of Medical Sciences
C_{max}:	maximum plasma concentration
CNIL:	Commission Nationale de l'Informatique et des Libertés
CPK:	creatine phosphokinase
CRP:	C-reactive protein
CSICF:	core study informed consent form
CYP:	cytochrome P450
D1:	first day of IMP intake, baseline, randomization
DDI:	drug-drug interaction
DLQI:	dermatology life quality index
DNA:	deoxyribonucleic acid
DTP:	direct to participant
ECG:	electrocardiogram
eCRF:	electronic case report form
EFPIA:	European Federation of Pharmaceutical Industries and Associations
EoS:	end of study
EoT:	end of treatment
ETIP:	experienced targeted immunotherapy population
EU:	European Union
EUDAMED:	European database for Medical Devices
[redacted]	
FDA:	Food and Drug Administration
FSH:	follicle stimulating hormone
GCP:	Good clinical practice
GDPR:	general data protection regulation
HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV:	hepatitis B virus

hCG:	human chorionic gonadotropin
HCV:	hepatitis C virus
HDL:	high-density lipoprotein
HIV:	human immunodeficiency virus
hsCRP:	high-sensitivity C-reactive protein
IB:	investigator's brochure
ICF:	informed consent form
ICH:	International council for harmonization of technical requirements for pharmaceuticals for human use
IDMC:	Independent data monitoring committee
IEC:	Independent Ethics Committee
IgM:	immunoglobulin
IGRA:	interferon gamma release assay
IL:	interleukin
IM:	intramuscular
IMP:	investigational medicinal product
IND:	investigational new drug
IRB:	institutional review board
ITT:	intent-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IWRS:	interactive web response system
LDL:	low-density lipoprotein
LTBI:	latent tuberculosis infection
MAD:	multiple ascending dose
MCH:	mean corpuscular hemoglobin
MCP-mod:	multiple comparison procedures modelling
MCV:	mean corpuscular volume
mTNFα:	membrane bound tumor necrosis factor alpha
MTX:	methotrexate
[redacted]	
NCT:	national center for tumor
NEMO:	nuclear factor kappa B essential modulator
NF-κB:	nuclear factor kappa B
NMPA:	National Medical Products Administration
NRS:	numeric rating scale
NTIP:	naïve targeted immunotherapy population
PASI:	psoriasis area and severity index
PCR:	polymerase chain reaction
PCSA:	potentially clinically significant abnormalities
PD:	pharmacodynamics
[redacted]	
P-gp:	P-glycoprotein
PK:	pharmacokinetic
PMDA:	Pharmaceuticals and Medical Devices Agency

POM:	proof of mechanism
[redacted]	
PRO:	patient reported outcome
[redacted]	
QD:	quaque die - once a day
QTLs:	quality tolerance limits
RBC:	red blood cell
RIPK-1:	receptor-interacting protein kinase 1
RNA:	ribonucleic acid
SAD:	single ascending dose
SAE:	serious adverse event
SAP:	statistical analysis plan
sPGA:	static psoriasis global assessment
sTNFα:	soluble tumor necrosis factor alpha
SUSAR:	suspected unexpected serious adverse reaction
t1/2z:	terminal elimination half-life
TB:	tuberculosis
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor
TNFR1:	tumor necrosis factor receptor 1
TNFR2:	tumor necrosis factor receptor 2
TNFα:	tumor necrosis factor alpha
Tregs:	regulatory T-cells
ULN:	upper limit of normal
WBC:	white blood cell
WHO:	World health organisation
W*number*:	week followed by the week number from baseline
WOCBP:	woman of child-bearing potential
WONCBP:	woman of non-child-bearing potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2, International, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging study of Efficacy and Safety of SAR441566 in Adults with Moderate to Severe Plaque Psoriasis

Brief title:

A study to evaluate efficacy and safety of SAR441566 in adults with plaque psoriasis

Regulatory agency identifier number(s):

IND:	166996
NCT:	NCT06073119
WHO:	U1111-1290-5787
EUDAMED:	Not applicable yet
EU trial number:	2023-503911-14

Rationale:

Tumor necrosis factor alpha (TNFα) is a cytokine with pleiotropic effects on both pathologic and homeostatic processes. In psoriasis, TNFα plays a key role in driving inflammation. Consequently, the inhibition of TNFα signaling is a frequently used therapy option in the management of psoriasis.

SAR441566 is a small molecule inhibitor of tumor necrosis factor receptor 1 (TNFR1) signaling, by changing the configuration of the soluble TNF alpha (sTNFα) trimer and preventing its interaction with TNFR1. SAR441566 binds to the center of sTNFα resulting in an allosteric stabilization of a naturally occurring asymmetric form of the sTNFα, which would otherwise be transient (1, 2). Using analytical size exclusion, O'Connell et al. (1) demonstrated that this asymmetric trimer has an impaired capacity to engage with TNFR1. The authors further demonstrated that stabilizing the asymmetric sTNFα trimer, impairs TNFR1 signaling *in vitro*. In contrast to biologic TNF inhibitors, this small molecule appears to preserve signaling through TNFR2. TNFR2 signaling contributes to Treg expansion and function; and is crucial for host defense against a variety of pathogens. Thus, maintenance of TNFR2 function can potentially result in lower infection risks and enhanced immune homeostasis by preserving Treg cells' functionality.

The doses to be tested in this study were selected according to the assessments of preliminary safety, pharmacokinetic and pharmacodynamics of SAR441566 in former single ascending dose (SAD, TDU16919) and multiple ascending dose (MAD, TDR16920) studies, and proof of mechanism phase 1 study (PDY16918) in mild to moderate Psoriasis participants. In these first-in-human studies, SAR441566 demonstrated favorable safety, pharmacokinetic and pharmacodynamic characteristics, which supports the advancement of SAR441566 into clinical

studies in participants with moderate to severe psoriasis. The aim of this Phase 2 trial is to evaluate the efficacy, suitable dose, and safety of SAR441566 in treating plaque psoriasis.

Two populations of participants are eligible for this study:

1. Naïve targeted Immunotherapy population (NTIP): Participants naïve to biologics and small molecules to treat psoriasis. This population is the primary population for efficacy analysis, to demonstrate the superiority of SAR441566 compared to placebo in the NTIP.
2. Experienced targeted Immunotherapy population (ETIP): Participants who previously received targeted immunotherapy for psoriasis. The ETIP is for exploratory purposes only, to assess efficacy of SAR441566 compared to placebo in the ETIP.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To demonstrate the superiority of SAR441566 over placebo in participants with moderate to severe plaque psoriasis, in the NTIP.	• Proportion of participants with a 75% or greater PASI score (Psoriasis Area and Severity Index score) improvement (reduction) from baseline (PASI75) at Week 12.
Secondary	
• To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo in the NTIP.	• PASI percent change from baseline to Week 12. • Proportion of participants with static Psoriasis Global Assessment (sPGA) score 0 (complete clearance) or 1 (minimal disease) at Week 12.
• To evaluate the safety of SAR441566.	• Incidence of TEAE, SAEs, and AEs of AESIs. • Incidence of study IMP permanent discontinuations and study withdrawals due to TEAEs. • Participants with medically significant changes in vital signs, ECG, and/or laboratory evaluations.
• To assess pharmacokinetics of SAR441566 in participants with moderate to severe plaque psoriasis.	• Plasma pre-dose and post-dose concentrations of SAR441566.

For China, see Section 10.7.1 details.

Overall design synopsis:

Phase 2, international, multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study of efficacy and safety of SAR441566 in adult participants with moderate to severe plaque psoriasis.

Summary:

This is a parallel group, Phase 2, randomized, double-blind, placebo controlled, dose-ranging, international, multicenter, 12-week study. It is designed to assess the therapeutic dose, efficacy, and safety of treatment with SAR441566 in male and female adults with moderate to severe plaque psoriasis.

Study details include:

- Screening period (4 weeks and not less than 11 days before Day 1).
- Treatment period (12 weeks ±3 days).
- Post-treatment period (safety follow-up) (4 weeks ±3 days).
- The total number of study visits will be 7.

Participants who satisfy the inclusion and exclusion criteria will be randomized to either SAR441566 or matching placebo, administered orally for 12 weeks.

Visits during the 12-week treatment period will occur at Week 0 (baseline/randomization), 2, 4, 8, and 12 weeks. Followed by a 4-week post-treatment period.

Number of participants:

Approximately 207 adult participants who meet the inclusion/exclusion criteria will be randomized to either SAR441566 or matching placebo in two different strata, ie, NTIP and ETIP.

- NTIP: Approximately 144 participants will be randomized to either SAR441566 or matching placebo (120 in the five SAR441566 groups and 24 in the placebo group) in this stratum. This population is the primary population for efficacy analysis.
- ETIP: Approximately 63 participants will be randomized to either SAR441566 or matching placebo (54 in the three SAR441566 groups and 9 in the placebo group) in this stratum. This population is for exploratory purposes only.

Study arms and duration:

In the NTIP, there are 6 arms in this stratum with parallel groups of 200 mg BID (n=24), 100 mg BID (n=24), 200 mg QD (n=24), 100 mg QD (n=24), 50 mg QD (n=24), or placebo (n=24), at a randomization ratio of 1:1:1:1:1:1. Duration of IMP treatment is 12 weeks. (See Figure 1 for schema).

In the ETIP, there are 4 arms in this stratum with parallel groups of 200 mg BID (n=18), 200 mg QD (n=18), 100 mg QD (n=18) or placebo (n=9), at a randomization ratio of 2:2:2:1. Duration of IMP treatment is 12 weeks. (See Figure 1 for schema).

Study interventions

Investigational medicinal product (IMP)

SAR441566

- Formulation: Tablets, [redacted].
- Route of administration: oral.

Matching placebo

- Formulation: Tablets (indistinguishable from SAR441566 tablets and contain the same inactive ingredients as [redacted], but do not contain SAR441566).
- Route of administration: oral.

SAR441566 and Placebo dose regimen:

[redacted]

SAR441566 or placebo can be given with or without food.

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

Study duration

- Screening period (up to 4 weeks and no less than 11 days).
- Treatment period (12 weeks ±3 days).
- Post-treatment period (safety follow-up) (4 weeks ±3 days).

Statistical considerations:

- **Primary endpoint:**
  - The proportion of participants with PASI75 response at Week 12 in the NTIP.

The primary endpoint analysis will be the comparison between SAR441566 treatment groups and placebo in the proportion of participants with PASI75 response at Week 12, using a Cochran-Mantel-Haenszel test, in the NTIP. To control the overall Type I error of 0.05, multiplicity adjustment will be made among SAR441566 three doses (200 mg BID, 100 mg BID, 200 mg QD) comparing to placebo.

- **Main secondary endpoints:**
  - Percent change from baseline in PASI score at Week 12 in the NTIP.
  - Proportion of participants with sPGA score of 0 or 1 at Week 12 in the NTIP.

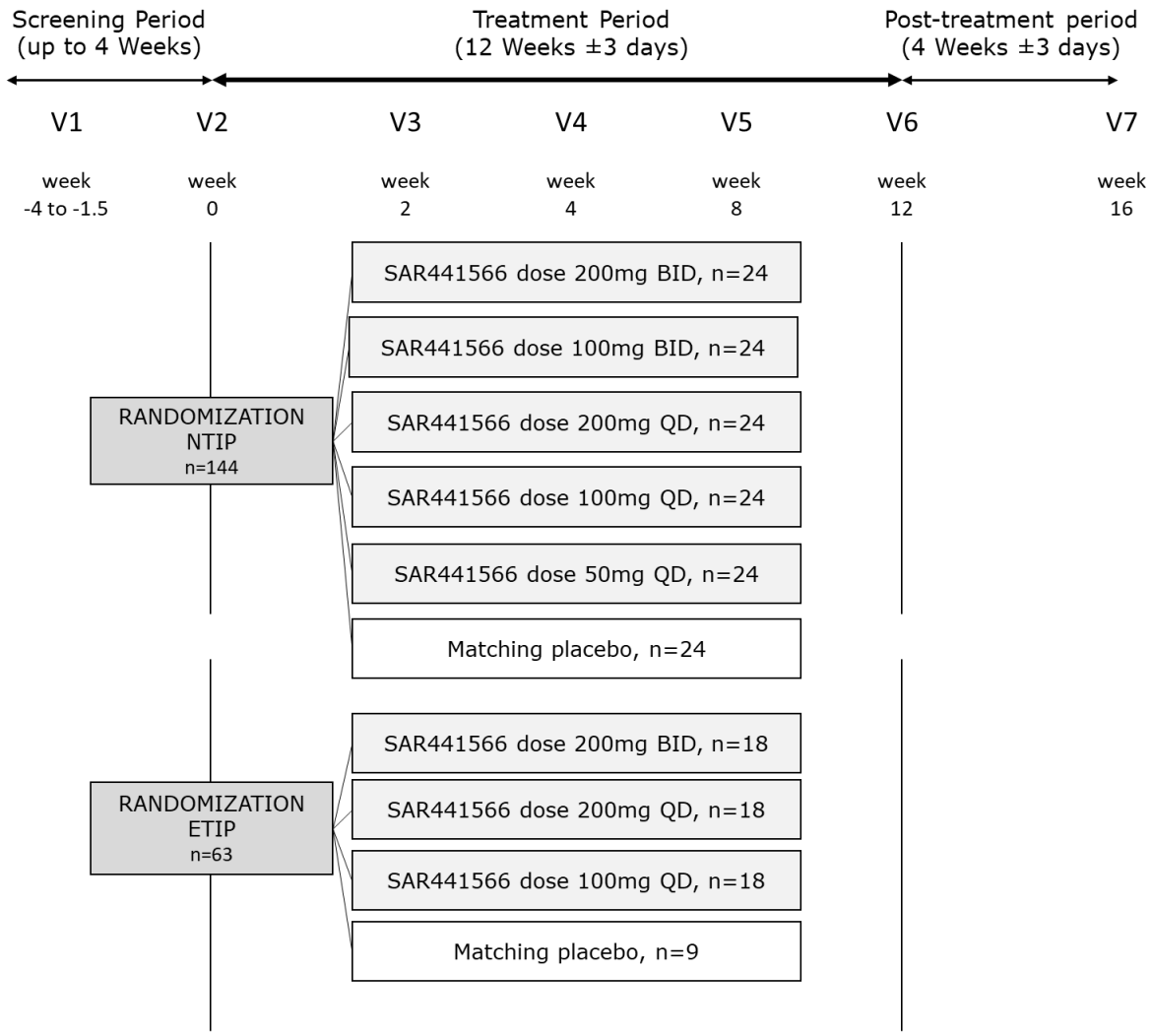
Categorical secondary endpoint will be analyzed using a Cochran-Mantel-Haenszel test in NTIP. Continuous secondary endpoint will be analyzed by fitting an Analysis of Covariance model with the baseline covariates in NTIP. No multiplicity adjustment for the secondary efficacy endpoints will be made.

Data Monitoring committee: Yes

An Independent Data Monitoring Committee (IDMC) has been appointed for this study. The IDMC is a group of independent scientists and physicians who are appointed to monitor the safety throughout the study and the scientific integrity of the study IMP. During the double-blind treatment period, the unblinded safety data will be reviewed by the IDMC. The IDMC will provide recommendations to the Sponsor regarding the study conduct to ensure the protection and the safety of the participants. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the study. The IDMC specific roles and interaction with the Sponsor will be described in the IDMC charter.

1.2 SCHEMA

Figure 1 - Graphical study design.



1.3 SCHEDULE OF ACTIVITIES (SoA)

Procedure[a]	Screening period (up to 4 weeks and not less than 11 days before Day 1)[b]	Treatment period (12 weeks)[c]					Post-treatment period (4 weeks after last dose IMP)
		Baseline/ randomization				End of Treatment (EoT)	End of Study (EoS)
VISIT	1	2	3	4	5	6	7
DAY	-28 to -11	1	15(±3)	29(±3)	57(±3)	85(±3)	113(±3)
WEEK	-4 to -1.5	0	2	4	8	12	16
Participant Eligibility							
Informed consent	X						
Inclusion and exclusion criteria	X	X[d]					
Demographics	X						
Height and weight measurements	X						
Complete physical examination[e]	X						
Medical history[f]	X						
Psoriasis history[g]	X						
Current medical conditions	X						
Highly sensitive pregnancy test (urine or serum) as per local regulations (WOCBP only)	X						
FSH (only when applicable to confirm post-menopausal status)	X						
Tuberculosis assessment and QuantiFERON®[h]	X						
HIV, Hepatitis B and C screening[i]	X						
Vital Signs[j]	X	X	X	X	X	X	X

Procedure[a]	Screening period (up to 4 weeks and not less than 11 days before Day 1)[b]	Treatment period (12 weeks)[c]					Post-treatment period (4 weeks after last dose IMP)
		Baseline/ randomization				End of Treatment (EoT)	End of Study (EoS)
VISIT	1	2	3	4	5	6	7
DAY	-28 to -11	1	15(±3)	29(±3)	57(±3)	85(±3)	113(±3)
WEEK	-4 to -1.5	0	2	4	8	12	16
Treatment[k]							
Targeted physical examination[e]		X	X	X	X	X	
Randomization		X					
Contact Interactive Web Response Systems (IWRS)	X	X	X	X	X	X	X
IMP intake[c]		X	X	X	X	X	
IMP dispensed for home administration[l]		X	X	X	X		
IMP compliance check[m]			X	X	X	X	
Medication Intake Questionnaire (paper)[n]		←==========				==========→	
Clinical Assessments[o]							
Psoriasis Area and Severity Index (PASI)	X	X		X	X	X	
static Psoriasis Global Assessment (sPGA)	X	X		X	X	X	
[redacted]							
Body Surface Area (BSA) assessment[p]	X	X		X	X	X	
[redacted]							
Patient Reported Outcome Measures (Questionnaires)[q]							
DLQI questionnaire		X				X	
[redacted]							

Procedure[a]	Screening period (up to 4 weeks and not less than 11 days before Day 1)[b]	Treatment period (12 weeks)[c]					Post-treatment period (4 weeks after last dose IMP)
		Baseline/ randomization				End of Treatment (EoT)	End of Study (EoS)
VISIT	1	2	3	4	5	6	7
DAY	-28 to -11	1	15(±3)	29(±3)	57(±3)	85(±3)	113(±3)
WEEK	-4 to -1.5	0	2	4	8	12	16
[redacted]							
Screening & Diagnostic tests							
Urine pregnancy test (WOCBP only)[t]		X		X	X	X	X
12-lead Triplicate ECG[u]	X	X	X	X	X	X	X
Laboratory tests (include hematology- CBC with differential and liver chemistries- complete metabolic panel)[v]	X	X	X	X	X	X	X
Fasting lipids panel[w]		X		X		X	
Pharmacodynamics [redacted]							
[redacted]							

