AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: SAR156597

Efficacy and safety of SAR156597 in the treatment of diffuse cutaneous Systemic Sclerosis (dcSSc): A randomized, double blind, placebo controlled, 24 week, proof of concept study

STUDY NUMBER: ACT14604

VERSION DATE / STATUS: Approval date (09-Aug-2017) / Approved

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CLINICAL TRIAL SUMMARY

COMPOUND: SAR156597	**STUDY No.: ACT14604**
TITLE	Efficacy and safety of SAR156597 in the treatment of dcSSc: A randomized, double-blind, placebo-controlled, 24-week, proof of concept study
INVESTIGATOR/TRIAL LOCATION	International
PHASE OF DEVELOPMENT	2
STUDY OBJECTIVES	**Primary objective:** • To evaluate, in comparison with placebo, the efficacy of SAR156597 administered subcutaneously for 24 weeks on skin fibrosis in patients with dcSSc. **Secondary objectives:** • To evaluate the efficacy of SAR156597 compared to placebo on physical/functional disability in patients with dcSSc. • To evaluate the efficacy of SAR156597 compared to placebo on respiratory function in patients with dcSSc. • To evaluate the safety profile of SAR156597 compared to placebo in patients with dcSSc. • To evaluate the potential for immunogenicity anti-drug antibodies (ADA) response of SAR156597 in patients with dcSSc. • To evaluate the pharmacokinetics (PK) (trough plasma concentrations) of SAR156597 administered subcutaneously for 24 weeks. **Exploratory objectives:** • To explore the efficacy of SAR156597 compared to placebo on other manifestations of Systemic Sclerosis (SSc) (gastrointestinal, joint pain, cardiovascular, and renal manifestations) in patients with dcSSc. • To explore the effect of SAR156597 on the Quality Of Life in patients with dcSSc. • To measure the effect of SAR156597 on biomarkers of the disease activity and the interlukin-4/interlukin-13 pathway (IL-4/IL-13) pathway.
STUDY DESIGN	• Multinational, randomized, double-blind, placebo-control, 2 parallel groups • Patients will be randomized in a 1:1 ratio to receive subcutaneous (SC) administrations of either: - SAR156597 200 mg every week (qw) - Placebo qw • Randomization will be stratified based upon the patients' medical history of SSc-Interstitial Lung Disease (SSc-ILD) (yes or no).

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Systemic Sclerosis according to the American college of Rheumatology/The European League against Rheumatism (ACR/EULAR) 2013 criteria. I 02. Diffuse cutaneous form of SSc according to Leroy's criteria. I 03. Able and willing to sign the written informed consent form with comprehension of its contents and comply with the requirements of the study protocol. **Key exclusion criteria:** E 01. Age <18 years. E 02. Disease duration of >36 months from time of first non-Raynaud's phenomenon manifestation. E 03. Modified Rodnan Skin Score (mRSS) <10 or >35 at screening and baseline visits. E 04. History of vasculitis, active or in remission. E 05. Diagnosis of connective tissue disease (other than SSc) or overlap syndrome (eg, polymyositis/SSc).
Total expected number of patients	Approximately 94 randomized patients (47 patients per group)
STUDY TREATMENT(s) **Investigational medicinal products (IMPs)** **Formulation:** **Route of administration:** **Dose regimen:**	 SAR156597 or placebo • SAR156597 in lyophilized form (each vial containing 125 mg total of SAR156597 plus excipients, to be reconstituted with 1.1 mL of sterile water for injection to achieve a final concentration of 100 mg/mL of SAR156597). • Placebo in lyophilized form (each vial containing excipients, to be reconstituted with 1.1 mL of sterile water in order to achieve at least 1 mL of placebo for injection). SC qw

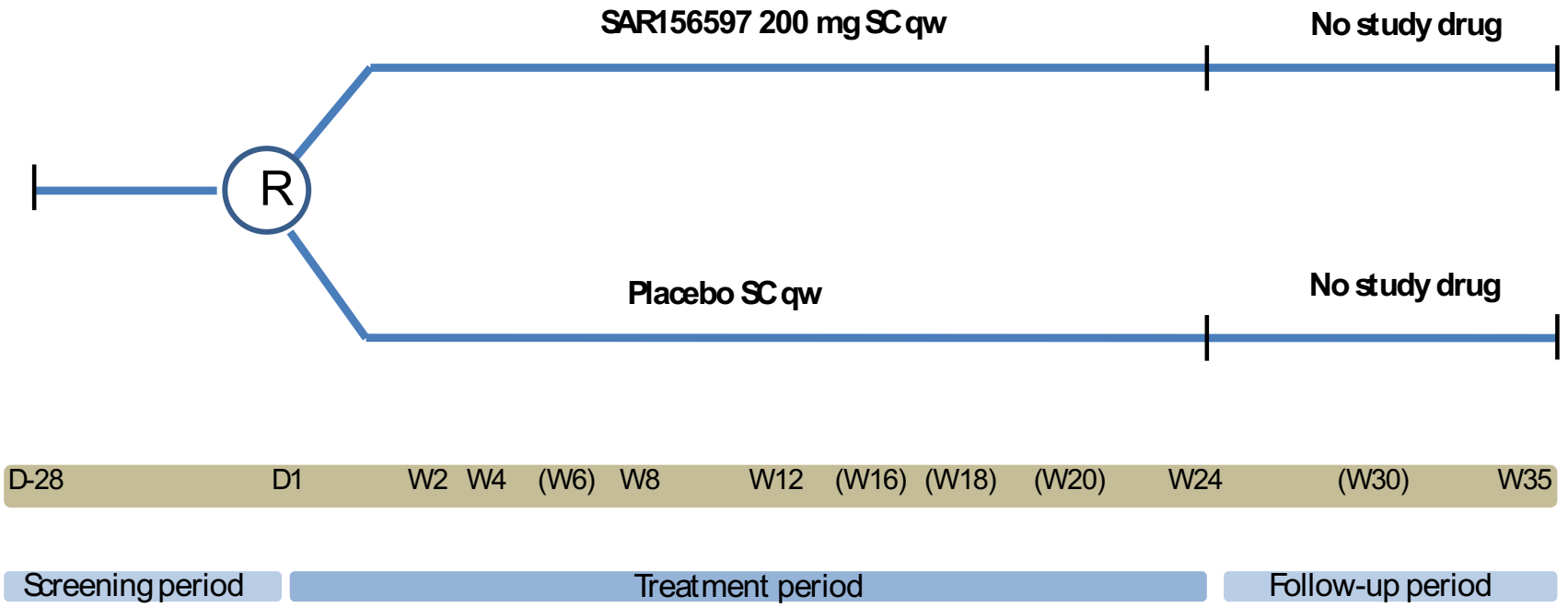
ENDPOINTS	**Efficacy** **Primary endpoint:** • Change in mRSS from baseline to Week 24. **Secondary endpoints:** • Change in Health Assessment Questionnaire Disability Index (HAQ-DI), assessed with Scleroderma health assessment questionnaire (SHAQ), from baseline to Week 24. • Change in respiratory function as measured by observed Forced Vital Capacity (FVC) and observed Carbon Monoxide Diffusing Lung Capacity (DLco [corrected for hemoglobin]) from baseline to Week 24. **Exploratory endpoints:** • Proportion of patients with improvement in mRSS of at least 20%, 40% and 60% from baseline to Week 24. • Change in Visual Analog Scales (VAS) for pain, breathing function, vascular function (Raynaud's phenomenon), gastrointestinal function, digital ulcers, and global assessment from SHAQ from baseline to Week 24. • Change in respiratory function as measured by % predicted FVC and % predicted DLco (corrected for hemoglobin) from baseline to Week 24. • Change in UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) score from baseline to Week 24. • Change in Tender Joint Count 28 (TJC28) from baseline to Week 24. • Change in digital ulcer count from baseline to Week 24. • Composite Response Index for diffuse cutaneous Systemic Sclerosis (CRISS) from baseline to Week 24. • Change in EQ-5D-5L index from baseline to Week 24. • Change in efficacy endpoints (mRSS, HAQ-DI, VAS from SHAQ, observed FVC, % predicted FVC, observed DLco [corrected for hemoglobin], % predicted DLco [corrected for hemoglobin], UCLA SCTC GIT 2.0, TJC28, digital ulcer count, CRISS, and European Quality of Life-5 Dimension-5 Level [EQ-5D-5L]) from baseline to Week 35 (up to end of follow-up period) and proportion of patients with improvement in mRSS of at least 20%, 40% and 60% from baseline to Week 35. • Proportion of patients with improvement in SHAQ (HAQ-DI and VAS) and EQ-5D-5L (index value and VAS) based upon Minimally Important Change (MIC) at Week 24. **Safety:** • Adverse events (AEs)/treatment-emergent adverse events (TEAEs) • Physical examination and body weight • Vital signs and 12-lead electrocardiogram (ECG) • Clinical laboratory evaluations including hematology, biochemistry and urinalysis