Procedure[a]	Screening period (up to 4 weeks and not less than 11 days before Day 1)[b]	Treatment period (12 weeks)[c]					Post-treatment period (4 weeks after last dose IMP)
		Baseline/ randomization				End of Treatment (EoT)	End of Study (EoS)
VISIT	1	2	3	4	5	6	7
DAY	-28 to -11	1	15(±3)	29(±3)	57(±3)	85(±3)	113(±3)
WEEK	-4 to -1.5	0	2	4	8	12	16
Pharmacokinetic (PK) Assessments							
SAR441566 PK		X[y]	X[z]	X[aa]	X[z]	X[aa]	
Safety							
AE, SAE, TEAE and AESI review	←==========→						
Concomitant medication review	←==========→						

a Participants who discontinue IMP treatment prior to completing the 12-week treatment period should be assessed as per the EoT visit at the earliest opportunity and no later than 7 days from the last dose of IMP. After the EoT visit: (a) Participants who accept to stay on study without IMP intake: all remaining visits described in the SoA should be performed until the EoS, but only clinical assessments, AE and concomitant medication review and patient reported outcomes should be carried out at the study visits. (b) Participants who withdraw consent from the study: should have an EoS visit 4 weeks after their last dose of IMP.

b The screening period may be extended to 6 weeks (+/- 3 days) if participants are awaiting consultation with a specialist to rule out or treat active TB infection, or approval from Sponsor, according to *E 30*.

c The morning IMP at visit days should be taken on site.

d Prior to randomization.

e The complete physical examination will consist of evaluation of the following systems: general, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, and musculoskeletal. The targeted physical exam will consist of evaluation of the following systems: general, eyes, throat, cardiovascular, lungs, abdominal, extremities, and skin, musculoskeletal. Complete and targeted physical examinations may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant, or a Nurse Practitioner. A targeted physical examination may note any changes in the participant's condition since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

f Including but not limited to personal or family history of long QT syndrome, vaccination history, alcohol, nicotine, and current and past 2 years history of drug usage.

g Include date of psoriasis's symptoms onset, date of psoriasis diagnosis, history of prior therapies used to treat psoriasis (medication generic name, doses, clinical efficacy response [responder or no-responder], reason for discontinuation [side effects, lack of clinical efficacy, medication interaction with other concomitant therapy, remission/lack of symptoms, and other], and length of the therapy), current treatments, and history of psoriasis in the family.

h For TB assessment refer to exclusion criteria *E 30*.

i HIV, Hepatitis B and C screening: HIV-1 and HIV-2 antibodies, Hepatitis B surface antigen (HBsAg), IgM Hepatitis B core antibody (HBcAb), total HBcAb, total Hepatitis C antibodies (HCVAb). In case of results showing HBcAb positivity, HBV-DNA testing must be performed and confirmed negative prior to randomization. In case of HCVAb positivity, HCV-RNA testing must be performed and confirmed negative before randomization. For Japan, HBsAb needs to be tested in addition to HBsAg and (IgM or total) HBcAb - see Section 10.7.3.

j Vital signs include body temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mm Hg).

k When several assessments take place at the same visit, the following order is recommended: Patient Reported Outcome Measures (Questionnaires), Triplicate ECG (after 10min of rest), Blood sampling, Urine test (when applicable), IMP administration, Vital signs, Physical examination, Clinical assessments, IMP compliance check, verification of the Medication Intake Questionnaire (paper), Prior and concomitant medications, AE reporting, IMP dispensed for home administration. And during Post-IMP PK blood sampling visits, conclude with Triplicate ECG (after 10min of rest and within 15min prior to PK blood sampling), followed by PK blood sampling.

l Dispensed with Medication Intake Questionnaire (paper).

m Compliance will be assessed by the investigator by direct questioning, verifying the Medication Intake Questionnaire (paper), and counting returned tablets in each pack during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen must be recorded.

n Questionnaire provided to the trial participant on D1 and at each visit, then returned by the participant at each visit and checked by the investigator to verify the IMP intake and potential adverse events.

o Clinical assessments should be completed by the same physician for a given participant, if possible, to secure longitudinal comparison and avoid any bias.

p BSA will be extracted from PASI assessment (Section 8.2.3).

[redacted]

s Refer to Section 5.3.2 for further details.

t Refer to Section 8.3.6 – Pregnancy testing for instruction on timepoints.

[redacted]

v Hematology: RBC, RBC indices, hemoglobin, hematocrit, thrombocyte count (platelets), leukocyte count (white blood cell count) with differential in absolute counts (including neutrophils, eosinophils, basophils, lymphocytes (including CD4 count), monocytes).
Clinical chemistry: Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, creatinine clearance, CPK, calcium, phosphate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin, glucose (non-fasting).

w Fasting total cholesterol, fasting triglycerides, HDL, and LDL. Participant must be fasting for 8 hours prior to laboratory testing (may consume water). A light meal will be provided by the site after the laboratory tests, lipids panel and pre-dose-PK.

[redacted]

2 INTRODUCTION

SAR441566 is a small molecule that binds to a pocket in the center of the soluble TNFα trimer, resulting in allosteric stabilization of a naturally occurring asymmetric form of sTNFα that is naturally a transient intermediate. This asymmetric trimer has an impaired capacity to engage TNFR1 and therefore TNFR1 signaling is impaired. In contrast to biologic TNF inhibitors, this small molecule appears to preserve signaling through TNFR2, which might decrease infectious risks associated with biologic TNF inhibitors. In psoriasis, TNFα plays a key role in driving inflammation. Consequently, TNFα inhibitors, are currently a frequently used therapy option in the management of psoriasis.

2.1 STUDY RATIONALE

The aim of this Phase 2 trial is to evaluate the safety and efficacy of SAR441566 in treating moderate to severe plaque psoriasis. The doses to be tested in this study are selected according to the assessments of preliminary safety, pharmacokinetic (PK), and pharmacodynamics (PD) of SAR441566 in previous single ascending dose (SAD, TDU16919) and multiple ascending dose (MAD, TDR16920) studies. In the proof-of-mechanism study (PDY16918), repeated administration of 200 mg BID SAR441566 over 28 days was safe and well-tolerated by participants with mild to moderate psoriasis. In first-in-human studies, SAR441566 demonstrated favorable safety and PK characteristics which supports the advancement of SAR441566 into clinical studies in participants with moderate to severe plaque psoriasis. Furthermore, psoriasis remains a chronic disease requiring novel therapeutic options that are efficacious, reliable, safe, and that can be administered orally.

2.2 BACKGROUND

TNFα is a cytokine with pleiotropic effects on both pathologic and homeostatic processes. TNFα plays a key pathophysiological role in psoriasis (3). Consequently, biological TNFα inhibitors are often successfully used and approved to treat psoriasis.

TNFα is a member of the TNF superfamily of cytokines. It is produced by a variety of cell types, most notably, T cells. It is initially expressed as a transmembrane protein, also known as membrane bound TNFα (mTNFα). At the cell surface, mTNFα may undergo cleavage by a TNFα-converting enzyme to generate sTNFα. Structurally, both mTNFα and sTNFα exist as homotrimers which can bind 3 cognate receptors. This trimeric engagement is critical for receptor multimerization and subsequent signal transduction. sTNFα mainly signals via TNFR1, which is expressed on most cell types. In contrast, mTNFα mainly uses TNFR2 for signaling. TNFR2 is expressed primarily on neurons, endothelial cells, and immune cells, with enrichment on certain subpopulations of regulatory T-cells (Tregs).

Functionally, sTNFα and mTNFα play different roles in pathologic and homeostatic processes. sTNFα engagement of TNFR1 leads to activation of pro-inflammatory and pro-apoptotic pathways that play pivotal roles in the effect of TNFα in certain autoimmune conditions. In

contrast, mTNFα signaling contributes to a variety of homeostatic functions, including tissue regeneration and cell survival. From an inflammatory standpoint, mTNFα has been shown to enhance function and proliferation of specific subsets of suppressive Tregs. TNFR2 agonism has also been shown to promote death of autoreactive CD8+ T-cells. Of note, mTNFα mice, which express only a non-cleavable form of TNFα, have been generated to study the specific effects of mTNFα. In respiratory tuberculosis infection models, multiple studies have demonstrated reduced mortality and bacterial burden in mTNFα mice compared with TNFα knockout mice. Similar results have been demonstrated in Listeria monocytogenes, Mycobacterium bovis bacilli Calmette-Guérin, and Leishmania major murine infection models (4, 5).

SAR441566 is a small molecule that binds to a pocket in the center of the sTNFα trimer. This results in allosteric stabilization of a naturally occurring, asymmetric form of sTNFα that is normally a transient intermediate. Using analytical size exclusion, O'Connell et al. (2019) (1) demonstrated that this asymmetric trimer has an impaired capacity to engage TNFR1. They further demonstrated that UCB-9260, a related molecule to SAR441566, impairs TNFR1 signaling *in vitro*. Jurkat cells were treated with sTNFα, sTNFα pre-incubated with UCB-9260, or sTNFα preincubated with etanercept. TNFR1 signaling, as measured by Western Blot analysis of kinases receptor-interacting protein kinase 1 (RIPK-1) ubiquitination and nuclear factor kappa B (NF-κB) phosphorylation, was impaired in both the etanercept- and UCB-9260-treated samples as compared with the samples treated with sTNFα alone. Nonclinical studies have demonstrated that targeting of sTNFα with SAR441566 is effective in reducing disease severity in murine model of inflammatory arthritis (2).

Psoriasis is a T cell-mediated disease with autoimmune properties modulated by genetic susceptibility and environmental triggers. Inflammatory pathways characterized by excessive production of the cytokines Interleukin (IL)-12 and IL-23 promote the differentiation of pathogenic T cell responses, resulting in TNF and IL-17 production. These cytokines are an integral part of the TNF/IL-23/IL-17 axis involved in maintaining inflammation in psoriatic skin (6).

In summary, it has been shown that TNFR1 and TNFR2 signaling have differential impacts on the immune system. TNFR1 contributes to acute inflammation, whereas TNFR2 plays roles in homeostasis, Treg expansion and function, and host defense against a variety of pathogens. Nonclinical studies have demonstrated that specific targeting of TNFR1 is effective in reducing disease severity in a murine model of inflammatory arthritis. The evidence supports the advancement of SAR441566, an inhibitor of TNFR1 signaling, into clinical studies for further treatment of psoriasis and SAR441566 is expected to reduce the side effects compared with the other TNF inhibitors.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SAR441566 may be found in the Investigator's brochure (IB).

2.3.1 Risk assessment

[redacted]. In completed Phase 1 clinical studies (up to 600 mg single dose or 300 mg BID), there were four AESI of ALT elevation observed in the MAD study (Grade 1 in 3 participants at the dose level 100 mg QD and Grade 2 in one participant at the highest dose, 300 mg BID) and no AESI regarding QTc prolongation. However, [redacted]

In the clinical study with [redacted] is used as concomitant medication. Importantly in additional completed Phase 1 studies, INT17671 exploring DDI with a [redacted], there were no safety concerns reported throughout the studies. [redacted]The PDY16918 study (200 mg BID for 28 days) in mild to moderate psoriasis is completed and there were no safety concerns.

Based on the class effect of anti-TNF biologics, the following potential risks are considered: increased risk of serious infections leading to hospitalization and death, increased risk of serious infections including reactivation of tuberculosis (TB), bacterial sepsis, invasive fungal infections, malignancies, hepatitis B virus reactivation, demyelinating disease (exacerbation, or new onset), cytopenia, pancytopenia, heart failure (worsening or new onset), and lupus-like syndrome.

2.3.2 Benefit assessment

The administration of SAR441566 is expected to prevent sTNF from activating TNFR1, which is assumed to be a key pathway of inflammation in plaque psoriasis. Accordingly, SAR441566 could provide to participants a reduction (improvement) of signs and symptoms of plaque psoriasis similar to current biological TNF inhibitors without any development of Anti-drug antibodies. In the proof-of-mechanism study (PDY16918), repeated administration of 200 mg BID SAR441566 over 28 days was safe and well-tolerated by participants with mild to moderate psoriasis. Furthermore, participants may benefit from having regular clinical and laboratory evaluations throughout the study.

2.3.3 Overall benefit/risk conclusion

SAR441566 is a small molecule inhibitor of TNFR1 signaling. It has been shown that TNFR1 and TNFR2 have differential impacts on the immune system. TNFR1 contributes to acute inflammation, whereas TNFR2 plays roles in homeostasis, Treg expansion and function, and host

defense against a variety of pathogens. Nonclinical studies have demonstrated that specific targeting of sTNFα, and therefore inhibition of TNFR1 is effective in reducing disease severity in a murine model of inflammatory arthritis (2). In addition, sTNFα occupancy levels as PD markers were in the range of 100% at all dose levels in MAD studies.

SAR441566 was generally well tolerated with a good safety profile in clinical studies performed to date. Based on the clinical First-in-human TDU16919-SAD, TDR16920 -MAD and INT17025 [redacted], INT17671 [redacted] and BDR17662, in healthy participants and proof of mechanism phase 1 study (PDY16918) in participants with mild to moderate psoriasis, there are no identified safety concerns to date.

To date, there are no identified risks for SAR441566, and appropriate risk mitigation strategies are in place for well-defined potential risks associated with SAR441566. These risk mitigation strategies include close monitoring of participants and monitoring for the emergence of any undesirable clinical signs or biologic effects. The available nonclinical and clinical data support further clinical development of SAR441566.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the superiority of SAR441566 over placebo in participants with moderate to severe plaque psoriasis, in the NTIP.	• Proportion of participants with a 75% or greater PASI score (Psoriasis Area and Severity Index score) improvement (reduction) from baseline (PASI75) at Week 12.
Secondary	
• To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo in the NTIP.	• PASI percent change from baseline to Week 12. • Proportion of participants with static Psoriasis Global Assessment (sPGA) score 0 (complete clearance) or 1 (minimal disease) at Week 12.
• To evaluate the safety of SAR441566.	• Incidence of TEAE, SAEs, and AEs of AESIs. • Incidence of study IMP permanent discontinuations and study withdrawals due to TEAEs. • Participants with medically significant changes in vital signs, ECG, and/or laboratory evaluations.
• To assess pharmacokinetics of SAR441566 in participants with moderate to severe plaque psoriasis.	• Plasma pre-dose and post-dose concentrations of SAR441566.
Exploratory/Tertiary	
• To evaluate the efficacy of SAR441566 in plaque psoriasis as compared to placebo change over time.	• PASI change from baseline to Week 4 and 8. • [redacted] • The proportion of participants with a 90% or greater PASI reduction from baseline (PASI90) at Week 4, 8 and 12. • [redacted] • The proportion of participants with PASI75 at Week 4, and 8. • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • Proportion of participants with sPGA score of clear or almost clear (0 or 1) at Week 4, and 8. • [redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• To characterize the pharmacodynamic profile of SAR441566 in participants with plaque psoriasis.	• Change in peripheral blood soluble biomarkers (including but not limited to hsCRP, IL-17A, IL-17F, IL-22, IL-19) from baseline to Week 4 and 12.
[redacted]	[redacted]
[redacted]	[redacted]
• To evaluate the impact of SAR441566 on health-related quality of life.	• Change in Dermatology Life Quality Index (DLQI) from baseline to Week 12.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

For China, see Section 10.7.1 for details.

Primary estimands defined for primary endpoint are summarized in Table 2 below. More details are provided in Section 9.2.

For all these estimands, the comparison of interest will be the comparison of SAR441566 vs. placebo.

Table 2 - Summary of primary estimands for main endpoints

Endpoint	Estimands			
Category (estimand)	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate the superiority of SAR441566 over placebo in NTIP with moderate to severe plaque psoriasis.				
Primary endpoint (treatment policy/ composite estimand).	Proportion of participants with PASI75 response at Week 12.	NTIP	Initiation of selected concomitant medication which could have an impact on the efficacy of the IMP: It will be handled with the composite strategy, ie, participants will be considered as non-responders after such event.	Difference in the percentage of participants achieving PASI75 response at Week 12 between each active arm and placebo, using the Cochran-Mantel-Haenszel test.
			Discontinuation of IMP: It will be handled with the treatment policy strategy. The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.	Missing data will be imputed to non-responders when the response to PASI75 is missing.

3.1 APPROPRIATENESS OF MEASUREMENTS

3.1.1 Measurements of disease severity and extension by the clinician

PASI, sPGA and BSA have been the corner stone of drug evaluation and approval by health authorities in Psoriasis over the last ten years.

3.1.1.1 Psoriasis Area and Severity Index (PASI)

PASI represents a composite score of a variety of physical signs of psoriasis and their extension. PASI is currently the most often cited instrument of this type. It is recommended by the Guideline on Clinical Investigation of Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02). PASI is calculated using a formula for rating the skin surface area involved with psoriasis and the degree of erythema, desquamation, and induration of the psoriatic plaques. PASI was developed more than 40 years ago, and it has been largely used and validated to measure the severity and progression of plaque psoriasis (7).

3.1.1.2 static Psoriasis Global Assessment (sPGA)

sPGA of psoriasis severity is used as a global static assessment of all lesions on 6- or 7-point scale (from severe to none); it gives a general impression of severity or improvement of psoriasis on treatment. It is part of the instruments recommended in the Guideline on Clinical Investigation of Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02).

3.1.1.3 Body Surface Area (BSA)

BSA is the most common measurement of efficacy used in clinical trials to support the approval of psoriasis drugs. The strengths of this metric are its ease of use, familiarity for physician and patient, and the low variability of test-retest statistics by the same observer.

[redacted]

3.1.2 Appropriateness of patient reported outcome measures

[redacted]

[redacted]

3.1.2.5 Dermatology Life Quality Index (DLQI)

The impact of the disease on patient's quality of life will be assessed with the DLQI, which is a validated and widely used PRO in patients with dermatologic diseases. The instrument has good evidence of content validity and psychometric properties supporting its reliability, construct validity and responsiveness (11, 12). It has been widely recommended for inclusion as an endpoint in all psoriasis clinical trials in which Health-Related Quality of Life of patients is a relevant outcome. The DLQI data generated from this phase II study provides the opportunity to further validate the PSSD.

[redacted]

4 STUDY DESIGN

4.1 OVERALL DESIGN

The DRI17849 study is a phase 2, international, multicenter, randomized, double-blind, placebo-controlled, 6-arm dose-ranging study of efficacy and safety of SAR441566 in adult participants with moderate to severe plaque psoriasis.

The objectives are to demonstrate that SAR441566, a small molecule specific inhibitor of TNFR1 signaling, is effective and safe in the treatment of plaque psoriasis, and to define the best dose/dosage regimen for further development.

Two populations of participants are eligible for this study:

1. Naïve targeted Immunotherapy population (NTIP): Participants naïve to biologics and small molecules to treat psoriasis (refer to E 15).
2. Experienced Targeted Immunotherapy population (ETIP): Participants who previously received targeted immunotherapy for psoriasis (refer to E 16 *and* E 19*)*.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1 Patient input into design

The preliminary abbreviated protocol was presented and discussed during 90 minutes to a panel of 4 psoriasis patients (2 male, 2 female, age 24-60yo) from the Netherlands. They recommended to remove the [redacted].
They recommended patient convenient organization such as light meals and working places during waiting times in the visits, which will be implemented where feasible.

4.3 JUSTIFICATION FOR DOSE

SAR441566 has been well tolerated by all participants with an acceptable safety profile in First-in-human studies in healthy participants over the range of 5 to 600 mg single dose and repeated doses of 100 to 600 mg total daily (100 mg QD, 100/200/300 mg BID) administered over 14 days. There were no safety concerns (SAEs or severe TEAEs) throughout additional studies in healthy participants:

- Interaction study (INT17025) with a single dose of [redacted] SAR441566 alone or co-administered with [redacted].
- Interaction study (INT17671) with a single dose and repeated once daily doses of [redacted] SAR441566 over 13 days, co-administered with a single dose of [redacted]).
- Relative bioavailability study (BDR17662) comparing [redacted] at a single dose of [redacted] SAR441566.

In the proof-of-mechanism study (PDY16918), repeated administration of 200 mg BID SAR441566 over 28 days was safe and well-tolerated by participants with mild to moderate psoriasis.

It is anticipated that up to a dose of 200 mg BID, SAR441566 can be co-administered [redacted] with negligible risk of clinically relevant increase in SAR441566 systemic exposure with the following rationale:

- [redacted]
- There was an approximately 2-fold difference between the SAR441566 exposure observed at 200 mg BID as compared to 300 mg BID in the MAD study (TDR16920).
- Repeated oral administration of 300 mg BID over 14 days has been well tolerated by healthy participants.

Overall, SAR441566 showed consistent PK and PD characteristics which support advancement into further clinical studies in participants. Both QD and BID dosing without regard to food are deemed feasible considering SAR441566 $t_{1/2z}$ of approximately 20 to 30 hours, negligible food effect at 200 mg single dose. High target occupancy was observed across the investigated dose levels in the MAD study (100 mg QD, 100/200/300 mg BID). The published estimates of TNFα occupancy indicate >98% for marketed TNFα inhibiting biologics (13) at average steady state concentration of efficacious dose. The mean TNFα occupancy measured on Day 14 was ~95% for 100 mg QD and at pre-dose (trough level) and ~100% for all other time points assessed across the investigated dose range, ie, at 3 hours post-dose (~Cmax) for 100 mg QD, at pre-dose and 3 hours post-dose for 100 mg, 200 mg and 300 mg BID, respectively, which is in line with the exposure-occupancy relationship established by *in vitro* studies (see also IB Section 5.1.2.4). These results suggest that 100 mg to 400 mg total daily doses can be considered potential therapeutically relevant doses. 50 mg QD is considered a sub-therapeutic dose based on the target occupancy results of doses >100 mg.

In the POM study (PDY16918) in participants with mild to moderate psoriasis, serum IL-17A, IL-17F and IL-22 levels markedly declined following 4-week treatment of 200 mg BID SAR441566, in contrast to placebo. Notably, the biomarker decreases were in line with the observed clinical improvement in TLS score of 17.7% with 90% CI [4.98 to 30.49] at Week 4 compared to placebo. The adjusted mean % improvement of 19.4% with 90% CI [6.28 to 32.48] in PASI at Week 4 was consistent with the clinically relevant improvement in the TLS score. The results obtained in the proof-of-mechanism study support the initiation of Phase 2 dose ranging studies as part of the further clinical development of SAR441566.

In summary, the dose levels selected for the current study are expected to be safe and, based on the target occupancy data from the MAD study, as well as the efficacy and biomarker outcomes from the proof-of-mechanism study, to span a range of potential therapeutically relevant as well as subtherapeutic doses which will allow to explore the dose-response relationship and the determination of the optimal therapeutic dose for future large-scale studies.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as the date of the last scheduled visit at the end of the 4-week post-treatment period (safety follow-up), as shown in the schedule of activities.

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 the following criteria apply:

Age

I 01. At least 18 years old [or the legal age of consent in the jurisdiction in which the study is taking place] to 75 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with moderate to severe plaque psoriasis for at least 6 months, meeting the following criteria at screening and D1 (prior to randomization):

a) PASI ≥12 points; and

b) sPGA score ≥3 points; and

c) BSA score ≥10%.

I 03. Must be a candidate for phototherapy or systemic therapy.

Weight

I 04. Total body weight >=50 kg (110 lb) and body mass index (BMI) within the range [18 - 35] kg/m^2 (inclusive).

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

I 05. All contraceptive methods used 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 treatment period and for at least 3 months after the last administration of study IMP:

- Refrain from donating or cryopreserving sperm;

PLUS, either:

- Be abstinent from heterosexual 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 as detailed below:

  A male condom and an additional highly effective contraceptive method (as described in Section 10.4), when having sexual intercourse with a woman of child-bearing potential (WOCBP) who is not currently pregnant.

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-child-bearing potential as defined in the 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 Section 10.4) during the study intervention period (to be effective before starting IMP) and for at least 3 months after the last administration of study IMP 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 (urine or serum as required by local regulations) at screening and a negative urine pregnancy test before the first administration of study IMP.

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 06. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative (see Section 10.7).

Other inclusion criteria

[redacted]

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Other forms of psoriasis than plaque psoriasis, such as guttate psoriasis, psoriatic arthritis, or pustular psoriasis. Nail psoriasis is accepted for inclusion.

E 02. Plaque psoriasis is restricted to scalp, palms, soles, or flexures only.

E 03. Any other skin diseases that can interfere with psoriasis evaluation or treatment response (eg, atopic dermatitis, fungal or bacterial superinfection).

E 04. Other immunologic (autoimmune or inflammatory) disorder, except medically controlled diabetes or thyroid disorder as per Investigator's judgement.

E 05. History of recurrent or recent serious infection (eg, pneumonia, septicemia), or infection(s) requiring hospitalization or treatment with IV anti-infectives (antibiotics, antivirals, antifungals, antihelminthics) within 30 days prior to D1, or infections(s) requiring oral anti-infectives (antibiotics, antivirals, antifungals, antihelminthics) within 14 days prior to D1.

E 06. Known history of or suspected significant current immunosuppression, including history of invasive opportunistic or helminthic infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration.

E 07. Participant with personal or family history of long QT syndrome.

E 08. History of moderate to severe congestive heart failure (New York Heart Association Class III or IV), or recent cerebrovascular accident, or any other condition in the opinion of the Investigator that would put the participant at risk by participation in the protocol.

E 09. History of solid organ transplant.

E 10. History of alcohol or drug abuse within the past 2 years.

E 11. History of diagnosis of demyelinating disease such as but not limited to:

- Multiple Sclerosis.
- Acute Disseminated Encephalomyelitis.
- Balo's Disease (Concentric Sclerosis).
- Charcot-Marie-Tooth Disease.
- Guillain-Barre Syndrome.
- Human T-lymphotropic virus 1 Associated Myelopathy.
- Neuromyelitis Optica (Devic's Disease).

E 12. Planned surgery during the treatment period.

E 13. Active malignancy, lymphoproliferative disease, or malignancy in remission for less than 5 years, except adequately treated (cured) localized carcinoma in situ of the cervix or ductal breast, or squamous cell carcinoma, or basal cell carcinoma of the skin.

E 14. Any live (attenuated) vaccine within 6 weeks prior to randomization (eg, varicella zoster vaccine, oral polio, rabies) or plan to receive one during the trial.

History of targeted immunotherapy for psoriasis

E 15. For NTIP: previous or current use of biologics, biosimilars or small molecules to treat psoriasis [such as targeting IL-23, IL-17, IL-12, TNFα (eg, Ustekinumab, secukinumab, ixikizumab), or phosphodiesterase 4, janus kinase or tyrosine kinase 2 inhibitors (apremilast, tofacitinib, deucravacitinib)].

E 16. For ETIP: never received biologics, biosimilars or small molecules to treat psoriasis such as targeting IL-23, IL-17, IL-12, TNFα (eg, Ustekinumab, secukinumab, ixikizumab), or phosphodiesterase 4, janus kinase or tyrosine kinase 2 inhibitors (apremilast, tofacitinib, deucravacitinib).

E 17. Deleted in Amended protocol 04.

Prior/concomitant therapy

E 18. Simultaneous treatment with phototherapy or the following systemic therapies, however participants can go through washout to be considered for the study. Participants should not be withdrawn from a treatment if the disease is well controlled in order to be considered for the study. Emollients are accepted, as much as needed, during the duration of the study (see Table 5).

- Natalizumab, rituximab or agents that modulate B or T cells (eg, alemtuzumab, abatacept, visilizumab) requires washout of 6 months until D1.
- Systemic immunosuppressants (eg, MTX, Azathioprine, cyclosporine, 6-thiouganine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) or anakinra, or phototherapy requires washout of 4 weeks until D1.
- Systemic medications/treatments (including but not limited to oral or (intramuscular, intravenous, or intraarticular) injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues when administered at high doses with the intent to treat psoriasis, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivative, Lithium, antimalarias, gold injections, leflunomide) requires washout of 4 weeks until D1.
- Topical Treatments (eg, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, tazarotene, methoxsalen, trimethylpsoralens, picrolimus, tacrolimus, vitamin A analogues, retinoids, salicylvaseline, salicylic acid, lactic acid, tar, andanthralin, `-hydroxy, fruit acids). See Table 5, for considerations regarding topical corticosteroids.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Prior/concurrent clinical study experience

E 25. Participation in any other study of investigational drug within 30 days or 5 times the terminal half-life of the investigational drug, whichever was longer, prior to randomization.

Diagnostic assessments

E 26. At screening visit or Day 1 a marked prolongation of QTcF interval >450 milliseconds (ms) (Fridericia QT correction formula, mean of triplicate measurement).

E 27. At screening visit, presence of any of the following laboratory findings:

a) Hemoglobin <8.0 g/dL.

b) Platelet count <100 000 platelets/microliter.

c) White blood cells <3500 cells/microliter.

d) Neutrophils <1500 cells/microliter (or<1000/mm^3 for participants of African descent).

e) AST or ALT ≥2 × ULN.

f) Total Bilirubin >2 × ULN; unless the participant has been diagnosed with Gilbert disease documented by genetic testing.

g) Creatinine clearance <45 mL/min using Cockcroft-Gault equation.

Retest can be done to reassess the eligibility during the Screening period as per Investigator's judgement that observed abnormality is not clinically significant and not consistent with patient's medical history.

E 28. At the screening visit, participants with positive:

- Hepatitis B surface antigen (HBsAg), or IgM Hepatitis B core antibody (HBcAb) or total HBcAb confirmed by positive HBV-DNA (for participants in Japan, see Section 10.7.3), or
- Hepatitis C virus antibody (HCVAb) confirmed by positive HCV-RNA.

E 29. Exclusion related to Human immunodeficiency virus (HIV):

- Positive HIV-1 or HIV-2 serology without antiretroviral therapy and CD4 count <200 cells per milliliter of blood (cells/mm^3) (for participants in the Czech Republic, see Section 10.7.4).

E 30. Exclusion related to TB (Section 8.3.5):

- Active TB or a history of incompletely treated TB.
- Undergoing treatment for latent TB infection (LTBI).
- Positive QuantiFERON®-TB test at Screening visit.
- Participants with current household contacts with active TB.
- Indeterminate QuantiFERON®-TB may be repeated once during screening period and will be considered positive if retest results are positive or indeterminate.
- Patient who received BCG-vaccination within 12 months prior to screening.
- Participants meeting all the following criteria would not be excluded:
  - **a)** documented completed appropriate LTBI treatment, OR treated for active TB infection (with a treatment regimen as per local guidelines), AND
  - **b)** have obtained consultation with a specialist to rule out or treat active TB infection (for participants in the Czech Republic, see Section 10.7.4), AND
  - **c)** for whom review and approval from Sponsor have been granted are eligible.

  Note: TB testing is mandatory to rule out active/latent TB and a blood sample for QuantiFERON® Tuberculosis Gold Interferon- Gamma Release Assay (IGRA) testing should be sent to the central laboratory.

  The screening period may be extended to 6 weeks (+/- 3 days) if participants are awaiting consultation with a specialist to rule out or treat active TB infection, or approval from Sponsor.

Other exclusion criteria

E 31. Inability to tolerate oral medication.

E 32. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 33. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, incapacitated or participants potentially at risk of noncompliance to study procedures.

E 34. Participants who 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 35. 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 36. Any country-related specific regulation that would prevent the participant from entering the study – see Appendix 7 in Section 10.7 of the protocol (country-specific requirements).

5.3 LIFESTYLE CONSIDERATIONS

Participants will be asked to inform the Investigator or sub-investigator during the screening visit about their vaccination history. Based on the provided information, the Investigator or Sub-investigator will determine if the participants received the appropriate immunization for their age according to the current immunization guideline in place in the participant's local country.

[redacted].

5.3.1 Meals and dietary restrictions

- Refrain from [redacted] before the start of IMP until after the final dose.
- Participants should come to Visits 2, 4 and 6 in fasting conditions (except water) and abstain from caffeine containing beverages/foods for 8 hours prior to arrival. A light meal will be provided by the site after the laboratory tests, lipids panel and pre-dose-PK.
- It is recommended to record the ECG under fasting conditions (except water). If this is not possible, a light snack with minimal carbohydrate content (eg, crackers, fruit, or yogurt, maximum 100-200 calories, no caffeine containing beverages or foods) can be consumed at least 2 hours prior to the ECG assessment.

5.3.2 Fasting, caffeine, alcohol, and tobacco

- Fasting: During Visit 2, 4 and 6 (Week 0, 4 and 12), participant should be fasting (except water), and abstain from caffeine containing beverages/foods for 8 hours prior to arrival.
- [redacted]
- Alcohol: During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Tobacco: Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3 Activity

- No restrictions on activity.

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 Consolidating Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

The Investigator will maintain a screening log to record reasons for screening failure, as applicable.

5.5 RE-TESTING: LABORATORY INCLUSION/EXCLUSION CRITERIA

In cases where original screen failure was due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the participant may be rescreened only once for this study after notification of the Sponsor. Rescreened participants will be assigned a new participant number for the re-screening event. There is no requirement for a waiting period between the screen-failure and the re-screening. A new consent form must be signed and Visit 1 procedures that did not initially meet eligibility criteria or that were performed earlier than 28 days before randomization must be repeated for re-screened participants.

If a hematology/chemistry laboratory value falls outside the normal range and is judged by the Investigator to be clinically significant, it may be repeated once and if the repeat value is no longer considered clinically significant then that specific laboratory testing result should not disqualify a participant from the study. Consultation with the medical monitor may help to identify whether repeat testing of any parameter is clinically relevant.

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

5.6 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY IMP

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 Section 10.8.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and AxMPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Study intervention administered

Intervention label	SAR441566 [redacted] mg and [redacted] mg	Placebo
Intervention name	SAR441566	SAR441566 matching placebo
Intervention description	[redacted]	
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strengths	[redacted]	0 mg
Dosage levels	[redacted]	
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP and AxMP	IMP	IMP
Packaging and labeling	Study IMP will be provided in wallet. Each wallet will be labeled as required per country requirements.	Study IMP will be provided in wallet. Each wallet will be labeled as required per country requirements.
[Current/former name(s) or alias(es)]	Not applicable	Not applicable

Table 4 - Study arms

Arm title	200 mg BID	100 mg BID	200 mg QD	100 mg QD	50 mg QD	Placebo
Arm type	Experimental	Experimental	Experimental	Experimental	Experimental	Placebo
Arm description	Participants will receive 200 mg of SAR441566 BID for 12 weeks	Participants will receive 100 mg of SAR441566 BID for 12 weeks	Participants will receive 200 mg of SAR441566 QD for 12 weeks	Participants will receive 100 mg of SAR441566 QD for 12 weeks	Participants will receive 50 mg of SAR441566 QD for 12 weeks	Participants will receive Placebo for 12 weeks

The SAR441566 or placebo may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company when 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 Section 10.8.

6.1.1 Devices

- Not Applicable.

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 IMP received and any discrepancies are reported and resolved before use of the study IMP.
2. Only participants enrolled in the study may receive study IMP and only authorized site staff may supply, prepare, or administer study IMP.
3. All study IMP 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, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study IMP 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 8.4.10).

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, 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 TREATMENT

- At Visit 2 (Week 0), after all baseline evaluations have been completed, participants will be randomly assigned to study IMP (SAR441566 or matching placebo).
- The list of randomized IMP kit numbers is generated centrally by Sanofi. The IMPs (SAR441566 and placebo) are packaged in accordance with this list.
- The randomization and IMP allocation are performed centrally by an IWRS. Before the study is initiated the log in information, and directions for the IWRS will be provided to each site.
- The IWRS generates the participant randomization list and allocates the IMP number and the corresponding intervention kits to the participants according to it.
- Participant's randomization list will be stratified by prior targeted immunotherapy use history (NTIP vs. ETIP).
- Study IMP will be dispensed at the study visits as summarized in the SoA (see Section 1.3). Returned study IMP should not be re-dispensed to the participants. Details of the IWRS procedure will be provided in the IWRS site manual.
- During the treatment period, several IMP kit numbers will be allocated to participants by the IWRS 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 IMP regardless of whether the IMP is received or not.
- Time of randomization for a participant is defined as the time recorded by IWRS.
- A participant cannot be randomized more than once in the study. Due to the study duration, several IMP kits numbers will be allocated to participants by the IWRS across visits in the same arm assigned at the randomization visit. That is, in these cases, the IMP/kit number varies but the arm assignment at randomization does not change.

6.4 BLINDING

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

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

The IWRS 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 IMP 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 IMP 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 database lock. Bioanalysts are excluded from the clinical study operation's 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 and the Sponsor will also be blinded to PK and hsCRP data. In addition, population PK analysis may be conducted prior to data base lock leading to unblinding of personnel in charge of dataset creation and data analysis. These personnel will be excluded from the clinical trial team.

Sponsor safety staff may unblind the IMP 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 IMP assignment.

Methods of blinding

- The placebo tablet will be identical to the SAR441566 tablet in appearance, quantity, taste, odor, packaging, and labeling. SAR441566 and placebo will be provided in indistinguishable wallets, in identical kits labeled with an IMP 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. Details about the distribution of unblinding data to the IDMC while protecting the blind are described in the IDMC charter.
- In case of an interim analysis, a Statistician, Programmer, and the Clinical Research Director will be unblinded for the analyses and work independently to the study team to ensure maintenance of the blind. They will keep the randomization schedule in a locked area, which is not accessible to the Sponsor's clinical 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 Section 10.2). In case of a safety concern, unblinding can be performed by the Investigator and/or Sponsor for the PD marker.

6.5 STUDY IMP COMPLIANCE

When participants are dosed at the site, the Investigator or the designee will provide IMP to the participant from a new IMP kit, and not from a previous IMP kit. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study IMP 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 IMP.

Compliance of IMP:

When participants self-administer study IMP at home, compliance with study IMP will be assessed at each visit. Compliance will be assessed by counting returned tablets in each pack during the site visits and documented in the source documents and relevant form. A participant is determined compliant with the treatment if the participant took 80% or more of scheduled IMP during the treatment period.

Omissions or deviations from the prescribed dosage regimen should be recorded in the medication administration questionnaire.

Accountability of IMP provided by the Sponsor:

- The Investigator counts the number of remaining tablets in the returned packs, and then fills in the IMP log form.
- The Investigator also checks the IMP administration questionnaire to evaluate patient compliance.