	• Tolerability at the IMP injection site: - Erythema/redness (diameter and graded severity) - Swelling/induration/edema (diameter and graded severity) - Pain assessment. **Immunogenicity:** • Testing for ADA **Pharmacokinetics:** • SAR156597 plasma concentrations **Biomarkers:** • Measurement of protein biomarkers associated with the activity of the disease (COMP, CCL2) and the IL-4/IL-13 pathway (TARC, periostin, and eotaxin-3). • Archived blood samples for future assays of protein and mRNA biomarkers related to the disease and the response to therapy (requires separate informed consent).
ASSESSMENT SCHEDULE	The study will comprise 8 on-site visits AND 4 phone calls: • Visits: - V1 (screening visit) between Day -28 and Day -1. - V2 (baseline visit) at Day 1 (first dosing). - Treatment period*: V3 at Week 2, V4 at Week 4, V5 at Week 8, V6 at Week 12, V7 at Week 24. - V8 (End-of-Study [EOS] visit) at Week 35. - A time window of ±2 days will be allowed for each visit. • Phone calls: - For safety considerations phone calls will be made at Week 6, 16 and 20 during the treatment period, and at Week 30 during the follow-up period. *IMP administration given qw starting at V2 with the last dose given at Week 23.
STATISTICAL CONSIDERATIONS	**Sample size determination:** Ninety-four (94) patients (47 patients per group) will yield 80% power to detect a difference versus placebo group of 3.6 in the mean change from baseline in mRSS at 24 weeks, assuming a standard deviation (SD) of 7 and using a 1-sided alpha of 5% (type I error). The impact of treatment discontinuations in the context of an intent-to-treat (ITT) analysis where all mRSS data will be included in the analysis (regardless of adherence to treatment) was evaluated. Assuming that 10% of patients will discontinue the treatment, the estimated treatment effect at 24 weeks will be decreased from 4 (targeted treatment effect if all patients adhered to treatment) to 3.6 (targeted treatment effect in all randomized patients). **Analysis population:** The efficacy population will be the ITT population, which includes all randomized patients. Patients in the ITT population will be analyzed according to the

	treatment group allocated by randomization. The safety population will include all randomized patients who received at least 1 dose or part of a dose of the IMP. Patients in the safety population will be analyzed in the treatment group as actually received. Patients receiving more than 1 study treatment during the trial will be analyzed in the treatment group from which they received the majority of injections. **Primary efficacy analysis:** All measurements are assigned to analysis windows in order to provide an assessment for Week 4 to Week 24 time points. With regards to the primary efficacy analysis, the change in mRSS from baseline to Week 24 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available from Week 4 to Week 24 analysis windows will be used and missing data will be accounted for by the MMRM. The model includes the fixed categorical effects of treatment group, randomization strata, time points (Week 4 to Week 24), randomization strata-by-time point interaction and treatment-by-time point interaction, as well as the continuous fixed covariates of baseline mRSS value and baseline value-by-time point interaction. This model will provide baseline adjusted least-squares means (LSmeans) estimates at Week 24 for both treatment groups with their corresponding 95% confidence interval. To compare SAR156597 to the placebo group, an appropriate statement will be used to test the differences of these estimates at the 5% one sided alpha level. The 95% and 90% confidence intervals of the difference will be provided. **Analysis of secondary efficacy endpoints:** Continuous secondary efficacy endpoints will be analyzed using the same MMRM model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. **Safety:** Safety analyses will be descriptive, based on the safety population. The safety analysis will focus on the TEAE period. This period is defined as the time from the first administration of the IMP to the last administration of the IMP + 12 weeks.
DURATION OF STUDY PERIOD (per patient)	The study can last up to 39 weeks per patient as follows: • 4 weeks of screening. • 24 weeks of study treatment. • 11 weeks of follow-up with no study treatment.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R: randomization
SC: subcutaneous
D: day
W: week
qw: once a week