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

6.6 DOSE MODIFICATION

Dose modification is not allowed.

6.7 CONTINUED ACCESS TO IMP AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

For this study, any dose of SAR441566 greater than 50% more than the intended daily dose within 24-hour period ±2 hours will be considered an overdose.

Participants who are overdosed should be treated symptomatically. Currently, there is no known antidote for SAR441566.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Evaluate the participant to determine whether study IMP should be interrupted.
- Obtain a plasma sample for PK analysis as soon as possible.
- Document appropriately in the eCRF.

- Contact the Sponsor as soon as possible. Of note: Asymptomatic overdose must be reported as standard AE.

6.9 PRIOR AND CONCOMITANT THERAPY

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

- Drug generic name.
- 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.

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

Treatments in addition to the IMPs should be kept to a minimum during the study. However, if these are considered necessary for the participant's welfare and are unlikely to interfere with the IMPs, they may be given at the discretion of the Investigator, with a stable dose (when possible).

Participant should report in their IMP administration questionnaire any change in the ongoing specific treatment or newly taken concomitant medication(s), if any between the on-site study visits. The investigator can request [redacted] during the study (Day 1 to EoS).

6.9.1 Prior Therapy

Prior therapies restricted for participants eligible for this study are detailed in the exclusion criteria (Section 5.2).

6.9.2 Prohibited concomitant therapy

Refer to the exclusion criteria (Section 5.2) and Table 5. For China, refer to Section 10.7.1.

[redacted]

[redacted]

[redacted]

For China: Any Chinese medicine containing Tripterygium and/or Total glucosides of peony, or other Chinese medicine aimed at treating psoriasis.	1 month

1. There is no restriction on corticosteroids that only have a topical effect to treat other indications than psoriasis (eg, inhalant corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).
2. Use of 1,25-dihydroxy vitamin D3 and analogues is prohibited only when administered at high doses with the intent to treat psoriasis. Oral intake of vitamin D for the treatment of other indications is not prohibited. Ensure any type of vitamin D administration is recorded on the eCRF.
3. Exception: Topical corticosteroids of US class 6 (mild, such as desonide) or US Class 7 (least potent, such as hydrocortisone) will be permitted for limited use to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits on D1, W4, W8 and W12.

6.9.3 Permitted concomitant therapy

There is no restriction on topical corticosteroids used to treat other indications than psoriasis (eg, inhaled corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

Topical corticosteroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits on Day 1, Week 4, 8 and 12.

Any therapy other than the prohibited concomitant therapy that may be given at the discretion of the Investigator has to be recorded in the source data (Section 10.1.8) and the eCRF.

[redacted]

Caution should be exercised with [redacted].

If the patient has been using any allowed concomitant therapy, he/she should continue it at the same dose and regimen throughout the entire study (if reasonable from the medical point of view). On days when blood samples are taken, the patient should continue the usual regimen of his/her concomitant therapy (except the use of topical corticosteroids of US class 6/mild or US Class 7/least potent, which cannot be used 24 hours prior to clinic visits).

6.9.4 Rescue medicine

Topical corticosteroids of class least potent or mild (US class 6 or 7) (such as hydrocortisone) are permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits on Day 1, Week 4, 8 and 12.

7 DISCONTINUATION OF STUDY IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study are detailed in Appendix 1 (Section 10.1.9).

7.1 DISCONTINUATION OF STUDY IMP

An individual should discontinue study IMP if any of the following occurs:

- At the request of the participant, ie, withdrawal of consent.
- Pregnancy of a female participant.
- Occurrence of SAE if further participation could jeopardize the safety of the participant.
- Any clinically relevant safety laboratory deviation, including but not limited to [redacted] (refer to Section 7.1.3).
- Worsening of psoriasis requiring intensification of therapy outside of substances permitted in the study (refer to Section 6.9.2 and Section 6.9.3).
- Any other medically important AE in the judgement of the investigator.

All study IMP withdrawals should be recorded by the Investigator on the appropriate case report form screens for eCRF when considered as confirmed.

In case of premature study IMP discontinuation, see Section 7.1.1 below.

For any participant who fails to return to the site, the Investigator should make every effort to recontact the participant (eg, contact the participant's family or private physician, review available registries or health care database), and to determine his/her health status, including at least his/her vital status. Attempts to contact the participant must be documented in the participant's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

7.1.1 Permanent discontinuation

It may be necessary for a participant to permanently discontinue study IMP. In this case the participant must be followed up as described below.

Abnormal laboratory value or ECG parameter should be rechecked for confirmation, according to Investigator's judgement before deciding on possible permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent IMP discontinuation

Participants who discontinue IMP treatment prior to completing the 12-week treatment period should be assessed as per the EoT visit at the earliest opportunity and no later than 7 days from the last dose of IMP. After the EoT visit:

a) Participants who accept to stay on study without IMP intake: all remaining visits described in the SoA should be performed until the EoS, but only clinical assessments, AE and concomitant medication review and patient reported outcomes should be carried out at the study visits.
b) Participants who withdraw consent from the study: should have an EoS visit 4 weeks after their last dose of IMP.

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

The recommended wash out period for SAR441566 is [redacted] (>5 x the half-life of SAR441566).

7.1.4 Temporary discontinuation

Temporary IMP discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.8). For all temporary IMP discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary IMP discontinuation decided by the Investigator corresponds to ≥2 consecutive IMP doses not administered to the participant.

7.1.5 Rechallenge

Reinitiating the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

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 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 IMP should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

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

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for IMP 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 will 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 (when 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. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations should 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 cannot be utilized for screening or baseline purposes even if they were performed within the timeframe defined in the SoA, Central laboratory analysis is required. See Section 8.3.6 for pregnancy testing and Section 8.3.5 for local Quantiferon Testing.
- 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/independent ethics committee requirements (Section 10.8).
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Blood sampling details including volume for all laboratory assessments will be provided in the laboratory manual and the ICF.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 ADMINISTRATIVE AND GENERAL/BASELINE PROCEDURES

Baseline demographic characteristics will consist of:

1. Age (years)
2. Height (cm)
3. Weight (kg)
4. Race and Ethnicity
5. Gender, if applicable
6. Psoriasis history including date of symptom onset, date of the diagnosis, previous treatments (medication generic name, doses, clinical efficacy response [responder or no-responder], reason for discontinuation [side effects, lack of clinical efficacy, medication interaction with other concomitant therapy, remission/lack of symptoms, and other] and length of the therapy), and current treatments.
7. History of psoriasis in the family.

8. Concomitant disease such as diabetes mellitus, arterial hypertension, obesity, dyslipidemia, myocardial infarction, etc.
9. Details regarding current therapies and vitamins for concomitant therapies.
10. Smoking status, specifying if participant is current, former, or never smoker.

Study participant race or ethnicity will be collected in this study because analysis of results according to race/ethnicity are required by several Regulatory Authorities (eg, African American population for FDA in United States, Japanese population for the Pharmaceuticals and Medical Devices Agency [PMDA] in Japan or Chinese population for the National Medical Products Administration [NMPA] in China).

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA.

To minimize any bias, it is recommended participants to complete their PRO measures before clinician assessments and discussion of their clinical condition, treatment plan, AEs, and any other related topics that could influence participant's perception and feelings prior to responding to the questions. There will be a specific training on ePRO technology. For the ePRO data it is mandatory that a key person (for example research nurse) at each site is responsible for ePRO data collection, to optimize participant compliance and to ensure data completeness. Reason for non-completion will be documented in the eCRF.

8.2.1 Psoriasis area and severity index (PASI)

The PASI is an established measure of clinical efficacy for psoriasis medications (7). The PASI is a tool that provides a numeric scoring for participants' overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an X% reduction (or PASIX), where X is 50, 75, 90 and 100.

To calculate the PASI, the four main body areas are assessed: head (h), trunk (t), upper extremities (u) and lower extremities (l). These correspond to 10, 30, 20 and 40% of the total body area respectively.

The physician quantifies the percentage of the considered body area covered by plaque psoriasis. This percentage of psoriatic involvement is translated into a numerical value "Ax" for each body area: 0 = no involvement, 1 = <10%, 2 = 10 to <30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, and 6 = 90 to 100% involvement. These scores are noted Ah, At, Au, and Al in the formula below.

The signs of severity, erythema (E), induration (I) and desquamation (D) of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u, and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = striking erythema, and 4 = exceptionally striking erythema.

The PASI score is calculated according to the following formula:

$$PASI = 0.1(E_h+I_h+D_h)A_h + 0.3(E_t+I_t+D_t)At + 0.2(E_u+I_u+D_u)A_u + 0.4(E_l+I_l+D_l)A_l$$

8.2.2 static Psoriasis Global Assessment (sPGA)

The sPGA is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions (14). The assessment is considered "static", which refers to the participant's disease state at the time of the assessments, without comparison to any of the participant's previous disease states, whether at Baseline or at a previous visit. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

Erythema

- 0 Normal (post-inflammatory hyper/hypopigmentation may be present).
- 1 Faint, diffuse pink or slight red coloration.
- 2 Mild (light red coloration).
- 3 Definite red coloration (Dull to bright red).
- 4 Bright to Deep red coloration of lesions.

Induration (plaque elevation)

- 0 None.
- 1 Just detectable (slight elevation above normal skin).
- 2 Mild thickening (slight but definite elevation, typically edges are indistinct or sloped).
- 3 Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges).
- 4 Severe thickening with hard edges (marked elevation typically with hard or sharp edges).

Desquamation

- 0 No scaling.
- 1 Minimal focal scaling (surface dryness with some desquamation).
- 2 Predominately fine scaling (fine scale partially or mostly covering lesions).
- 3 Moderate scaling (coarser scale covering most or all of the lesions).

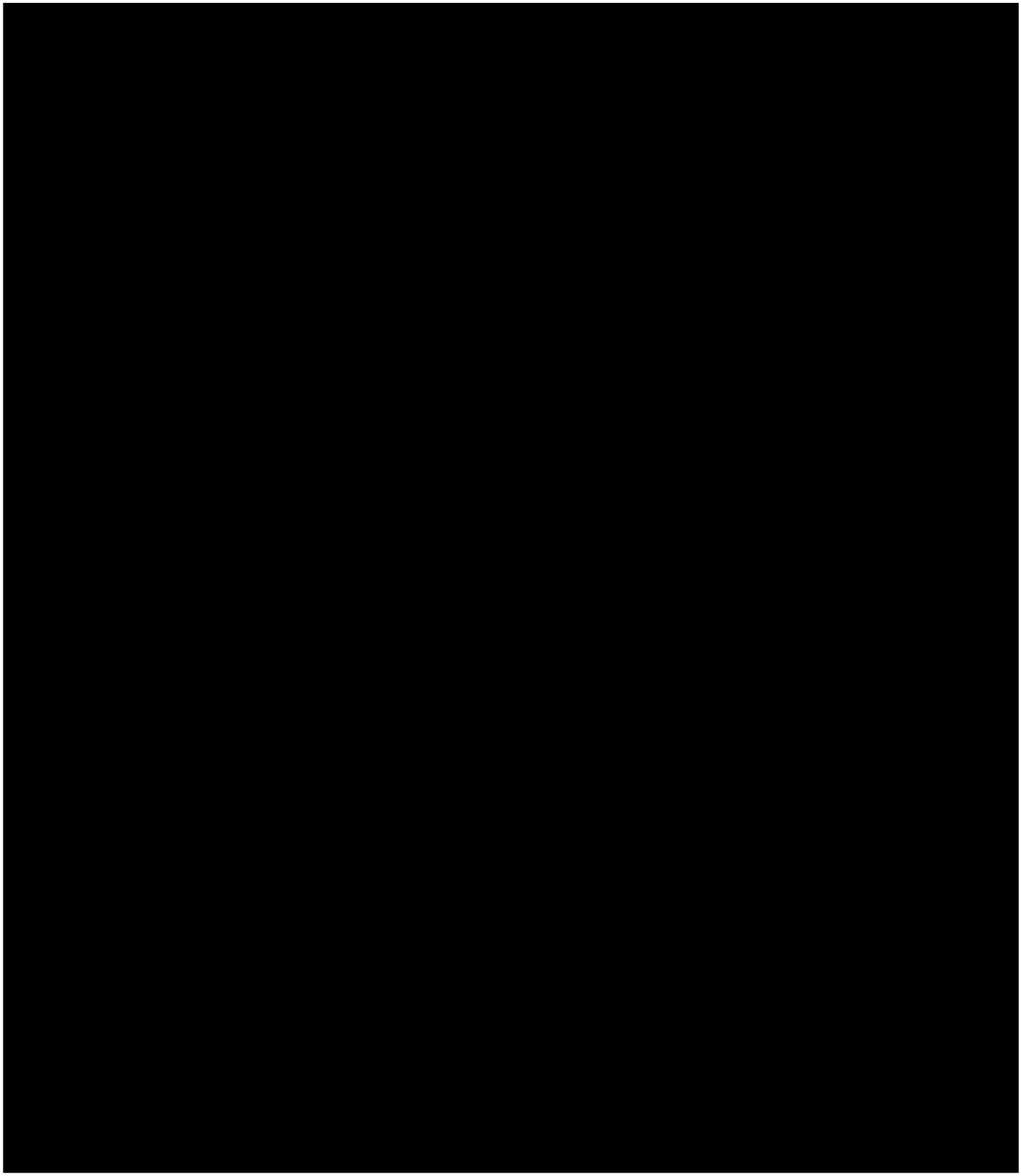
Overall Scoring resulting of the average of the Erythema, Induration and Desquamation score:

- Clear 0 = 0 for all three symptoms. Post-inflammatory hyper/hypopigmentation may be present.
- Almost clear 1 = mean >0, <1.5. Normal to pink coloration; just detectable (possible slight elevation above normal skin). No to minimal focal scaling.
- Mild 2 = mean >= 1.5, <2.5. Pink to light red coloration; mild thickening (slight but definite elevation, typically edges are indistinct or sloped). Predominantly fine scaling.
- Moderate 3 = mean >=2.5, <3.5. Dull to bright red coloration; clearly distinguishable to moderate thickening; moderate scaling.
- Severe 4 = mean >=3.5. Bright to deep dark red coloration; severe thickening with hard edges; severe coarse scaling covering almost all or all lesions.

8.2.3 Body surface Area (BSA)

BSA will be calculated from the integrated BSA within the PASI assessment.

Percent BSA will be evaluated as the percent involvement of psoriasis on each patient's BSA on a continuous scale from 0% (no involvement) to 100% (full involvement), where 1% corresponds to the size of the patient's hand (including the palm, fingers, and thumb) (15).



[redacted]

[redacted]

8.2.8 Dermatology Life Quality Index (DLQI)

The DLQI is one of the most widely used measures in dermatology populations to evaluate participants' Health-Related Quality of Life. It is a patient-reported outcome instrument consisting of 10 items exploring six dimensions: 'Symptoms and feelings" (2 items), "Daily activities" (2 items), "Leisure" (2 items), "Work and school" (1 item), "Personal relationships" (2 items), "Treatment" (1 item). Each item is rated on a dichotomous: Yes/No and 3- and 4-point Likert/Likert-type scale for capturing skin symptom-related experiences over the previous weeks.

Scores are computed overall and for the six domains. The total DLQI score ranges from 0 to 30 which higher scores indicating better QoL. The instrument has good evidence of content validity and psychometric properties supporting its reliability, construct validity and responsiveness (16).

The DLQI questionnaires are provided in Section 10.10.1.

[redacted]

8.3 SAFETY ASSESSMENTS

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

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

8.3.1 Physical examinations

- The complete physical examination will consist of evaluation of the following systems: general, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, and musculoskeletal.
- The targeted physical exam will consist of evaluation of the following systems: general, eyes, throat, cardiovascular, lungs, abdominal, extremities, and skin, musculoskeletal.
- Complete and targeted physical examinations may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant, or a Nurse Practitioner. A targeted physical examination may note any changes in the participant's condition since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

8.3.2 Vital signs

- Vital signs include body temperature (°C), heart rate (beats per minute), and systolic and diastolic blood pressure (mm Hg) (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed sitting with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

8.3.3 Electrocardiograms

- Standard 12-lead ECGs are recorded after at least 10 minutes of rest in supine position using an electrocardiographic device. The electrodes will be positioned at the same place for each ECG recording throughout the study (eg, attachment sites of the leads will be visualized on a transparent paper).
- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. [redacted].
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained within 5 minutes, with at least 1 minute between 2 replicates.
- The ECG should be recorded [redacted]
- [redacted]

- Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:
  - A single 12-lead ECG (50 mm/s, 10 mm/mV) printout with heart rate, PR, QRS, QT, QTcF automatic correction evaluation using Fridericia formula (by the ECG device), including date, time, number of the participant, and at least 3 complexes for each lead. The Investigator should revise the results of the printout and his/hers medical opinion together with the automatic values will be recorded in the eCRF. This printout will be retained at the site. A second printout may be performed also, if needed.
  - A digital storage that enables potential further reading by an ECG central laboratory: each digital file will be identified by theoretical time (day and time Dxx Txx Hxx), real date and real time (recorder time), Sponsor study code, participant number (eg, 3 digits), and site and country numbers, if relevant. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (ie, FDA 21 code of federal regulations [CFR], Part 11).

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed by central laboratory and the 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 3 days after the last dose of study IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If values do not return to normal/baseline within a period 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 central 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 in eCRF.

8.3.5 Tuberculosis assessment and QuantiFERON®

Medical history, including assessment of active TB, history of incompletely treated TB, undergoing treatment for latent TB or with current household contacts with active TB is considered part of the process to assess a participant's eligibility as outlined in E 30 at the screening visit. All participants will have a screening test, the QuantiFERON® (an interferon gamma release assay, IGRA), performed centrally. If unable to obtain central lab results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally

(eg, T-spot®, QuantiFERON®), after consultation with the study medical monitor. Indeterminate IGRA may be repeated once during screening period and will be considered positive if retest results are positive or indeterminate.

Participants with a positive screening test will not be eligible for the study unless participants have documented completed appropriate active/latent TB treatment and consultation with a specialist has been obtained to rule out or treat active TB infection (for participants in the Czech Republic, see Section 10.7.4) and Sponsor approval has been granted in writing (Refer to exclusion criteria E 30).

8.3.6 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing entry 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.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at prespecified intervals described in SoA during IMP treatment.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator, or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4 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 8.4.8.

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

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 legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up all AEs, considered related to the study IMP or study procedures, or that caused the participant to discontinue the study IMP (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 the 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 IMP 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 AEs of special interest (as defined in Section 8.4.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.4.4 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 IMP 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 IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor

will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study IMP and until and until EoS visit.
- 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 “contraception and barrier guidance” (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.
- Any post-study pregnancy-related SAE considered reasonably related to the study 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 study IMP or be withdrawn from the study.

Prior to continuation of study IMP following pregnancy, the following must occur:

- The Sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.4.6 Cardiovascular and death events

Cardiovascular events should be reported if they meet AE/SAE criteria. Events with fatal outcome events should be reported as SAEs.

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

Not applicable.

8.4.8 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 to characterize and understand them. AESIs may be added, modified, or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/AxMP;
  - 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/AxMP (see definition of an overdose in Section 6.8).

[redacted]

8.4.9 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 eCRF 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 eCRF.

8.4.10 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 the quality issue must be reported together with an AE or SAE.

8.4.11 Medical device deficiencies

Not applicable.

8.5 PHARMACOKINETICS

- Whole blood samples will be collected for measurement of plasma concentrations of SAR441566 as specified in the SoA (Section 1.3).
- A maximum of 5 samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations or to optimize PK timepoints during the course of the study based on the updated knowledge of drug behavior) to ensure appropriate monitoring.
- 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. PK samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of SAR441566 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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 and/or drug interaction. The exploratory data will not be included in the study report but will be kept on file.

SAR441566 concentrations at selected time points after IMP administration will be reported using descriptive statistics. Population PK and PK/PD approaches will be used for the estimation of PK parameters such as C_{max}, t_{max}, and $AUC_{0\text{-}tau}$, and for possible exposure-response analyses if appropriate. These results will be presented in a separate stand-alone report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

For China, see Section 10.7.1 for details.

8.6 PHARMACODYNAMICS

See Section 8.7 Genetics and Section 8.8 Biomarkers for a description of pharmacodynamic parameters.

[redacted]

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual. Results will be presented in reports separate from the clinical study report (CSR). See Appendix 5 (Section 10.5) [Genetics] for information regarding genetic research.

Genetic analyses will not be done for participants enrolled in China (Section 10.7.1).

8.8 BIOMARKERS

Whole blood, plasma and serum blood samples will be collected to assess the [redacted] of systemic inflammation associated to psoriasis, as well as disease markers and their correlation with clinical response. Samples will be collected pre-IMP dose and at the timepoints specified in the SoA, as detailed in a laboratory manual provided separately to sites.

Quantitative analysis of soluble blood proteins associated with psoriasis and/or SAR441566 activity will be performed in serum or plasma including but not limited to:

- IL-17A, IL-17F, IL-22, IL-19, [redacted] IL-17A and IL-17F are

released by skin infiltrating immune cells and are commonly accepted as key disease drivers. IL-22 is released by lesional psoriatic skin, whereby high concentrations correlate with disease activity. IL-19 is a component of IL-23/IL-17 cascade, which is increased in psoriasis and correlated to PASI.

Soluble protein biomarkers will be assessed through standardized methods. Instructions for the collection and handling of the biological samples will be provided in a separate document.

Whole blood samples will also be collected for [redacted]

Blood samples will be collected for [redacted]

With specific consent, optional blood samples will be collected for future biomarker analysis and/or retrospective safety follow-up, potentially including but not limited to [redacted] exploratory analysis reflecting effects of SAR441566 and/or to identify markers potentially predictive of clinical response. Participation is optional. Participants who do not wish to participate in the research may still participate in the study.

Analyses may also seek to identify which markers are associated with clinical response to SAR441566, or can be predictive of clinical response, or correlate to clinical response and clinical features.

For China, see Section 10.7.1 for details.

8.9 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics 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) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing, or treating diseases (Section 10.7.1 for specification related to China). 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 data may be shared.

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 clinical data

The study participant will be provided will all mandatory details of the data processing in Section 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, end of study as defined in the study protocol, upon consent of the participant. 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 Section 2 of the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (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 6 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IWRS regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who 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 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 received.
Naive targeted Immunotherapy population (NTIP)	All randomized participants who have never received targeted immunotherapy for psoriasis. Participants will be analyzed according to the intervention allocated by randomization.
Experienced Targeted Immunotherapy population (ETIP)	All randomized participants who previously received targeted immunotherapy for psoriasis. Participants will be analyzed according to the intervention allocated by randomization.

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.

Unless otherwise specified, analyses will be performed by intervention group/dose level and overall, for baseline and demographics characteristics.

The observation period will be divided into 3 segments:

- The **pre-treatment** period is defined as the period up to first double-blind IMP administration.
- The **treatment-emergent period** is defined as the period from the first IMP administration to the last IMP administration +5 days. 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 +1 day.
    - 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 from the end of the treatment-emergent period.

9.2.2 Primary endpoint analyses

9.2.2.1 Definition of endpoint

The primary endpoint is the response in PASI75, which is defined by proportion of participants with a 75% or greater PASI improvement from baseline at Week 12.

9.2.2.2 Main analytical approach

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

- Endpoint: Proportion of participants with a 75% or greater PASI score improvement from baseline at Week 12.
- Intervention condition: SAR441566 200 mg BID, 100 mg BID, 200 mg QD, 100 mg QD and 50 mg QD will be compared to placebo.
- Analysis population: NTIP population

- Intercurrent events:
  - The IMP discontinuation: It will be handled with the treatment policy strategy. The primary endpoint will be assessed based on all assessments irrespective of the IMP discontinuation.
  - Starting the selected concomitant medication which could have an impact on the efficacy of IMP: It will be handled with the composite variable strategy. For primary endpoint, participants who receive selected concomitant medications will be considered as non-responders for time points after the medication usage. For other participants, all available data including those collected during the off-treatment period will be used to determine the responder/non-responder status.

  Of note, details of selection of concomitant medications which could have an impact on the efficacy of IMP will be specified in the SAP.
- Population-level summary: Difference in the percentage of participants achieving PASI75 response at Week 12 between each active arm and placebo. The Cochran-Mantel-Haenszel test will be used for the primary endpoint analysis. Multiplicity adjustment will be provided (See Section 9.2.5). Further details will be specified in the SAP.

Missing data will be imputed to non-responders when the response to PASI75 is missing.

9.2.2.3 Sensitivity/Supplementary analysis

Supplementary/sensitivity analyses to assess the robustness of the conclusion of the primary analysis might be performed. To assess the consistency of treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoint, such as age, gender, etc. Further details will be specified in SAP.

9.2.3 Secondary endpoints analyses

Categorical secondary endpoints will be analyzed using Cochran-Mantel-Haenszel test including treatment group in the NTIP.

Continuous secondary endpoints will be analyzed by fitting an Analysis of Covariance model with the Baseline covariates in NTIP. Further details on missing data and intercurrent events handling will be specified in SAP.

Other secondary analyses will be defined in Section 9.2.6.1 (AE, SAE, AESIs), Section 9.2.6.2 (laboratory abnormalities), Section 8.5 (PK).

No multiplicity adjustment for the secondary efficacy endpoints will be made.

9.2.4 Exploratory/Tertiary endpoint(s) analyses

The details about the analysis of tertiary endpoints will be described in the study SAP. The primary and key secondary endpoints will also be analyzed in ETIP population for exploratory purpose.

9.2.5 Multiplicity adjustment

To control the overall Type I error of 0.05 under circumstance of multiple comparisons for the primary endpoint in the NTIP, the comparison between each dose of SAR441566 three doses (200 mg BID, 100 mg BID, 200 mg QD) and placebo will be conducted in a pairwise manner following a step-down procedure. The hierarchy will be 200 mg BID vs placebo, 100 mg BID vs placebo and 200 mg QD vs. Placebo. The testing will continue to the next level only if the previous comparison is statistically significant.

9.2.6 Safety analyses

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

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

AE 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/each analysis window, the last value, and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables. For ECG variables, only the on-site automatic reading will be used in the quantitative analysis.

Analyses according to PCSA

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

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

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

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

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

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

9.3 INTERIM ANALYSES

An interim analysis will be performed when approximately [redacted]f the participants in the primary analysis population have completed the EoS visit. The purpose of the interim analysis would be to provide early information for the Sponsor to plan for future development. The results of the interim analysis will not impact the conduct of the study. The SAP will describe the planned interim analysis in greater details.

9.4 SAMPLE SIZE DETERMINATION

A total sample size of approximately 207 participants will be randomized to the intervention groups in two different strata, ie, NTIP vs. ETIP.

In the stratum of NTIP, approximately 144 participants will be randomized in a randomization ratio 1:1:1:1:1:1 to SAR441566 200 mg BID, SAR441566 100 mg BID, SAR441566 200 mg QD, SAR441566 100 mg QD, SAR441566 50 mg QD and placebo, ie, 24 participants in each of six groups. The NTIP is the primary population for efficacy analysis.

In the stratum of ETIP, approximately 63 participants will be randomized in a randomization ratio 2:2:2:1 to SAR441566 200 mg BID, SAR441566 200 mg QD, SAR441566 100 mg QD and placebo, ie, 18 participants in each of SAR441566 200 mg BID, 200 mg QD and 100 mg QD groups and 9 participants in the placebo group. The ETIP is for exploratory purpose only.

In the NTIP, assuming a [redacted] dropout rate, the sample size of 24 participants per group will provide about [redacted]% power to demonstrate superiority of SAR441566 200 mg BID or 100 mg BID or 200 mg QD versus placebo with a [redacted] with the following assumptions on the primary endpoint:

- PASI75 Placebo rate of [redacted].
- PASI75 SAR441566 rate of [redacted].

To estimate the dose-response curve on QD regimen in the NTIP, the sample size of 24 participants per group will provide an minimum power of [redacted]% to detect the presence of a dose response, based on the assumption of a maximum effect in terms of PASI75 of treatment difference of [redacted]% in SAR441566 comparing with placebo rate of [redacted]%, using [redacted]

Calculations for Chi-square test were done using [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 Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH Good Clinical Practice (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 General Data Protection Regulation (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 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. If 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/ European Economic Area 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 participant 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.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants, and answer all questions regarding the study, including what happens to the participants when their participation ends (post-trial access strategy for the study).
- Potential participants must be informed that their participation is voluntary. They 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 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.

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 should be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking 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 Section 10.8.

For Germany, please refer to Section 10.7.2.

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. 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 PMDA in Japan or Chinese population for the NMPA in China). 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 participants 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 thirty (30) years, unless further retention is required by applicable regulations.
- 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 across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Data Monitoring Committee

The Sponsor will implement an IDMC for the duration of this study. The IDMC will be charged with monitoring the safety of patients participating in this clinical trial. The IDMC will review the safety and associated data (eg, labs) from the study at established frequencies, as defined in the IDMC charter. The IDMC will identify any concerning safety signals that merit further evaluation and make recommendations to the Sponsor on all safety aspects, based on their independent evaluation of unblinded data from study groups.

During this process, the IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the execution of its primary mission.

The IDMC will be comprised of at least 5 external members who specialize in the following areas: [redacted]
Members of the IDMC will be independent of those performing the study, being neither investigators nor employees of the Sponsor, and without conflict of interest regarding study outcome. The details of IDMC composition, schedule of meetings, and functions will be detailed in the IDMC charter. The IDMC's specific activities will be defined by a mutually agreed charter, which will define the IDMC membership, conduct and meeting schedule.

Sanofi retains final decision-making authority on all aspects of the study.

Follow-up actions may be taken based on data and recommendations generated by the IDMC including any change in the study design or communication with health authorities, as indicated.

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

[redacted]

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Instructions.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, 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 entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered the eCRF 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 IMP development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required if the central laboratory results are not available in time for either study IMP 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 IMP decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Hemoglobin
	Hematocrit
Clinical chemistry[a]	Bicarbonate
	Blood urea nitrogen (BUN)
	Potassium
	Creatinine
	Creatinine clearance
	Glucose non-fasting
	Sodium
	Calcium
	Chloride
	Phosphate
	AST/Serum glutamic-oxaloacetic transaminase
	ALT/Serum glutamic-pyruvic transaminase
	ALP[b]
	Albumin
	Total bilirubin

Laboratory tests	Parameters
	Conjugated bilirubin Unconjugated bilirubin Total protein CPK Total cholesterol fasting [redacted]
Pregnancy testing	[Serum or highly sensitive urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	FSH (as needed in women of nonchildbearing potential only) Serology (QuantiFERON®, HIV (HIV-1 and HIV-2) antibodies/CD4 count, HBsAg, IgM and total HBcAb and HCVAb. In case of HBcAb positivity, HBV-DNA testing must be performed. In case of HCVAb positivity, HCV-RNA testing must be performed (for Japan, HBsAb needs to be tested in addition to HBsAg and (IgM or total) HBcAb - Section 10.7.3) hsCRP All study-required laboratory tests will be performed by a central laboratory except for urine pregnancy.

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).
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 IMP, whether considered related to the study IMP.
- 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 IMP.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant questionnaire and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their questionnaire.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, 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 IMP 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 IMP 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.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes 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) Other situations:

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. These events should usually be considered serious.

The following list of medically important events is intended to serve as a guideline for determining which condition could be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm.
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented because of blood sampling).
- Bullous cutaneous eruptions.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

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, except for 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 assess 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 IMP 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 IMP 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's representative. However, **it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to** the Sponsor's representative.
- The Investigator may change his/her opinion of causality considering 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 the protocol cover page (Sponsor Monitoring team).

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

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

Women in the following categories are not considered WOCBP

- Premenarchal.
- 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, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.
- Postmenopausal
  - 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 hormone replacement treatment (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-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 enrolment.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study IMP, additional evaluation should be considered.

10.4.2 Contraception guidance

- Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study IMP, in line with the fact that study IMP may affect ova up to 3 months and sperm up to 3 months (see inclusion criteria).
- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

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

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion or ligation
- Azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

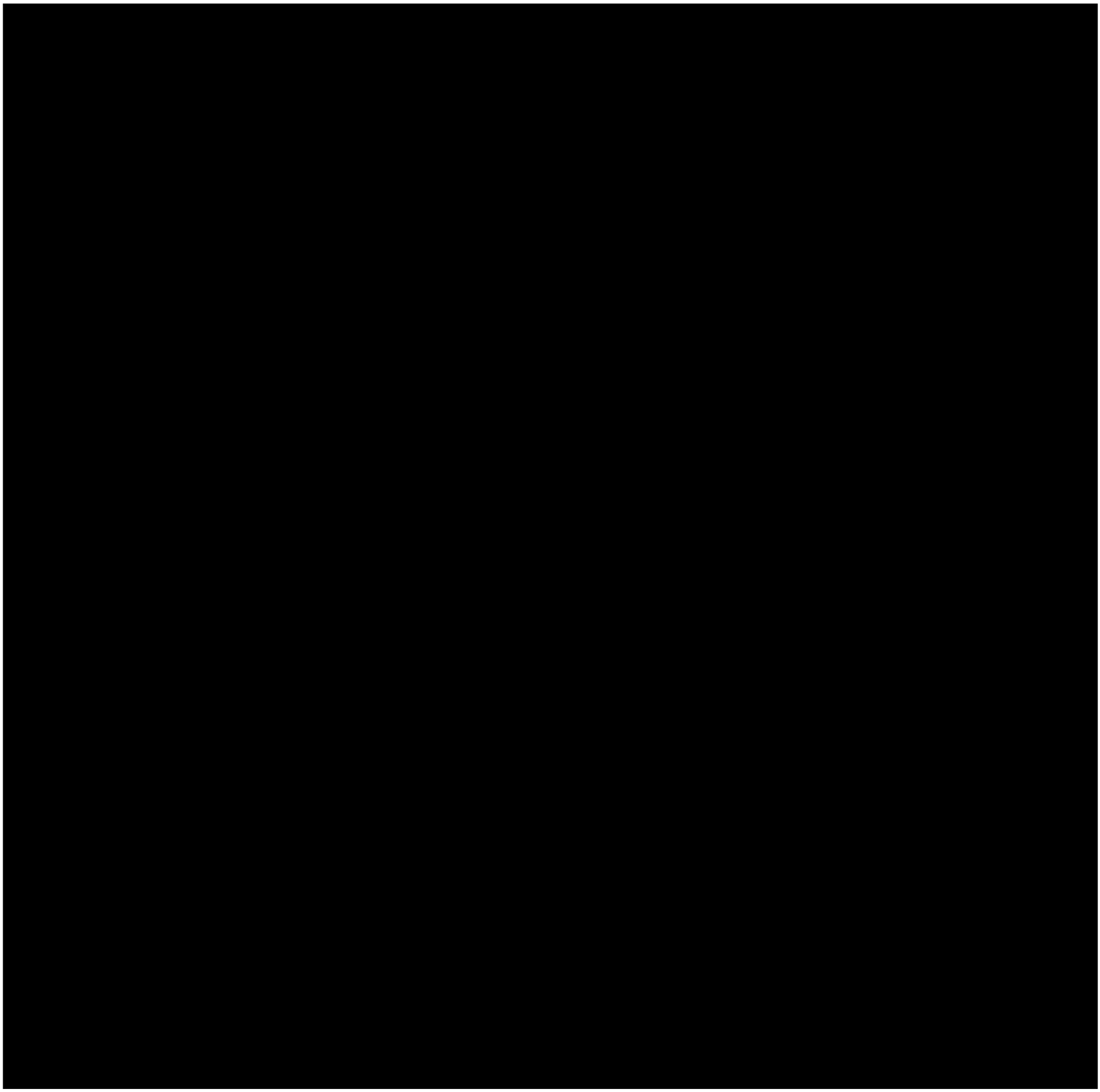
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  –oral
  –intravaginal
  –transdermal
  –injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  –oral
  –injectable

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

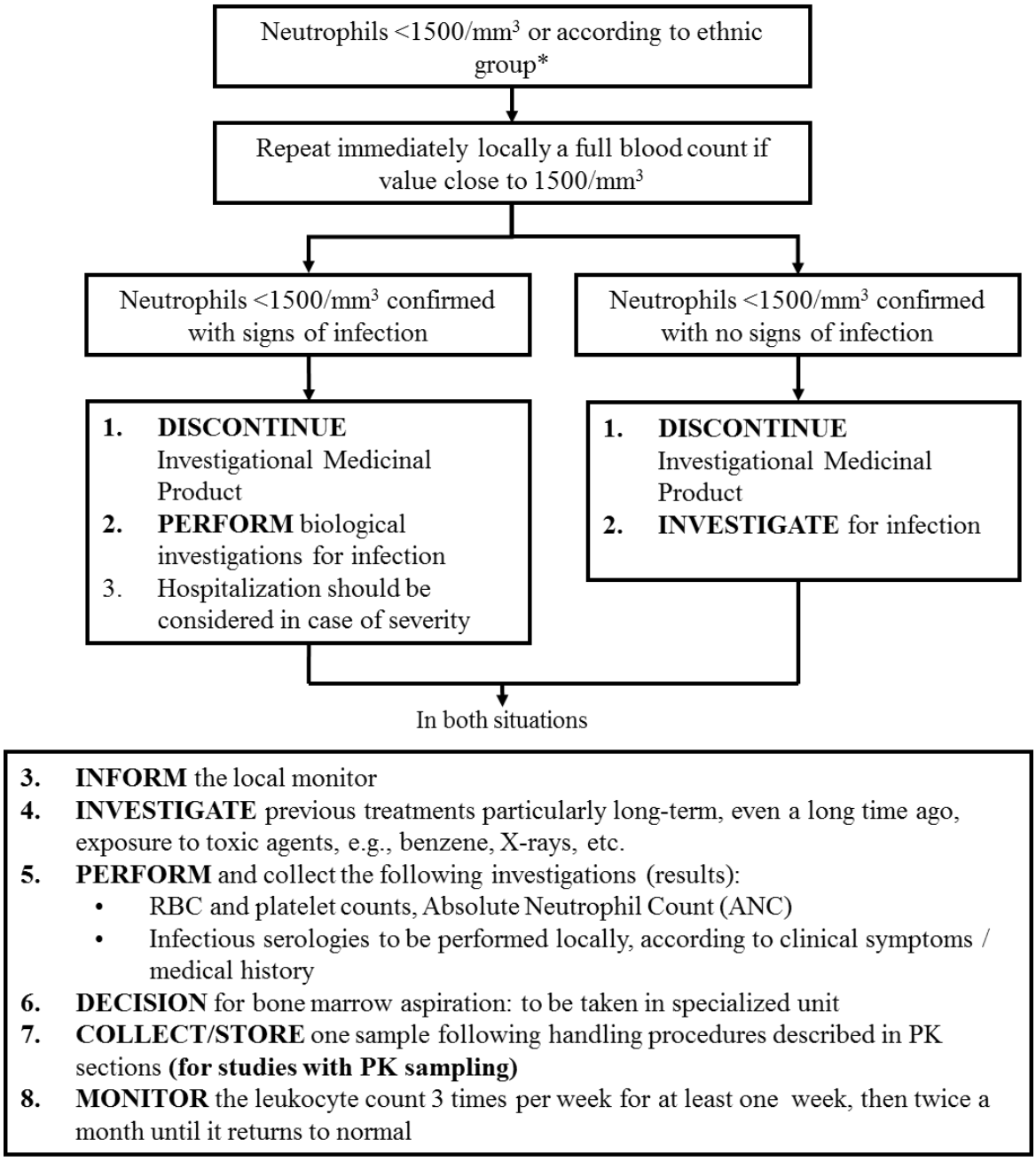
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c Male or female condoms must be used only in addition to hormonal contraception.