1.2 STUDY FLOW CHART

Period	Screening	Baseline visit	Treatment period									FU	
Visits/phone calls	**V1**	**V2**[a,b]	**V3**	**V4**	**Phone call**	**V5**	**V6**[r]	**Phone call**	**IVRS call**[r]	**Phone call**	**V7**[s] **(EOT)**	**Phone call**	**V8 (EOS)**
Day/Week	**D-28 to D-1**	**D1**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W18**	**W20**	**W24**	**W30**	**W35**
Informed consent	X												
Patient Demography	X												
Medical/surgical history	X												
Prior/concomitant medications	X	X	X	X	X	X	X	X		X	X	X	X
Inclusion/exclusion criteria	X	X											
Randomization		X											
Call IVRS	X	X	X	X		X	X		X		X		X
Study treatment administration													
SAR156597 or placebo[c]		Å----------									----------Æ		
Safety													
Physical examination[d]	X	X	X	X		X	X				X		X
Vital signs[e]	X	X	X	X		X	X				X		X
ECG[f]	X	X		X		X	X				X		X
Echocardiogram[g]	X												
Hematology, biochemistry, urinalysis[h]	X	X		X		X	X				X		X
Serology tests[i]	X												
[redacted]													
Tuberculosis screen[k]	X												
ß-HCG blood test[l]	X												
Urine pregnancy test[l]		X		X		X	X	X		X	X		X
Review patient booklet (Local tolerability of SC		X (post-dose)----------									----------/E		

injections/IMP compliance)[m]													
Period	**Screening**	**Baseline visit**	**Treatment period**									**FU**	
Visits/phone calls	**V1**	**V2**[a,b]	**V3**	**V4**	**Phone call**	**V5**	**V6**[r]	**Phone call**	**IVRS call**[r]	**Phone call**	**V7**[s] **(EOT)**	**Phone call**	**V8 (EOS)**
Day/Week	**D-28 to D-1**	**D1**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W18**	**W20**	**W24**	**W30**	**W35**
Adverse event reporting	X	X	X	X	X	X	X	X		X	X	X	X
Pharmacokinetics													
Blood samples for PK		X		X		X	X				X		X
Blood samples for ADA	X	X		X		X	X				X		X
Efficacy													
mRSS	X	X		X		X	X				X		X
SHAQ		X		X		X	X				X		X
PFTs (FVC & DLco)	X	X					X				X		X
UCLA SCTC GIT 2.0		X		X		X	X				X		X
Digital Ulcer Count		X		X		X	X				X		X
Tender Joint Count 28		X		X		X	X				X		X
CRISS[n]							X				X		X
Patient Global Assessment[o]		X		X		X	X				X		X
Physician Global Assessment[p]		X		X		X	X				X		X
EQ-5D-5L		X					X				X		X
Resource Utilization[q]		X					X				X		X
Blood samples for protein biomarkers analysis		X					X				X		X
Future Use of Sample: Archived blood samples for future protein assays and mRNA (Optional and requires signing of separate ICF)		X					X						X

a Randomization/baseline Visit is defined as Day 1. Visit windows for subsequent visits are ±2 days

b All assessments at Visit 2 (Day 1) are to be conducted pre dose with the exception of the assessment of local tolerability of SC injections

c Study treatment is to be administered once a week, either at the site or at home by a qualified healthcare professional – Last dose will be given at Week 23

d Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. For the dermatological examination the Investigator should evaluate for SSc related skin changes and some specific findings that may indicate vasculitis including, but not limited to: purpura, papules or non-blanching rashes. Nail beds (periungual areas) should be examined for “splinter lesions” and digital tuft for tuft purpura or ischemia. Gynecological and urogenital examinations will not be done in this study unless for cause

e Vital signs, including blood pressure (mmHg), heart rate (beats per minute) and body weight (kg) will be measured at screening, baseline and every subsequent visit. Height (cm) will be measured at screening (Visit 1) only. BMI will be calculated automatically at all visits

f All abnormal ECG interpretation will be reviewed and confirmed by a local cardiologist.

g Previous echocardiogram may be used if obtained within 6 months of V1 (screening visit).

h Hematology: Hemoglobin, hematocrit, red blood cell count, erythrocyte sedimentation rate (ESR), white blood cell count with differential and platelet count. Biochemistry: Fasting glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, CPK, hs CRP. Urinalysis (dipstick) to include: specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory

i Serology testing includes HIV-1/HIV-2 antibody, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B DNA (reflex to a positive hepatitis B core antibody), hepatitis C antibody and hepatitis C RNA (reflex to a positive hepatitis C antibody)

j [redacted]

k Tuberculosis screen: history and QuantiFERON-TB Gold test. If the result of the initial QuantiFERON-TB Gold test is indeterminate, the test should be repeated one time

l In women of child-bearing potential. After Visit 6 (W12) and until subsequent study visit the patient will have a urine pregnancy test at home on a monthly basis. Patients will be given sufficient urine pregnancy kits to take home for monthly testing up until the end-of-study visit. When the testing coincides with a study visit as indicated in the flow chart, the results should be reported in the e-CRF. When the testing is done at home between study visits, the results should be collected by the Investigator during the monthly phone calls (Week 16 and Week 20) and reported in the electronic case report form (e-CRF). If any interim urine pregnancy test performed by the patient is positive, the patient should immediately report to the investigator for appropriate follow-up and pregnancy reporting as appropriate

m Local tolerability of SC injections will be assessed by the study nurse either at patient's place or at the site for the inter-visit SC injection given once a week. One patient booklet to record information on injections administered at home will be provided to the patient at baseline and will be reviewed at each visit by Investigator

n Step 1 of CRISS will be assessed based upon available data and individual components of Step 2 of CRISS will be captured through other efficacy procedures (eg, Change in mRSS, HAQ-DI, patient and physician global assessments and FVC)

o This will be assessed using a Likert scale for CRISS calculations and will be a separate assessment from the global assessment conducted for the SHAQ using a VAS.

p This will be assessed using a Likert scale for CRISS calculations.

q Health care resources will include hospitalizations (reason, number of days per hospital admission, date of entry, date of discharge from hospital), number of out-patients visits by type (gastroenterologist, pulmonologist, occupational therapist, psychiatrist, physiotherapist, other), sick leaves (number of day off from work) and caregiver support (time spent per day to take care of the patient, number of days off from work to take care of the patient)

r An additional IVRS call will need to be made at Week 18 for IMP dispensation. Only 6 weeks of IMP will be dispensed with the IVRS call made at Visit 6 (W12)

s If a patient discontinues treatment before Week 24, a Premature/Early End-of-Treatment Visit (as labelled in the e-CRF) will be performed employing all assessments and procedures associated with EOT (V7). Irrespective of the timing of early treatment discontinuation, every effort should be undertaken to continue the patient in the study by conducting all the remaining scheduled visits on time including Week 24 (V7), and the End-of-Study visit at Week 35 (V8).

Abbreviations: ADA = anti-drug antibodies; ALT = Alanine transaminase; ANA = anti-nuclear antibodies; ANCA = anti-neutrophil cytoplasmic antibodies; AST = aspartate transaminase; β-HCG = beta-human chorionic gonadotropin; CD4 = T helper cells; CD8 = T suppressor cells; CD19 = total B cells; CPK = creatinine phosphokinase; CRISS = Composite Response Index for diffuse cutaneous Systemic Sclerosis; D = day; DLco = Carbon Monoxide Diffusing Lung Capacity; ECG = electrocardiogram; e-CRF = electronic case report form; EOT = end-of-treatment; EOS = end-of-study; EQ-5D-5L = European Quality of Life-5 Dimension-5 Level; ESR = erythrocyte sedimentation rate; FVC = forced vital capacity; FU = follow-up; HAQ-DI = Health Assessment Questionnaire Disability Index; HIV = Human Immunodeficiency Virus; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; IVRS = interactive voice response system; Mrss = modified Rodnan Skin Score; PFTs = Pulmonary function tests; PK = pharmacokinetics; RF = rheumatoid factor; SC = subcutaneous; SHAQ = Scleroderma Health Assessment Questionnaire; UCLA SCTC GIT 2.0 = University of California at Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0; V = Visit; VAS = visual analog scale; W = week.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

2.2 LIST OF FIGURES

Not Applicable.