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



10.6 APPENDIX 6: LIVER AND OTHER SAFETY SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY IMP RESTART/RECHALLENGE GUIDELINES

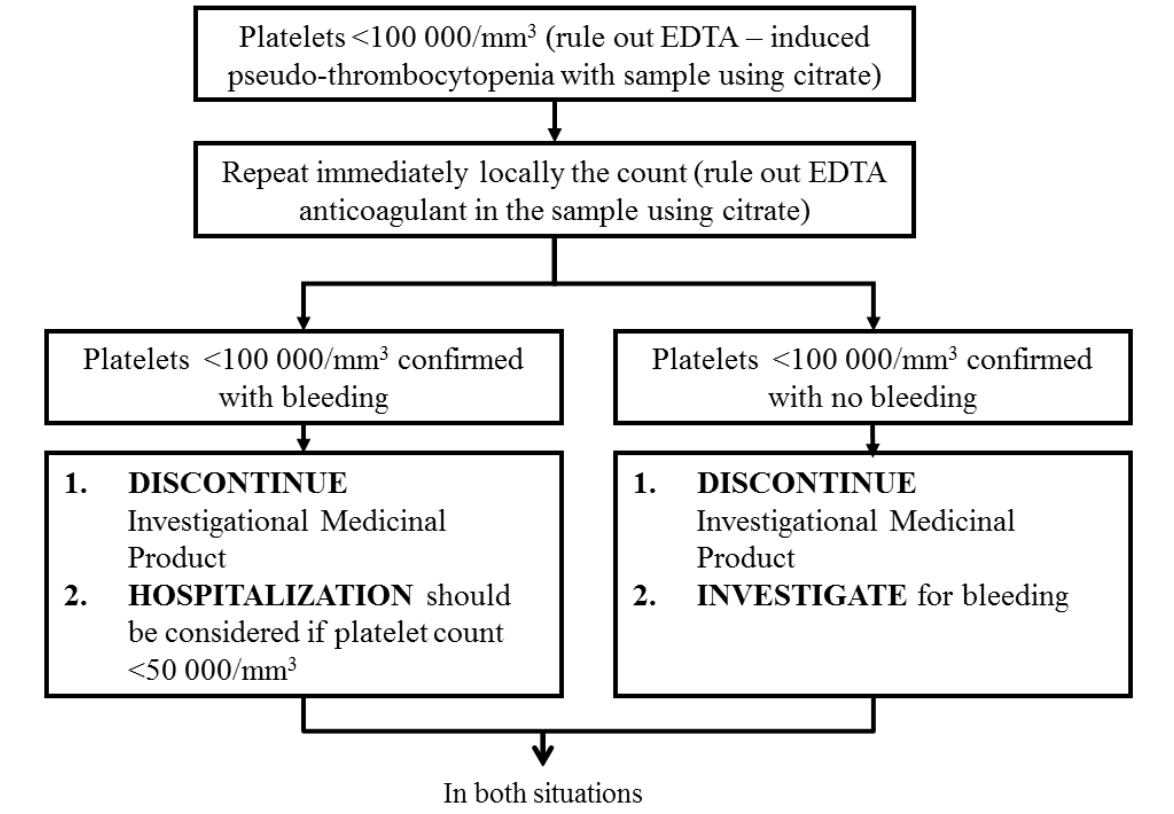
NEUTROPENIA



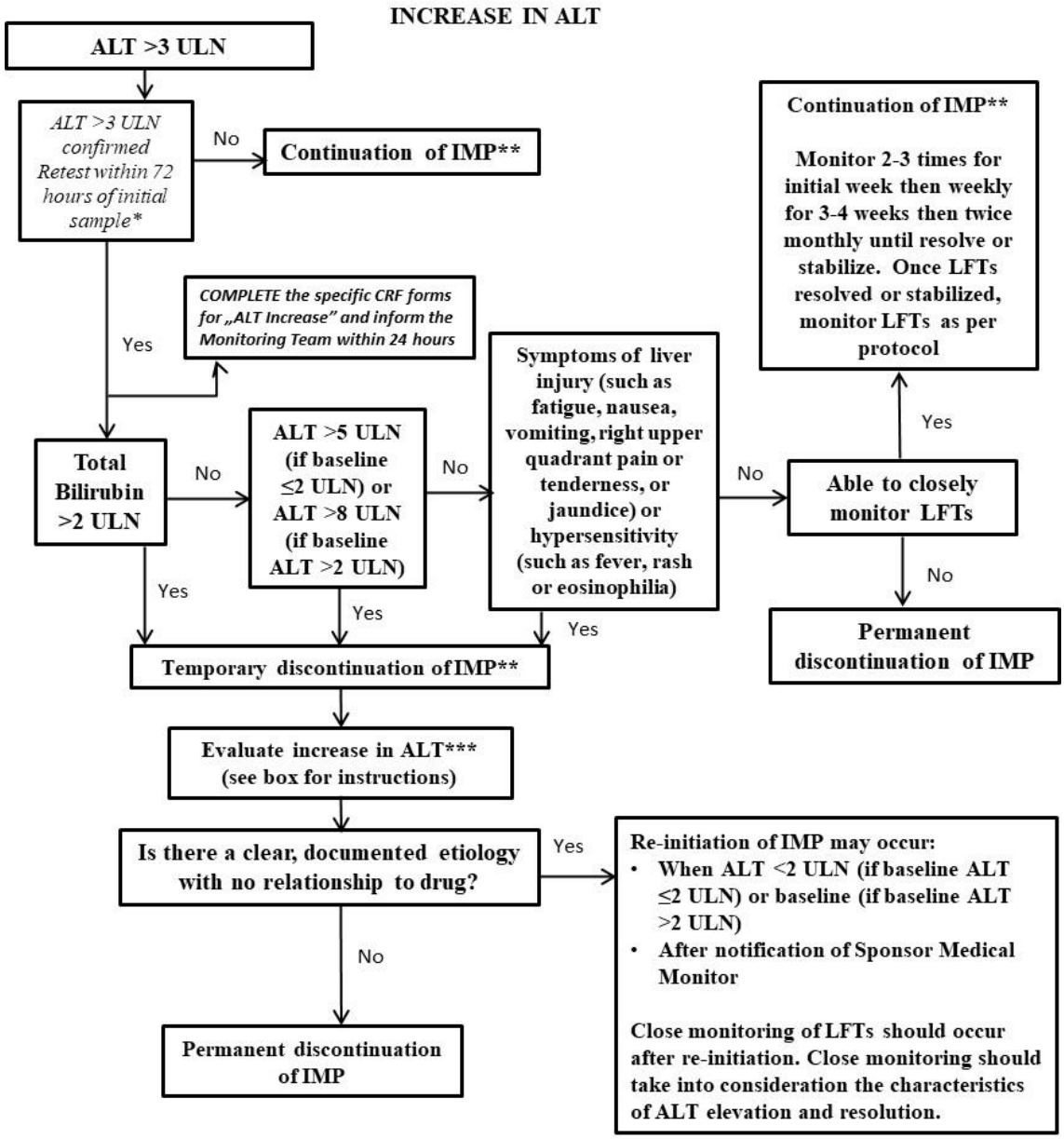
* For individuals of African descent, the relevant value of concern is <1000/mm3

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 8.4 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 8.4 is met.



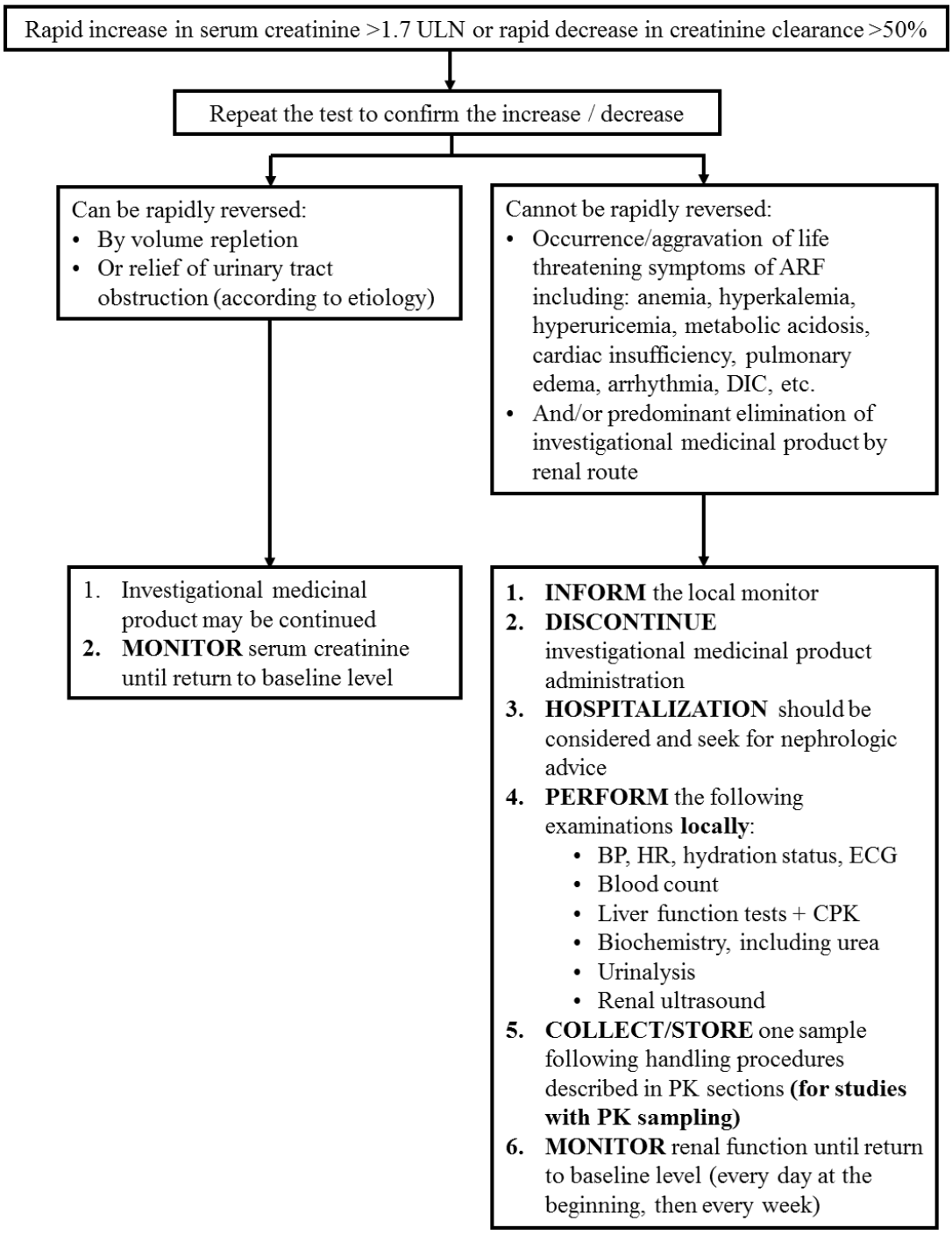
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met.
*** See box below
Note:

- "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 8.4 for guidance on safety reporting.

Evaluate Increase in ALT***

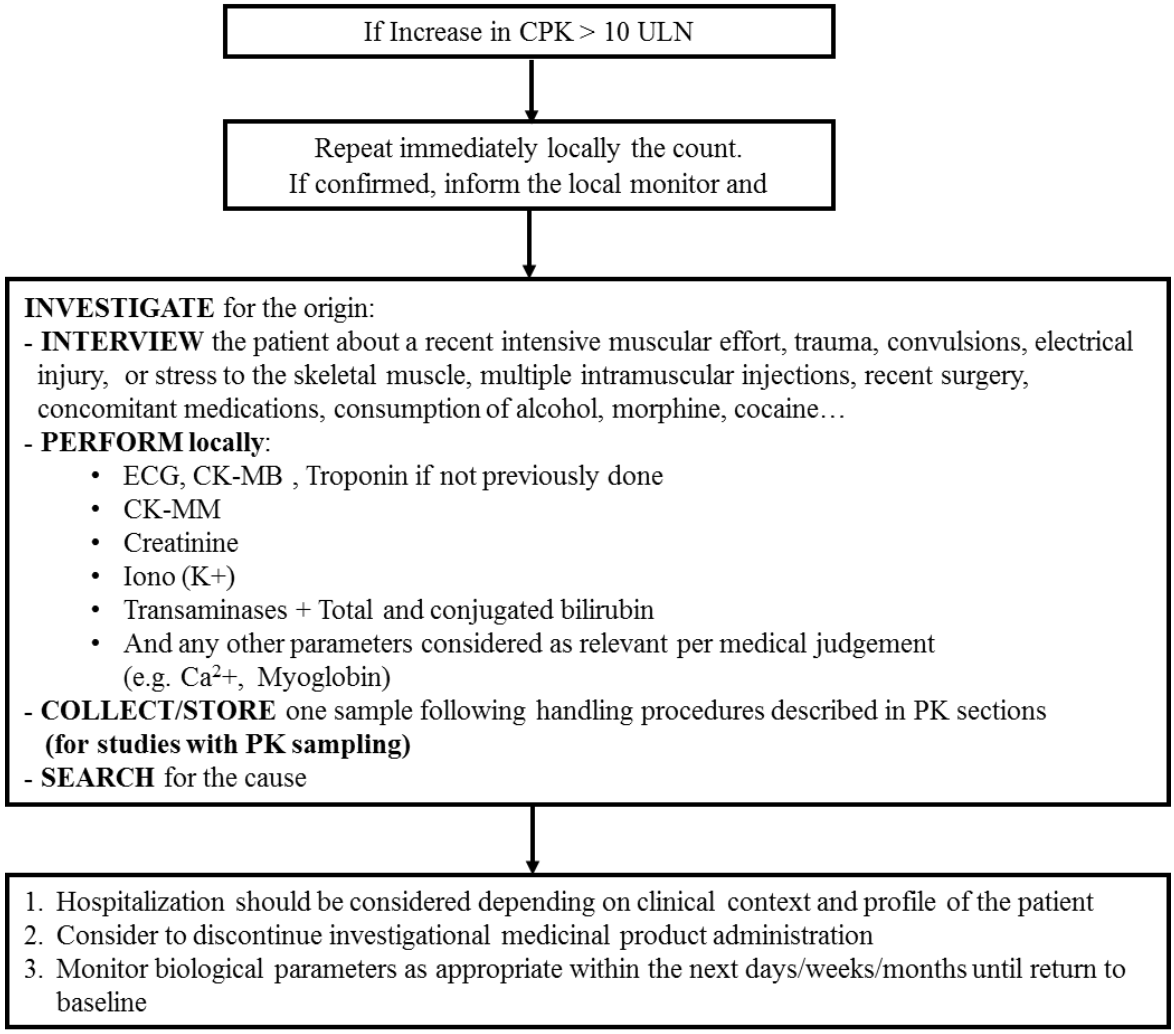
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any 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 8.4 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 8.4 is met.

10.7 APPENDIX 7: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.7.1 China

Exploratory/Tertiary biomarker samples to characterize immune cell populations including Th17, Treg, CD4 and CD8 as described in Section 1.3 and Section 8.8 will be optionally collected for participants in China.

Exploratory/Tertiary genetic and protein biomarker samples for future research, including RNA and DNA sequencing, and proteomics as described in Section 1.3, Section 8.7 and Section 8.8 are not applicable for participants in China.

In accordance with local requirements, the use of biological samples as described in Section 8.11 are not applicable for participants in China.

For prohibited concomitant medication refer to Section 6.9.2.

Furthermore, any Chinese medicine containing Tripterygium and/or Total glucosides of peony are not allowed 1 month prior to V1 or during the trial period. Other Chinese medicine aimed at treating psoriasis also cannot be used 1-month prior V1 or during the trial period.

10.7.2 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 10.1.3.

10.7.3 Japan

Participants in Japan need to be tested for HBsAb, in addition to HBsAg and (IgM or total) HBcAb. Positive results for HBsAb, or IgM or total HBcAb need to be confirmed by positive HBV-DNA.

Participants with positive HBsAg are excluded.

Participants with positive HBsAb or (IgM or total) HBcAb but negative (no detectable) HBV-DNA, are required to undergo HBV-DNA testing at Week 4, Week 8, Week 12.

10.7.4 Czech Republic

Participants with positive HIV-1 or HIV-2 serology are excluded.

Complete and targeted physical examinations may be performed only by a physician.

Participants with documented completed appropriate active or latent TB treatment would not be excluded from enrolment if their enrolment is approved by a TB specialist or an infectious diseases specialist.