3 LIST OF ABBREVIATIONS

ACE:	angiotensin-converting enzyme
ACR/EULAR:	American college of Rheumatology/European League against Rheumatism
ADA:	anti-drug antibodies
AEs:	adverse events
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine transaminase
ANA:	anti-nuclear antibodies
ANCA:	anti-neutrophil cytoplasmic antibodies
ANCOVA:	analysis of covariance
AST:	aspartate transaminase
AUC:	area under curve
BCG:	bacillus Calmette-Guérin
BMI:	body mass index
BP:	blood pressure
CD19:	total B cells
CD4:	T helper cells
CD8:	T suppressor cells
CIRs:	clinically important responders
C_{max}:	peak plasma concentrations
CNS:	central nervous system
CPK:	creatinine phosphokinase
CRISS:	composite response index for diffuse cutaneous systemic sclerosis
CRP:	C-reactive protein
CV:	curriculum vitae
CV%:	coefficient of variation
dcSSc:	diffuse cutaneous Systemic Sclerosis
DLco:	carbon monoxide diffusing lung capacity
DMC:	data monitoring committee
DRF:	discrepancy resolution form
DTP:	duties and taxes paid
ECG:	electrocardiogram
e-CRF:	electronic case report form
ELISA:	enzyme-linked immunosorbent assay
EOS:	end-of-study
EOT:	end-of-treatment
EQ-5D-5L:	European Quality of Life-5 Dimension-5 Level
ESR:	erythrocyte sedimentation rate
FVC:	forced vital capacity
GCP:	good clinical practice
HAQ-DI:	health assessment questionnaire disability index

HBcAb:	hepatitis B core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
HBV DNA:	hepatitis B DNA
HCV Ab:	hepatitis C virus antibody
HEOR:	health economics and outcome research
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
HRCT:	high resolution computer tomography
hsCRP:	high-sensitivity C-reactive protein
IB:	investigator's brochure
IEC:	independent ethics committee
Ig-G4:	immunoglobulin-G4
IL-13:	interleukin-13
IL-4:	interleukin-4
IL-4/IL-13 pathway:	interlukin-4/interlukin-13 pathway
ILD:	interstitial lung disease
IMPs:	investigational medicinal products
IPF:	idiopathic pulmonary fibrosis
IRB:	institutional review board
ITT:	intent to treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
IVIG:	intravenous immunoglobulin
IVRS:	interactive voice response system
lcSSc:	limited cutaneous systemic sclerosis
LSmeans:	least-squares means
MAD:	maximal administered doses
MedDRA:	Medical Dictionary for Regulatory Activities
MIC:	minimally important change
MMRM:	mixed-effect model with repeated measures
mRSS:	modified Rodnan Skin Score
MTD:	maximal tolerated dose
NK:	natural killer
NOAEL:	no observed adverse effect level
PAH:	pulmonary arterial hypertension
PCSA:	potentially clinically significant abnormality
PFTs:	pulmonary function tests , pulmonary function tests
PK:	pharmacokinetics
PNS:	peripheral nervous system
PROs:	patient reported outcome
PT:	preferred term
QALYs:	quality adjusted life years
qw:	every week
RF:	rheumatoid factor

SAEs:	serious adverse events
SC:	subcutaneous
SD:	standard deviation
SEM:	standard error of measurement
SHAQ:	scleroderma health assessment questionnaire
SMQ:	standardized MedDRA query
SOC:	system organ class
SSc:	systemic sclerosis
SSc-ILD:	SSc-Interstitial Lung Disease
SUSAR:	suspected unexpected adverse drug reaction
t1/2z:	terminal elimination half-life
TBILI:	total bilirubin
TEAEs:	treatment emergent adverse events
TH2:	T helper type 2
TJC28:	tender joint count 28
UCLA SCTC GIT 2.0:	UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0
ULN:	upper limit of normal range
VAS:	visual analog scales
WBC:	white blood cell
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

Systemic sclerosis (or scleroderma) is a chronic disabling condition characterized by three pivotal features: immune dysregulation, small vessel vasculopathy, and fibrosis. There are two major subgroups in the commonly accepted classification of SSc: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (1). In lcSSc, fibrosis is restricted to the distal upper and lower extremities, with possible facial involvement. While the fibrosis will tend to stabilize within the first several years of development, the condition may continue to evolve in the internal organs particularly in the lungs resulting in the development of pulmonary arterial hypertension (PAH) which is the leading cause of mortality associated with lcSSc in its later stages. In contrast, dcSSc is a rapidly progressive disorder that affects a larger area of the skin beyond the limited form with truncal manifestation likely. These patients will often have early internal organ involvement and more significant systemic symptoms such as arthralgia, tendon friction rubs and weight loss. Although skin fibrosis is the distinguishing hallmark, the pathological changes in the lungs, gastrointestinal tract, kidneys and heart ultimately determine the clinical outcome. The extent of skin involvement and its rate of progression, however, may reflect the severity of the visceral organ complications (2), outcome and survival (3). Survival in patients with dcSSc has improved over the last several decades; currently the average 10-year survival is estimated to be approximately 70% to 80%. Mortality associated with renal crisis has significantly declined during the last couple of decades with the use of angiotensin-converting enzyme (ACE) inhibitors while pulmonary involvement is the leading cause of death in these patients (4, 5, 6, 7).

The prevalence of SSc in 2014 is estimated to be around 120 000 persons in the US and EU5 nations combined with over 60% of the cases being of the diffuse form. The prevalence may increase by as much as 20% in the future using the new ACR/EULAR 2013 (8) classification criteria which is more sensitive than the previous ACR 1980 criteria. Overall, the disease is more frequent in women (3-6:1) and in certain races (eg, black).

Currently, there is no approved therapy for SSc. The general therapeutic strategy is to address specific SSc manifestations (eg, Raynaud's phenomenon, digital ulcers, gastrointestinal involvement, PAH) while controlling any underlying inflammatory process of the skin or internal organs with the use of potent immunosuppressive therapies (eg, cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, rituximab). Because these immunosuppressive therapies do not target specific pathways related to the fibrotic process, they are not particularly effective and are often fraught with significant side effects. Thus, there is an unmet need to find effective targeted therapies with limited side effect profile for this disease population.