10.8 APPENDIX 8: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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

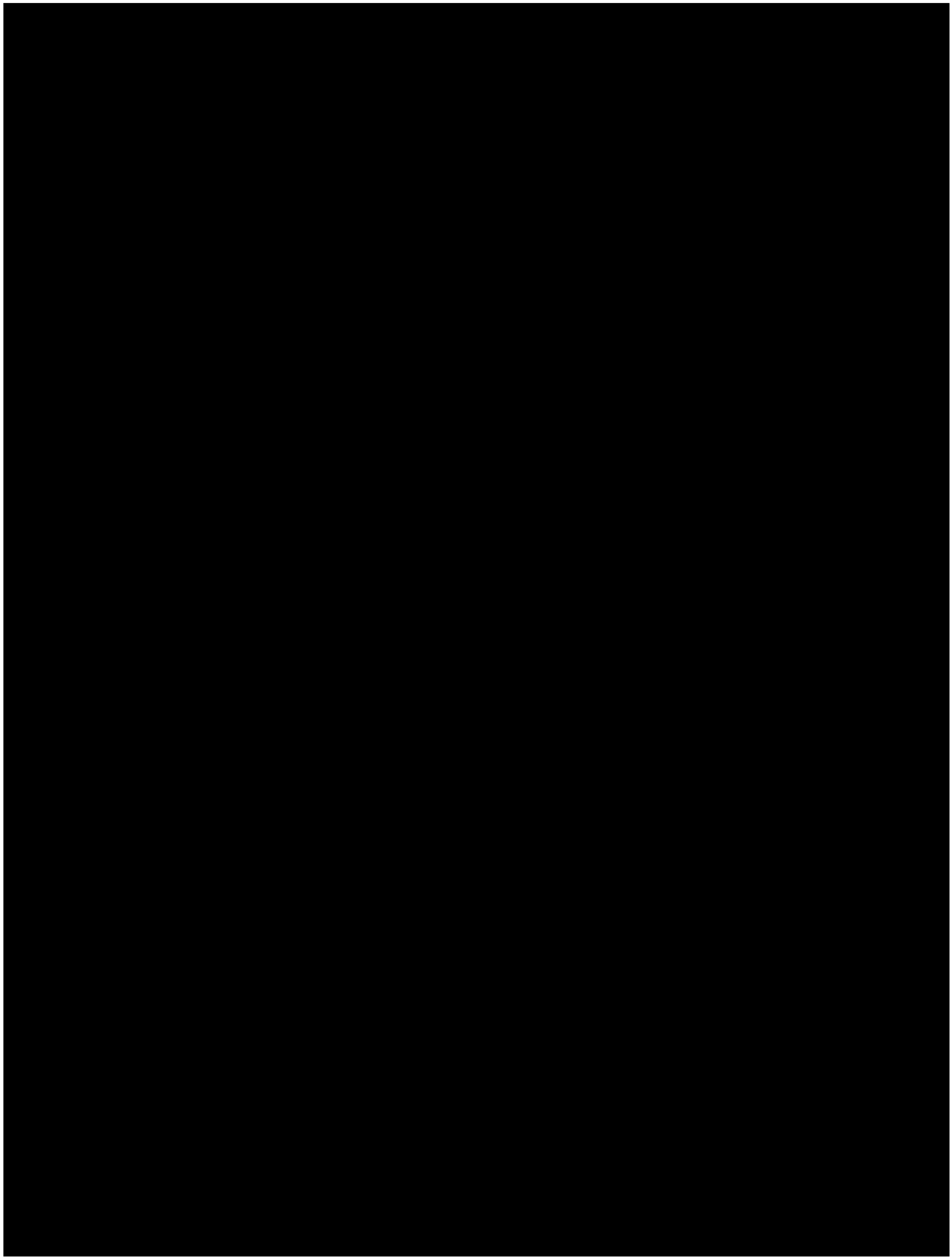
10.9 APPENDIX 9: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

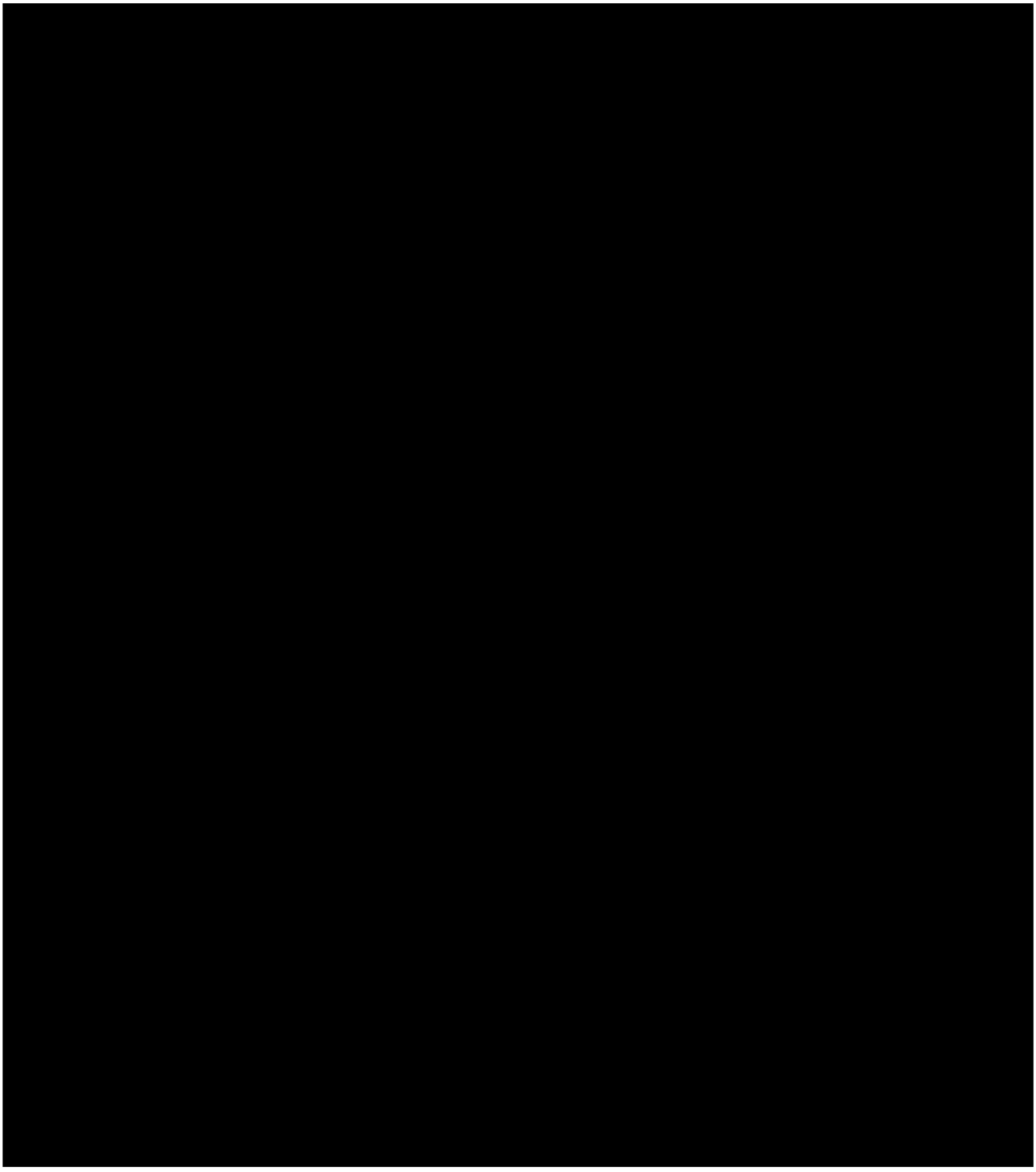
10.9.1 Compliance with Member State applicable rules for the collection, storage, and future use of human biological samples (Article 7.1h)

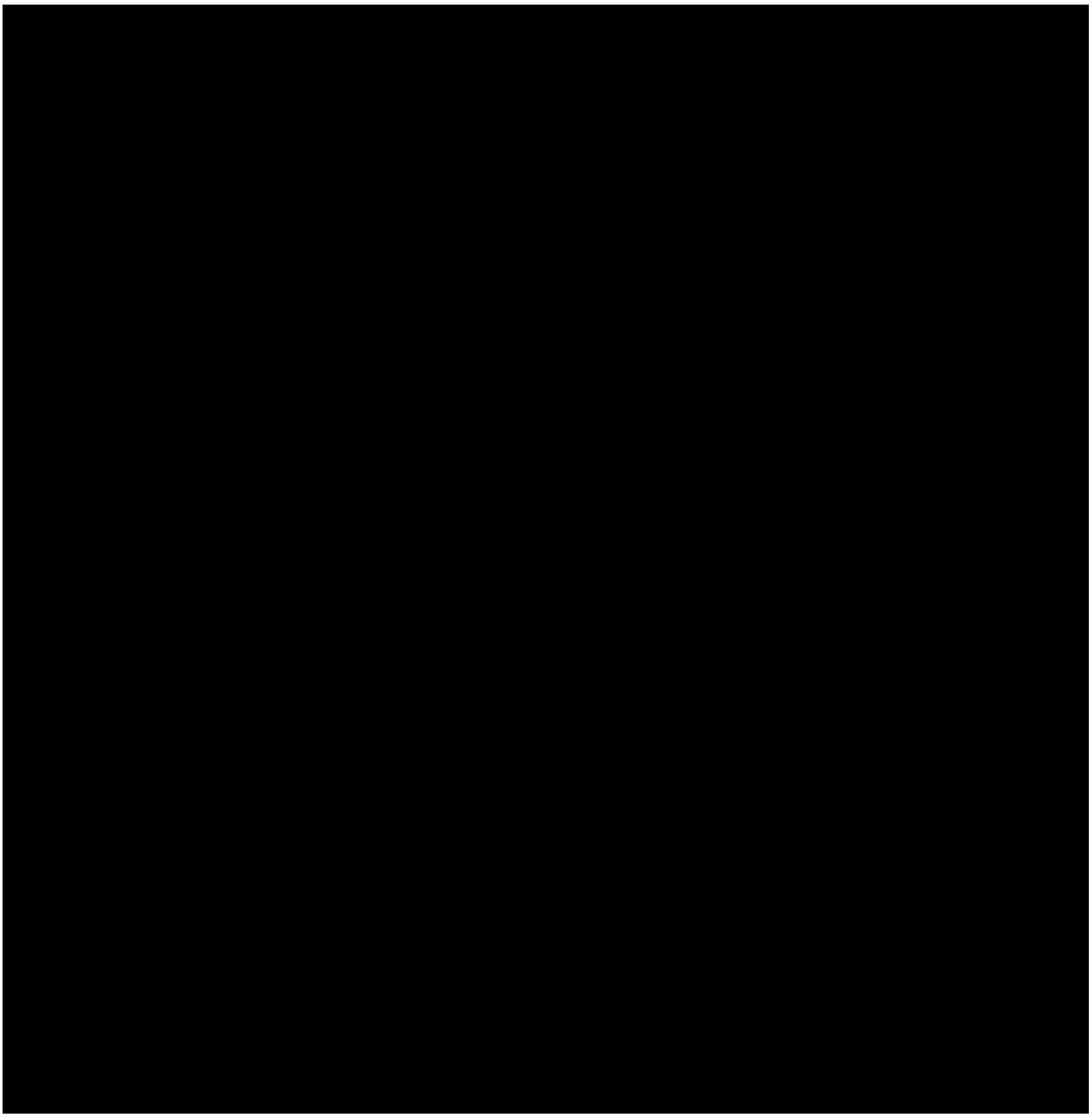
This appendix is provided separately.

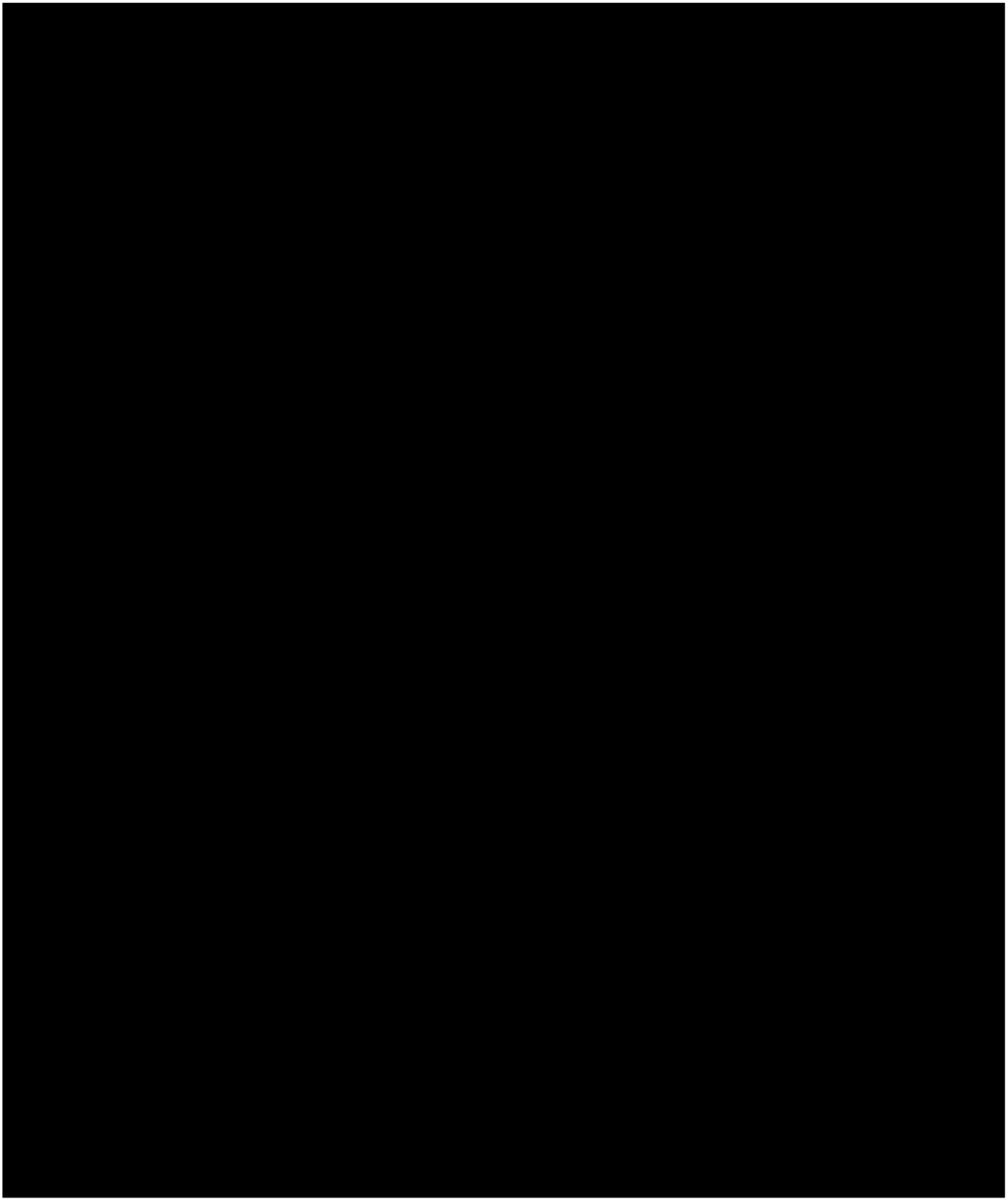
10.9.2 Compliance with Member State applicable rules for the collection, storage, and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

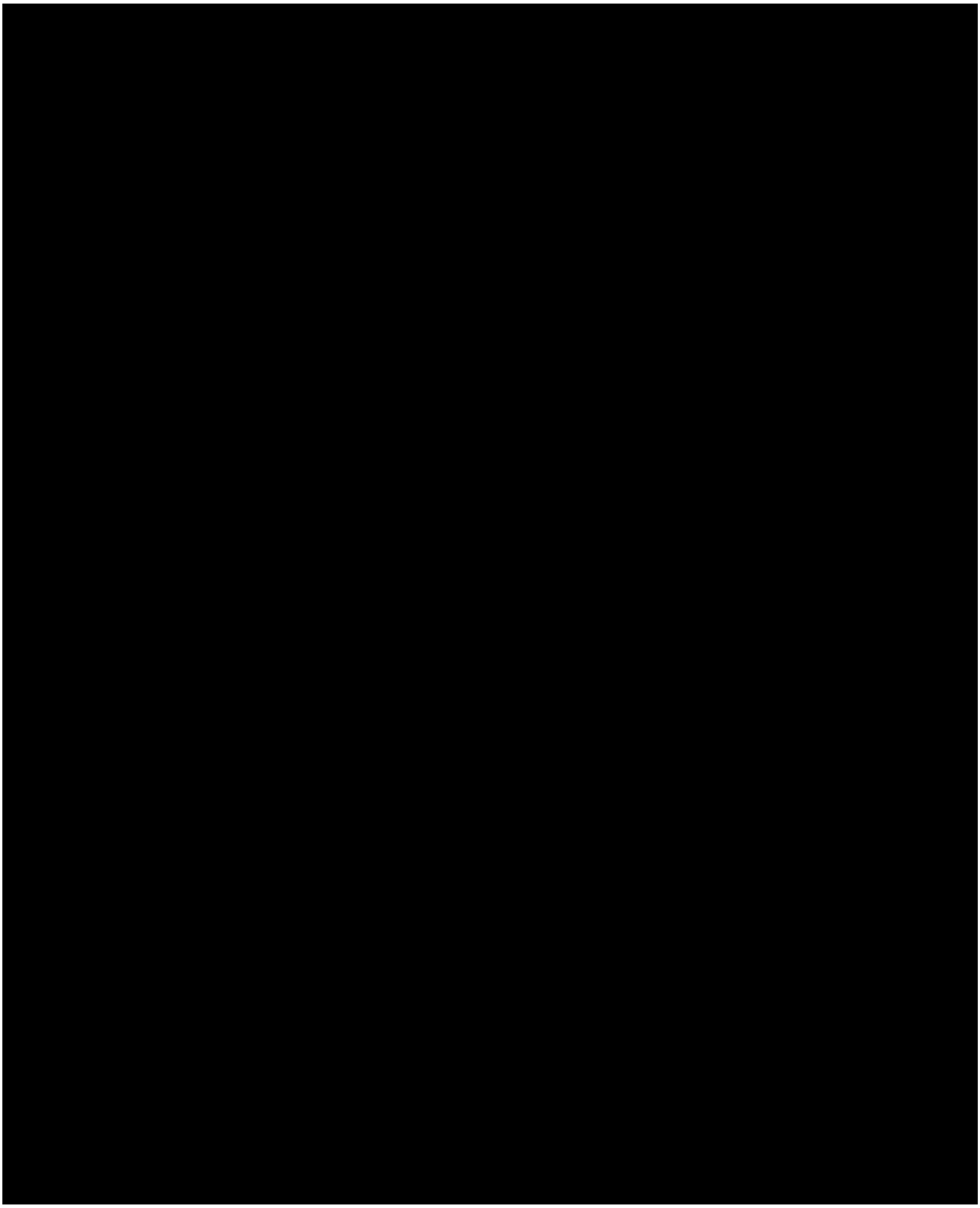








[redacted]



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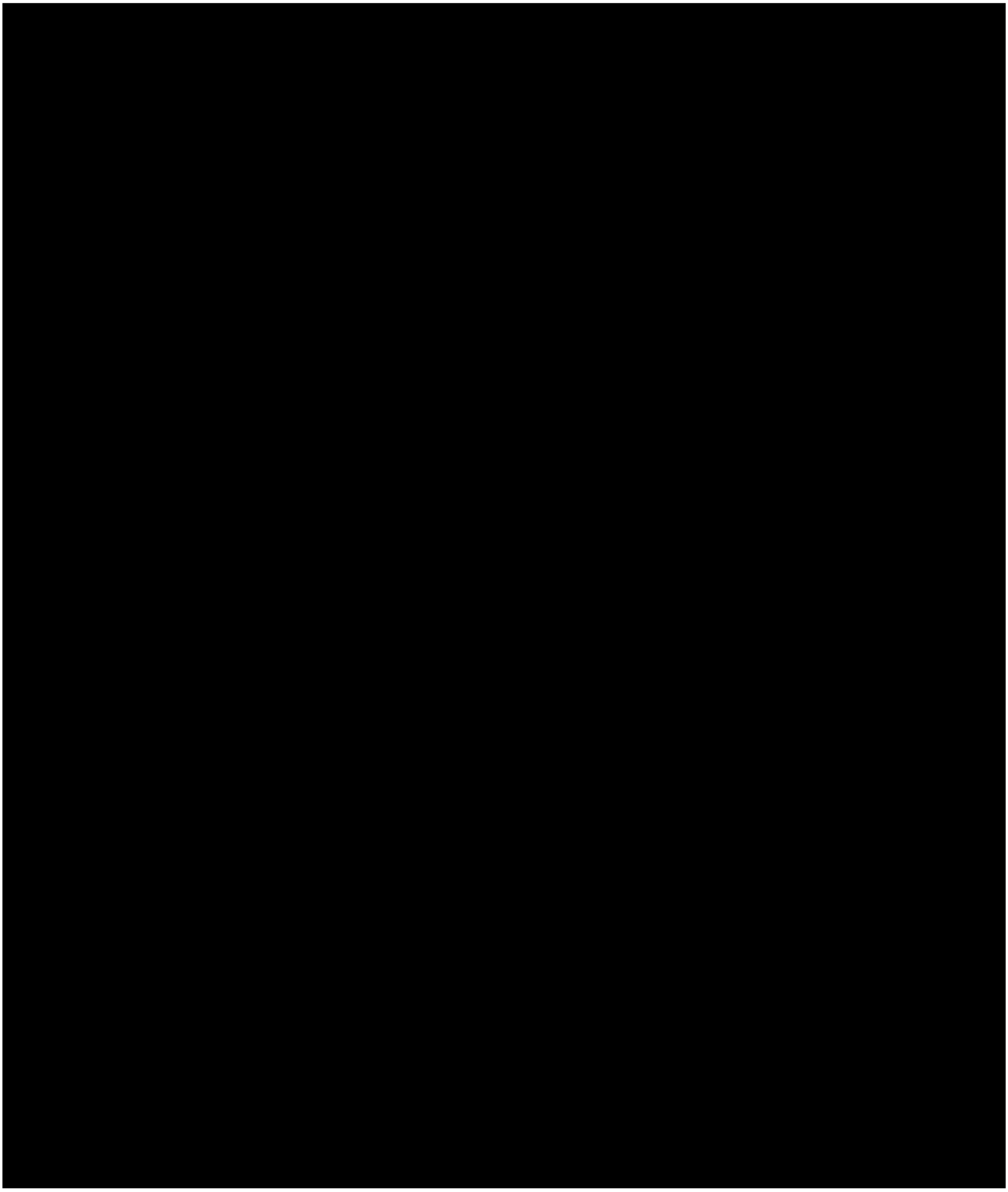
10.11 APPENDIX 11: LISTS OF CYP3A AND P-GP INHIBITORS AND INDUCERS

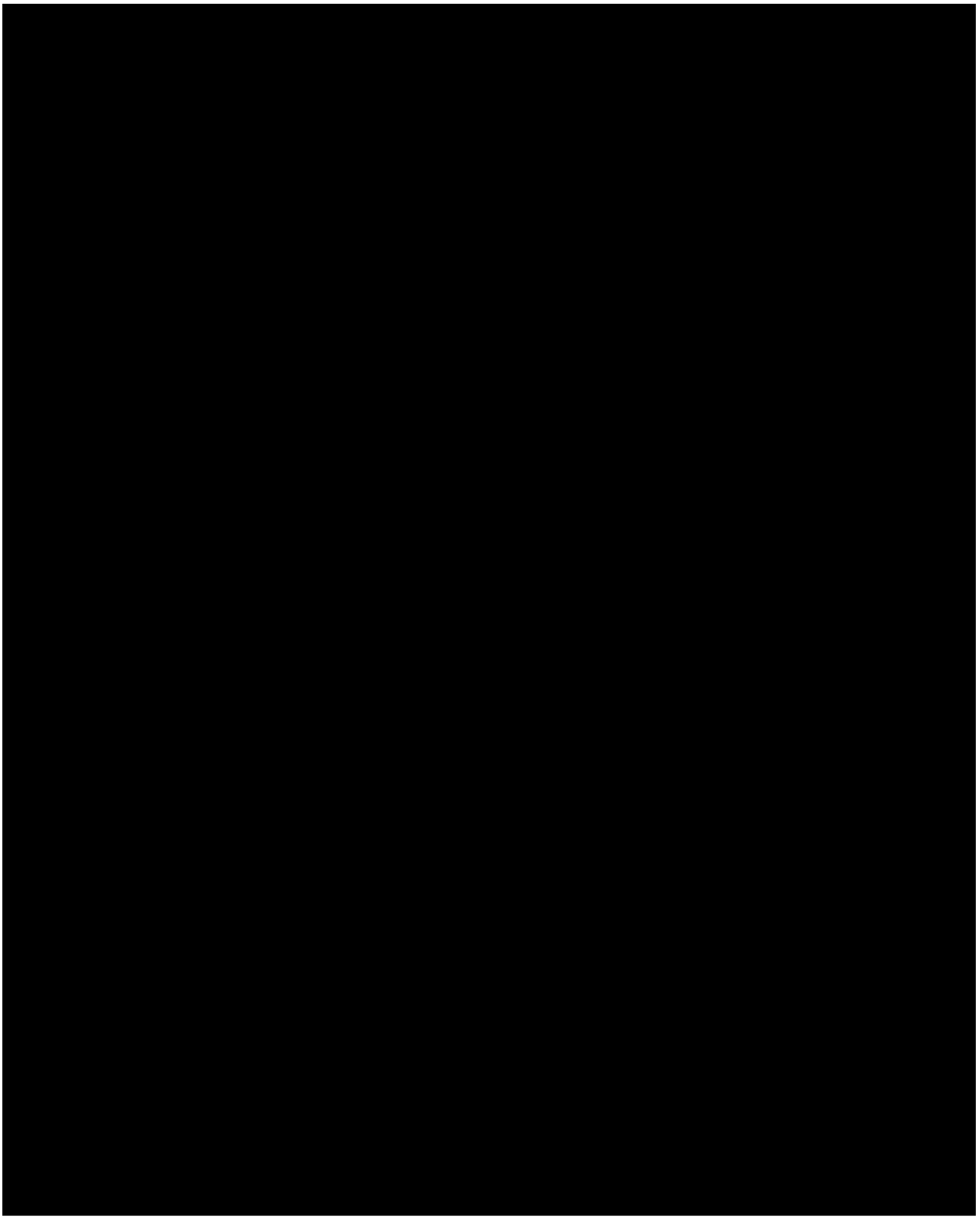
Concomitant administration of medications that are [redacted] of the study. [redacted] which triggered at least 2-fold changes of AUC of the victim probe[redacted] of the study.

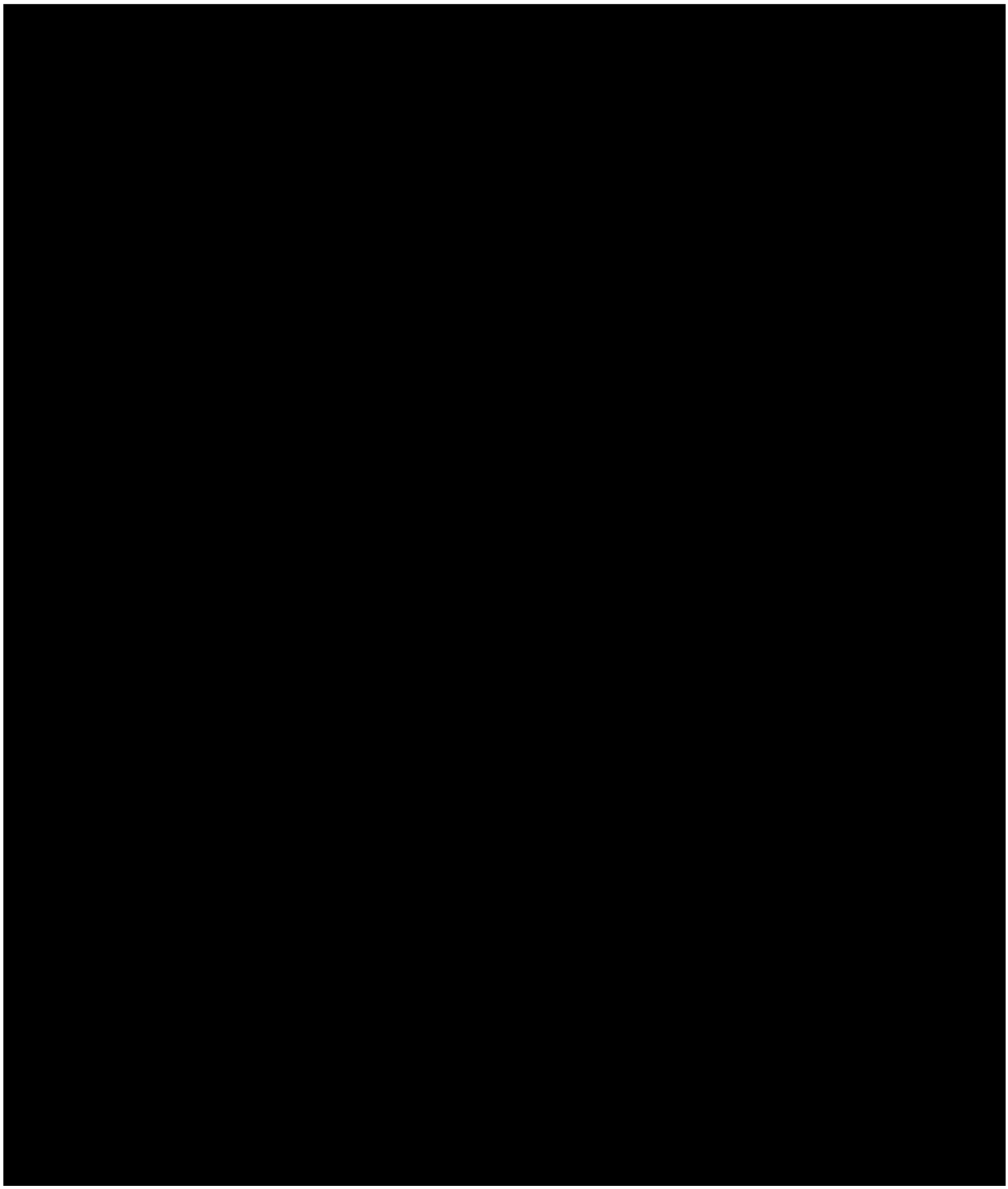
The following lists were extracted from the Drug Interaction Database from the University of Washington (www.druginteractionsolutions.org).

Note that the lists provided may not be exhaustive and that the product information of drugs intended for concomitant use should be consulted.

[redacted]







10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

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

10.13.1 Amended protocol 03 (04 December 2023)

This amended protocol (amendment 03) is considered to be non-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

This amendment is the result of the European Union (EU) consideration. It incorporates a specific country requirement for Czech Republic relative to TB exclusion criteria.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria – E30	The following statement has been added: "*b) have obtained consultation with a specialist to rule out or treat active TB infection* ***(for participants in the Czech Republic, see Section 10.7.4)****, AND*"	Country specific requirement
8.3.5 Tuberculosis assessment and QuantiFERON®	The last paragraph of the section has been amended to "*Participants with a positive screening test will not be eligible for the study. Participants with documented completed appropriate active/latent TB treatment would not be excluded if consultation with a specialist has been obtained to rule out or treat active TB infection* ***(for participants in the Czech Republic, see Section 10.7.4)*** *and Sponsor approval has been granted in writing (Refer to exclusion criteria E 30)."*	Country specific requirement
10.7.4 Czech Republic	The current section has been updated with the following wording: "*Participants with documented completed appropriate active or latent TB treatment would not be excluded from enrolment if their enrolment is approved by a TB specialist or an infectious diseases specialist.*"	Country specific requirement

10.13.2 Amended protocol 02 (22 November 2023)

This amended protocol (amendment 02) is considered to be non-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

This amendment is the result of the European Union (EU) consideration. It incorporates the recommendation to extend the follow-up period, update the frequency of urine pregnancy testing, clarify exclusion criteria related to washout period rules, incorporate drugs list that prolong QT interval, exclude incapacitated participants, clarify the rescue medication, clarify the process for including participants with active/latent TB treatment, provide interim analysis details, and to include specific country requirements for Czech Republic. In addition, medical photography assessments are no longer planned in this protocol and have been removed.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Considering the safety follow-up period, the previous wording "*2 weeks*" has been replaced by "*4 weeks*" 3 times in this section.	Extending the follow-up period to 4 weeks
1.2 Schema	Post-treatment has been changed from "*2 weeks*", "*Week14*" to "*4 weeks*", "*Week 16*"	Extending the follow-up period to 4 weeks
1.3 Schedule of Activities (SoA)	Post-treatment has been changed from *"2 weeks*" to "*4 weeks*"; corresponding End of Study day has been updated accordingly to Day 113 and "*Week 14*" to "*Week 16*".	Extending the follow-up period to 4 weeks
1.3 Schedule of Activities (SoA)	The row "*Optional: Medical Photography*[q]" has been deleted.	Medical photography is no longer planned in this protocol
1.3 Schedule of Activities (SoA)	Initial urine pregnancy testing planned at "*Screening and Weeks 0, 12*" have been updated to "*Screening and Weeks 0, 4, 8, 12 and 16 (EoS)*"	Setting-up the interval of the urine pregnancy testing to 4 weeks during IMP treatment in WOCBP, including at the EoS.
1.3 Schedule of Activities (SoA) - Footnotes	Footnote "*q*" related to "*Optional Medical Photography*" has been deleted. The order of the footnotes that followed has been updated both in the footnote part and in the SoA.	Medical photography is no longer planned in this protocol
4.4 End-of-study definition	Post-treatment period has been updated from "*2-week*", "*4-week*"	Extending the follow-up period to 4 weeks
5.2 Exclusion Criteria – E18	The first sentence of the E18 has been updated from "*Simultaneous treatment with phototherapy or the following systemic therapies, however participants can go through washout to be considered for the study. Emollients are accepted, as much as needed, during the duration of the study (see Table 5).*" to "*Simultaneous treatment with phototherapy or the following systemic therapies, however participants can go through washout to be considered for the study.* ***Participants should not be withdrawn from a treatment if the disease is well controlled in order to be considered for the study.*** *Emollients are accepted, as much as needed, during the duration of the study (see Table 5).*"	Wording update to avoid misinterpretation of E18
5.2 Exclusion Criteria – E20	Insert a reference to *Appendix 12: QT prolonging drug list*	Clarification
5.2 Exclusion Criteria – E29	The following statement has been added:"*(for participants in the Czech Republic, see Section 10.7.4)."*	Country specific requirement
5.2 Exclusion Criteria – E33	"*incapacitated*" has been explicitly added to the list of reasons indicating that a participant is not suitable for participation.	Wording update to avoid misinterpretation of E33

Section # and Name	Description of Change	Brief Rationale
6.9.4 Rescue medicine	The following indication has been added "*Topical corticosteroids of class least potent or mild (US class 6 or 7) (such as hydrocortisone) are permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits on Day 1, Week 4, 8 and 12.*"	Wording about the rescue medication needed to be explicit
8.2.11 Medical Photography (Optional) [*deleted*]	This section has been removed from the protocol.	Medical photography is no longer planned in this protocol
8.3.3 Electrocardiograms	Considering the safety follow-up period, the previous wording "*Week 14*" has been replaced by "*Week 16*".	Extending the follow-up period to 4 weeks
8.3.5 Tuberculosis assessment and QuantiFERON®	The last paragraph of the section has been amended to "*Participants with documented completed appropriate active/latent TB treatment would not be excluded* ***if consultation with a specialist has been obtained to rule out or treat active TB infection and Sponsor approval has been granted in writing (Refer to exclusion criteria E 30).***"	Clarification that participants with documented completed appropriate active/latent TB treatment would not be excluded from enrolment if a specialist consultation has been obtained as well as Sponsor approval.
9.3 Interim Analyses	An interim analysis will be performed. The section has been amended to: "*An interim analysis will be performed when approximately 70% of the participants in the primary analysis population have completed the Week 12 visit. The purpose of the interim analysis would be to provide early information for the Sponsor to plan for future development. The results of the interim analysis will not impact the conduct of the study. The SAP will describe the planned interim analysis in greater details.*"	Clarification
10.7.4 Czech Republic	The current section has been added with the following wording: "*Participants with positive HIV-1 or HIV-2 serology are excluded. Complete and targeted physical examinations may be performed only by a physician*."	Country specific requirement
10.12 Appendix 12: QT prolonging drug list	Appendix 10.12 has been included in the protocol to provide a list of drugs that prolong the QTcF interval with known risk for Torsades de Pointes or that can prolong the QT interval	Explicitly listing the concomitant medications known to prolong the QTcF interval
10.13 Appendix 13: Protocol amendment history	Appendix 12: Protocol amendment history is referred to Appendix13: Protocol amendment history in the current amendment	Table of Contents update

10.13.3 Amended protocol 01 (19 October 2023)

This amended protocol (amendment 01) is considered to be non-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 main rationale for the amendment pertaining to Japan is to align with the PMDA request. Following initial submissions in Japan, the PMDA requested changes to the HBsAg related

inclusion criteria for Japanese participants only. This amendment affects Appendix 10.7.3 of the study protocol. Japanese participants with a positive HBsAg are excluded.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
10.7.3 Japan (5.2 Exclusion Criteria E28; 1.3 Schedule of Activities; and Table 7)	"*Participants in Japan need to be tested for HBsAb, in addition to HBsAg and (IgM or total) HBcAb. Positive results for HBsAb, or HBsAg, or IgM or total HBcAb need to be confirmed by positive HBV-DNA.* *Participants with positive HBsAb or HBsAg or (IgM or total) HBcAb but negative (no detectable) HBV-DNA, are required to undergo HBV-DNA testing at Week 4, Week 8, Week 12.*" has been replaced by "*Participants in Japan need to be tested for HBsAb, in addition to HBsAg and (IgM or total) HBcAb. Positive results for HBsAb, **~~or HBsAg~~**, or IgM or total HBcAb need to be confirmed by positive HBV-DNA.* *Participants with positive **HBsAg are excluded.*** ***Participants with positive** HBsAb **~~or HBsAg~~** or (IgM or total) HBcAb but negative (no detectable) HBV-DNA, are required to undergo HBV-DNA testing at Week 4, Week 8, Week 12.*"	According to PMDA request, Japanese participants with a positive HBsAg are excluded.

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