T helper type 2 (TH2) cytokines, including interleukin-4 (IL-4) and interleukin-13 (IL-13), have prominent roles in the pathogenesis of SSc and are promising targets. The levels of TH2 cytokines are increased in the serum and fibrotic tissues, and they stimulate fibroblast proliferation and extracellular matrix synthesis in cell cultures (9). These findings are supported by studies in animal models, as illustrated by the attenuation of fibrosis in mice with the genetic deletion of IL-13, whereas targeted overexpression of IL-13 results in pulmonary fibrosis (10). Similarly, increased IL-4 activity has been described in the fibrotic pathway (11, 12).

SAR156597 is an engineered humanized bispecific immunoglobulin-G4 (Ig-G4) antibody that binds and neutralizes both IL-4 and IL-13. It utilizes an innovative tetravalent bispecific tandem immunoglobulin format to combine the antigen binding domains of an anti-IL-4 antibody and an anti-IL-13 antibody into a single molecule. SAR156597 shows high affinity for IL-4 and IL-13 from both humans and cynomolgus monkeys, and each antibody has binding sites for 2 IL-4 and 2 IL-13 cytokines. SAR156597 has the potential to provide benefits to patients with SSc by targeting these pro fibrotic pathways.

Clinical Studies

A placebo-controlled first time in man study (TDU11325 study) has shown that single SC doses ranging from 10 to 300 mg were safe and well tolerated in healthy subjects. After single SC administration of SAR156597 at doses of 10 to 300 mg, peak concentrations of SAR156597 in plasma (C_{max}) occurred, on average, 4 to 7 days after administration. SAR156597 exposure increased with dose but in a less than dose proportional manner. The overall terminal elimination half-life ($t_{1/2z}$) was about 15 days and was independent of dose over the dose range of 10 to 300 mg. Low titers of ADA were detected and confirmed in post-dose plasmas from 4 of 36 subjects who received SAR156597.

The repeated ascending dose study (TDR11326) was conducted in patients with Idiopathic Pulmonary Fibrosis (IPF) to evaluate the safety, tolerability, PK and pharmacodynamics of 3 dose levels of SAR156597 (50, 100, and 200 mg) administered SC once a week over a 6-week period (7 administrations) according to a double-blind, randomized, placebo-controlled, sequential

design. A total of 24 patients with IPF were randomized (6 in the placebo group and 18 in the SAR156597 groups). SAR156597 was generally safe and well tolerated. The most commonly reported AEs were infections with a comparable incidence across treatment groups. No significant emergent ADA reactivity developed as a consequence of treatment with SAR156597. Steady state of SAR156597 was achieved on Day 43 for all doses. The results of pharmacodynamic data showed that SAR156597 reduced, in an apparent dose-dependent manner from 50 to 200 mg once a week, the plasma level of TARC (or CCL17), a protein directly induced by IL-4 and IL-13 receptor activation. SAR156597 is currently in Phase 2b of clinical development for the treatment of IPF.

More detailed information is provided in the Investigator's Brochure (IB).

ACT14604 Study

The ACT14604 study will evaluate the efficacy and safety of SAR156597 administered subcutaneously over a 24-week period for the treatment of patients with dcSSc. It will be a multinational, randomized, double-blind, placebo-controlled, 2 parallel group study conducted in patients diagnosed with dcSSc.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate, in comparison with placebo, the efficacy of SAR156597 administered subcutaneously for 24 weeks on skin fibrosis in patients with dcSSc.

5.2 SECONDARY

- To evaluate the efficacy of SAR156597 compared to placebo on physical/functional disability in patients with dcSSc.
- To evaluate the efficacy of SAR156597 compared to placebo on respiratory function of patients with dcSSc.
- To evaluate the safety profile of SAR156597 compared to placebo in patients with dcSSc.
- To evaluate the potential for immunogenicity (ADA response) of SAR156597 in patients with dcSSc.
- To evaluate the PK (trough plasma concentrations) of SAR156597 administered subcutaneously for 24 weeks.

5.3 EXPLORATORY

- To explore the efficacy of SAR156597 compared to placebo on other manifestations of SSc (gastrointestinal, joint pain, cardiovascular and renal manifestations) in patients with dcSSc.
- To explore the effect of SAR156597 on the Quality Of Life in patients with dcSSc.
- To measure the effect of SAR156597 on biomarkers of the disease activity and the IL-4/IL-13 pathway.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study will be a multinational, randomized, double-blind, placebo-controlled, 2 parallel groups, proof of concept Phase 2 study to assess the efficacy and safety of SAR156597 200 mg administered subcutaneously once a week over a 24 week period to patients with diffuse SSc. Approximately 94 patients will be randomized in a ratio 1:1 to the following two treatment groups:

- SAR156597 group (n = 47): Patients will receive SAR156597 administered subcutaneously in 200 mg doses qw
- Placebo group (n = 47): Patients will receive placebo subcutaneously qw.

Randomization will be stratified based upon the patients' medical history of SSc-ILD (yes or no).

For a schematic presentation and a detailed flow chart, please refer to Section 1.2.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study can last up to 39 weeks as follows:

- 4 weeks of screening
- 24 weeks of study treatment
- 11 weeks of follow-up with no study treatment.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day the last patient completes his/her last visit planned in the protocol.

6.3 INTERIM ANALYSIS

A futility analysis will be conducted, if needed. A two-step analysis will be performed. Please refer to Section 11.5.

6.4 STUDY COMMITTEES

Data Monitoring Committee

A Data Monitoring Committee (DMC) will be charged with monitoring the safety of the patients participating in this clinical trial. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The DMC will, in due time, give appropriate recommendations to the Sponsor on safety aspects during the conduct of the study, if needed. The DMC is justified by the early stage of development of SAR156597 in patients with SSc. The DMC responsibilities and the data review processes are fully described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Systemic Sclerosis according to the ACR/EULAR 2013 criteria (8).

I 02. Diffuse cutaneous form of SSc according to Leroy's criteria.

I 03. Able and willing to sign the written informed consent form with comprehension of its contents and comply with the requirements of the study protocol.

7.2 EXCLUSION CRITERIA

E 01. Age <18 years of age.

E 02. Disease duration of >36 months from time of first non-Raynaud's phenomenon manifestation.

E 03. mRSS <10 or >35 at screening and baseline visits.

E 04. History of vasculitis, active or in remission.

E 05. Diagnosis of connective tissue disease (other than SSc) or overlap syndrome (eg, polymyositis/SSc).

E 06. Positive Human Immunodeficiency Virus (HIV) serology or a known history of HIV infection, active or in remission.

E 07. Abnormal hepatitis B and/or hepatitis C tests indicative of active or chronic infection:

- Abnormal Hepatitis B tests: Positive hepatitis B surface antigen (HBsAg) OR positive total hepatitis B core antibody (HBcAb) with negative hepatitis B surface antibody (HBsAb) OR positive total HBcAb with positive HBsAb and presence of hepatitis B DNA (HBV DNA).
- Abnormal Hepatitis C tests: Positive anti-hepatitis C virus antibody (HCV Ab) and positive HCV RNA.

E 08. Positive or 2 confirmed indeterminate Quantiferon-TB Gold tests at screening (regardless of prior treatment status).

E 09. Serious infection (eg, pneumonia, pyelonephritis) within 4 weeks of screening, infection requiring hospitalization or intravenous antibiotics within 4 weeks of screening or chronic bacterial infection (eg, osteomyelitis).

E 10. History of anaphylaxis to any biologic therapy.

E 11. Evidence of any clinically significant, severe or unstable, acute or chronically progressive, uncontrolled infection or medical condition (eg, cerebral, cardiac, pulmonary, renal, hepatic, gastrointestinal or neurologic other than SSc or SSc-ILD) or previous, active or pending surgical disorder, or any condition that may affect patient safety in the judgment of the investigator.

E 12. At screening, the % predicted forced vital capacity (FVC) is ≤75% AND % predicted carbon monoxide diffusing lung capacity (DLCO) after hemoglobin correction is ≤40%

E 13. History of heart failure (including acutely decompensated in the setting of preserved ejection fraction), Left Ventricular Ejection Fraction (LVEF) ≤ 45%, coronary artery disease, angina, myocardial infarction, ischemic cardiomyopathy and/or hypertrophic cardiomyopathy

E 14. Any prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully-treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to baseline.

E 15. Ischemic ECG changes (except those NOT supported by the findings of a left heart catheterization performed in the last year within screening) and/or other clinically significant ECG findings (Appendix L) at screening. (All abnormal ECG finding will be reviewed and confirmed by a local cardiologist.)

E 16. High dose steroids (>10 mg/day prednisone equivalent); or a change in steroid dose within 4 weeks prior to randomization (or baseline visit); or expected changes during the course of the study.

E 17. Previous treatment with rituximab within 12 months prior to screening.

E 18. Previous treatment with bone marrow transplantation, total lymphoid irradiation or ablative ultra-high dose cyclophosphamide.

E 19. Treatment with high dose immunosuppressive drug (eg, cyclophosphamide >1 mg/kg oral/day or >750 mg IV/month; azathioprine >100 mg/day; methotrexate >15 mg/week; mycophenolate mofetil >2 g/day) within 3 months of screening or a change in dose within 4 weeks prior to randomization (or baseline visit); or expected changes in dose during the course of the study.

E 20. Treatment with etanercept, cyclosporine A, intravenous immunoglobulin (IVIG), rapamycin, D-penicillamine, tyrosine kinase inhibitors within 4 weeks of screening or antithymocyte globulin within 6 months of screening.

E 21. Treatment with infliximab, certolizumab, golimumab, abatacept, or adalimumab, tocilizumab within 8 weeks of screening or anakinra within 1 week of screening.

E 22. Treatment with any investigational drug within 1 month of screening, or 5 half-lives, if known (whichever is longer).

E 23. Abnormal laboratory test(s) at screening:

- Alanine transaminase (ALT) or aspartate transaminase (AST) >2 times upper limit of normal range (ULN)
- Hemoglobin <11 g/100 mL for male and <10 g/100 mL for female
- Neutrophils <1500/mm^3 (except <1000/mm^3 for those of African descent)
- Platelets <100 000/mm^3
- Creatinine ≥150 µmol/L.

Note: Laboratory parameters may be repeated once during the screening period if felt to be spurious or due to technical error in order to determine eligibility.

E 24. Current history of substance and/or alcohol abuse

E 25. Current employee of Sanofi or has an immediate family member (eg, spouse, parents, child or sibling) who is a current employee of Sanofi.

E 26. Currently incarcerated or anticipated/scheduled to be incarcerated during the course of the study.

E 27. Any condition or circumstance that will preclude the patient from following and completing protocol requirements, in the opinion of the Investigator.

E 28. Pregnant or breastfeeding woman

E 29. Women who are of childbearing potential not protected by highly-effective contraceptive method(s) of birth control (defined in the informed consent form and/or Appendix G for United Kingdom), and/or who are unwilling or unable to be tested for pregnancy.

Note: Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use an effective contraceptive method throughout the entire duration of the study treatment, and for at least 12 weeks after the last administration of IMP. Postmenopausal women must be amenorrheic for at least 12 months.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

A complete description of the IMP and its proper handling will be provided in a pharmacy manual.

8.1.1 Pharmaceutical Form

- SAR156597 solution for injection at 100 mg/mL: SAR156597 is supplied as a sterile freeze-dried powder for solution for injection, in a glass vial. Each vial is filled with 125 mg of SAR156597 freeze-dried powder, and the final solution for injection is obtained by reconstitution of the entire vial content with 1.1 mL of sterile water for injection, leading to an amount of 125 mg of SAR156597 drug substance in a total volume of 1.25 mL equating to a concentration of 100 mg/mL of SAR156597 solution. One (1) mL of this 100 mg/mL SAR156597 solution can then be withdrawn for dose administration. Two (2) drug product vials are thus needed to reach a 200 mg dose and to prepare a 2 mL SAR156597 solution syringe.
- Placebo in lyophilized form: each vial containing excipients, is to be reconstituted with 1.1 mL of sterile water resulting in a total volume of 1.25 mL. Two (2) placebo product vials are required with 1 mL to be taken from each vial to prepare a 2 mL placebo solution syringe.

8.1.2 Dose of drug per administration

- SAR156597 group: 1 injection of SAR156597 200 mg administered subcutaneously qw.
- Placebo group: 1 injection of placebo administered subcutaneously qw.

8.1.3 Method of preparation

The SAR156597 and the placebo must be reconstituted prior to injection. The description of the reconstitution from lyophilizate vials will be provided in a pharmacy manual.

Once reconstituted, the placebo and the active vials are subtlety distinguishable. Thus, in order to maintain blinding at the study site, the reconstitution of the IMP and the preparation of the syringe must be done by an unmasked personnel (eg, pharmacist) other than those administering the drug and making clinical observations (Refer to Section 8.3).

At the patient's home, reconstitution must be prepared and administered by healthcare professionals (eg, visiting nurse).

The IMP should be reconstituted the day of dosing (no more than 3 hours prior to SC injection), at room temperature.

8.1.4 Route and method of administration

The route and method of administration are SC in the abdomen. SC injection sites should be alternated between the 4 quadrants of the abdomen (avoiding navel and waist areas) so that the same site is not injected for two consecutive weeks. The exact site of each injection will be documented on the source document. It is recommended that the injection occur at a site free of SSc involvement, if possible.

The IMP is administered every 7 days ±2 days from initial IMP administration. This window is permitted per protocol to accommodate various circumstances (eg, pending laboratory results, management of AE, visit scheduling difficulty). The IMP administration should be performed by other site personnel, blinded from the person in charge of the preparation of the solutions and syringes.

If IMP administration is missed or temporarily discontinued, the initial schedule of injections may be resumed upon the investigator's medical judgment and discretion while the missed dose(s) will not be administered. This does not apply to permanent treatment discontinuation.

On days when the patient has a study visit, the IMP will be administered by the Investigator or delegate after clinic procedures and blood collection.

For doses not administered at the study site, the IMP will be administered by qualified site personnel and /or healthcare professionals (eg, visiting nurse service).

Patients should be monitored by site personnel/visiting nurse for at least 30 minutes or up to 2 hours as per country specific requirements after each administration for potential signs and symptoms that may suggest a hypersensitivity reaction.

For doses not given at the study site, a booklet will be provided to the patient to record information related to the injections; this booklet will be completed by the visiting nurse after each injection and will be kept as source data in the patient's study file. Patients will be instructed to bring the booklet back at the subsequent site visit for Investigator's review.

Between the protocol-scheduled on-site visits, interim visits to the site may be required for IMP dispensing. As an alternative to these visits, the IMP may be supplied from the site to the patient via a Sponsor-approved courier company where allowed by local regulations and approved by the patient.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not Applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

SAR156597 and placebo will be provided in treatment kits indistinguishable in appearance and will be labeled with a treatment kit number. The list of treatment kit numbers will be generated by Sanofi. A patient randomization list will be generated by the interactive voice response system (IVRS). Both the randomization and treatment kit lists will be loaded into IVRS.

In accordance with the double-blind design, study patients, Investigators, and study site personnel (except the personnel who conduct the reconstitution of the IMP and preparation of syringes for injection) will remain blinded to study treatment and will not have access to the randomization code except under circumstances described in Section 8.3.2.

Before the reconstitution, the lyophilized SAR156597 and lyophilized placebo are similar. Once reconstituted, the active solution differs subtly in its appearance from the placebo solution. In order to maintain blinding conditions, the personnel involved with dose and syringe preparation will be required not to reveal to other study personnel the type or characteristics of IMP solution (SAR156597 versus placebo) in the vials and syringes.

Please refer to Section 10.4 for unblinding by the Sponsor related to suspected unexpected serious adverse drug reaction.

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IVRS and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of the day, and reason for code breaking.

If the blind is broken by the Investigator, the patient must withdraw from IMP administration.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patient will be randomized following a 1:1 ratio to one of the two treatment groups via a centralized randomization system using IVRS.

Randomization will be stratified based upon the patients' medical history of SSc-ILD (yes or no).

A randomized treatment kit number list will be generated centrally by Sanofi. The IMP (SAR156597 or placebo) will be packaged in accordance with this list.

At Visit 1 (screening), the study staff will contact the IVRS to obtain a patient number for each patient who signs the informed consent. Each patient will be allocated a patient number associated with the center and allocated in chronological order in each site.

At Visit 2 (baseline), after confirming that the patient is eligible for entry into the treatment period, the site coordinator will contact IVRS in order to receive the first treatment allocation kit numbers. Patients will be randomized to 1 of the 2 treatment groups at the ratio of 1:1. At subsequent visits during the treatment period, the site coordinator will call IVRS to obtain the next treatment kit numbers. A confirmation fax/e-mail will be sent to the site after each assignment.

A patient cannot be randomized more than once in the clinical trial.

Patients who meet exclusion criteria may be rescreened once during the open screening period of study; a different patient number will be assigned by IVRS. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen failure date and the re-screen date. The IVRS report will flag re-screened patients. Patients who are re-screened must sign a new informed consent and all Visit 1 procedures must be repeated.

One (1) treatment kit is sufficient for 1 week of treatment. As the treatment duration is 24 weeks, a patient will be allocated by IVRS to several treatment kit numbers corresponding to the same treatment group assigned from randomization.

The details of the centralized randomization procedure and IVRS are provided in a separate manual.

8.5 PACKAGING AND LABELING

SAR156597 and placebo will be supplied in a 1 week treatment kit containing 2 vials per kit.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All IMPs should be stored between 2°C and 8°C (36°F and 46°F), and should be kept upright. The Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

At home, the treatment kits will be stored by the patients in a refrigerator in accordance with the storage conditions indicated on the label of the IMPs.

After the supply of IMP kits are dispensed to the patients at the study site visits, appropriate provisions will be in place for transportation of the IMP kits from the study site to the patient's refrigerator, if home injections are permitted under local laws and regulations. As an alternative to

between study site visits, the IMP may be supplied from the site to the patient via a sponsor-approved courier company, where allowed by local regulations and approved by the patient.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

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

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

Under no circumstances will the Investigator supply IMP to a third party (except for duties and taxes paid [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.

8.7.1 Treatment accountability and compliance

The patient will be injected the study drug subcutaneously once a week during the treatment period. The patient will be injected the study drug at the trial site on the scheduled visits, and at weekly intervals in between scheduled visits. A home visiting nurse will administer the study drug at the patient’s place during the inter-visit period, should the patient choose this option and if permitted by local laws and regulations.

Measures taken to ensure and document treatment compliance and IMPs accountability include:

- Proper recording of treatment kit number or packaging number as required on appropriate electronic case report form (e-CRF) page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned or it is the End of Treatment visit. In case of Direct-To-Patient process, the treatment units can be returned by the carrier (if defined in the contract).
- The site personnel tracks treatment accountability/compliance comparing the treatment number recorded on the patient booklet with the treatment number of returned treatment kits (whether empty or unused) and fills in the patient treatment log.

- The monitor in charge of the reconciliation then checks the data entered on the IMPs administration page by comparing them with the IMPs that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

Whenever possible, all partially used, or unused IMP will be destroyed on site according to the standard practices of the site after reconciliation and verification by the monitor.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

The Investigator will not destroy any IMP unless the Sponsor provides written authorization. When destruction at site cannot be performed, all IMPs will be retrieved by the Sponsor.

A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Prohibited concomitant medications

- High dose immunosuppressive drugs will be prohibited (eg, cyclophosphamide >1 mg/kg oral/day or >750 mg IV/month; azathioprine >100 mg/day; methotrexate >15 mg/week, mycophenolate mofetil >2 g/day) within 3 months prior to screening and during the course of the trial, a change in dose within 4 weeks prior to randomization (or baseline visit) or expected changes in dose during the course of the study will be prohibited.
- High dose steroids (>10 mg/day prednisone equivalent); or a change in steroid dose within 4 weeks prior to randomization (or baseline visit) or expected changes in dose during the course of the study will be prohibited.
- Treatment with etanercept, cyclosporine A, IVIG, rapamycin, D-penicillamine, tyrosine kinase inhibitors within 4 weeks of screening, antithymocyte globulin within 6 months of screening and during the course of the study will be prohibited.
- Treatment with infliximab, certolizumab, golimumab, abatacept, or adalimumab, tocilizumab within 8 weeks of screening, anakinra with 1 week of screening and during the course of the study will be prohibited.
- Treatment with rituximab within 12 months prior to screening and during the course of the study will be prohibited.
- Treatment with any investigational drug for SSc during the course of the study will be prohibited.

8.8.2 Key Authorized Concomitant Medications

- Oral corticosteroids are permitted if dose ≤10 mg/day of oral prednisone or equivalent and at a stable dose for at least 4 weeks prior to the randomization (or baseline visit). No change in dose is permitted during the study unless for the management of an AE. Dose and any change will be recorded on the patient e-CRF. Oral corticosteroids cannot be started during the course of the study.
- Low dose immunosuppressive drugs (cyclophosphamide ≤1 mg/kg oral/day or ≤750 mg IV/month; azathioprine ≤100 mg/day; methotrexate ≤15 mg/week, mycophenolate mofetil ≤2 g/day) are permitted if at stable dose for at least 4 weeks prior to randomization (or baseline visit). No change in dose is permitted unless for the management of an AE. Dose and any change will be recorded on the patient e-CRF. Low dose immunosuppressive drugs cannot be started during the course of the study.
- Calcium channel blockers, alpha blockers, prostaglandins, endothelin receptor antagonists, phosphodiesterase inhibitors, angiotensin receptor blockers, nitrate therapy, other vasodilators, and anti-platelets/anticoagulants for the treatment of Raynaud's phenomenon and/or digital ulcers are permitted during the course of the study.
- Vasodilators, endothelin receptor antagonists, phosphodiesterase inhibitors, calcium channel blockers, soluble guanylate cyclase stimulators (eg, riociguat) and anticoagulants for the treatment of controlled PAH are permitted during the course of the study.
- Angiotensin-converting enzyme inhibitors for prevention of scleroderma renal crisis are permitted during the course of the study.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINT

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint will evaluate the efficacy of SAR156597 on skin fibrosis of patients with dcSSc by assessing:

- Change in mRSS from baseline to Week 24.

9.1.2 Secondary efficacy endpoints

Two secondary endpoints will evaluate the efficacy of SAR156597 on other aspects of dcSSc:

- Change in HAQ-DI, assessed with SHAQ, from baseline to Week 24.
- Change in respiratory function as measured by observed FVC and observed DLco (corrected for hemoglobin) from baseline to Week 24.

9.1.3 Exploratory endpoints

- Proportion of patients with improvement in mRSS of at least 20%, 40% and 60% from baseline to Week 24.
- Change in VAS for pain, breathing function, vascular function (Raynaud's phenomenon), gastrointestinal function, digital ulcers, and global assessment from SHAQ from baseline to Week 24.
- Change in respiratory function as measured by % predicted FVC and % predicted DLco (corrected for hemoglobin) from baseline to Week 24.
- Change in UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0) score from baseline to Week 24.
- Change in TJC28 from baseline to Week 24.
- Change in digital ulcer count from baseline to Week 24.
- CRISS from baseline to Week 24.
- Change in EQ-5D-5L index from baseline to Week 24.
- Change in efficacy endpoints (mRSS, HAQ-DI, VAS from SHAQ, observed FVC, % predicted FVC, observed DLco [corrected for hemoglobin], % predicted DLco [corrected for hemoglobin], UCLA SCTC GIT 2.0, TJC28, digital ulcer count, CRISS, and EQ-5D-5L) from baseline to Week 35 (up to end of follow-up period) and proportion of patients with improvement in mRSS of at least 20%, 40% and 60% from baseline to Week 35.

- Proportion of patients with improvement in SHAQ (HAQ-DI and VAS) and EQ-5D-5L (index value and VAS) based upon MIC at Week 24.

9.1.4 Assessment methods and activity parameters

9.1.4.1 Modified Rodnan Skin Score

The fibrosis of the skin will be assessed using the mRSS which is conducted by palpation of the skin in 17 areas of the body (fingers, hands, forearms, arms, feet, legs and thighs, face, chest and abdomen) using a 0–3 scale, where 0 = normal, 1 = mild thickness, 2 = moderate thickness and 3 = severe thickness. Total skin score can range from 0 (no thickening) to 51 (severe thickening in all 17 areas). Only those physicians or qualified medical personnel who have undergone a standardized training will be permitted to evaluate the skin thickening. Every effort will be undertaken for the same medical personnel to evaluate a given patient from baseline to EOS participation in order to minimize any inter-rater variability. In the unlikely event of the evaluation being carried out by different personnel, the reason will be documented. The baseline and Week 24/Visit 7 mRSS assessment must be conducted by the same medical personnel.

9.1.4.2 Respiratory Function

The pulmonary function test is a secondary endpoint that will assess the change in respiratory function as measured by observed FVC and observed DLco (corrected for hemoglobin) from baseline to Week 24. The absolute change in observed and % predicted change in FVC and DLco from baseline to Week 24 and/or Week 35 will also be assessed as exploratory endpoints. The manual correction of DLco for hemoglobin will be based upon the following equation unless it is automatically corrected during measurement:

1. For male patients: $DLco_{observed}$/(factor), where factor is = (1.7 x Hb)/(10.22 + Hb)
2. For female patients: $DLco_{observed}$/(factor), where factor is = (1.7 x Hb)/(9.38 + Hb)

   Note: Hb = Hemoglobin. The value of hemoglobin will be taken from the same visit where the DLco is conducted.

The spirometry should be performed in compliance with the 2005 ATS/ERS guideline (13) while the DLco should be performed in compliance with standard guidance (14).

9.1.4.3 Gastrointestinal Manifestations

The UCLA SCTC GIT 2.0 instrument is a validated self-reported questionnaire used to assess QOL related to gastrointestinal function in patients with SSc (15). It employs a 7-multi-item scale with areas of reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being, and social functioning. This will be captured at all visits except V1 and V3.

9.1.4.4 Renal Function

Renal function will be assessed through the measurement of blood urea nitrogen, creatinine and urinalysis (dipstick) at all visits except V3. The urinalysis (dipstick) will capture specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. If any parameter on the dipstick is abnormal, a urine sample will be sent to the central laboratory for testing. If the dipstick is positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory.

9.1.4.5 Cardiac Manifestations

Systemic sclerosis associated cardiac manifestations will be assessed by physical examination and ECG which is an established method of monitoring for cardiac conduction and potential coronary and myocardial diseases. Electrocardiogram will be captured at all scheduled visits except Visit 3. Cardiovascular events will be reported as AEs.

9.1.4.6 Joint Pain Assessment

The TJC28 is an assessment of the overall joint pain based upon the examination of 28 key joints. It is a reliable and validated method of assessing general joint pain and will be captured at all visits except V1 and V3. The 28 joints that are part of the assessments include: shoulders (2), elbows (2), wrists (2), metacarpophalangeals (10), proximal interphalangeals (10), and knees (2).

9.1.4.7 Digital Ulcer Count

The digital ulcer count captures the number of active open sores (or digital ulcers) on fingertips secondary to SSc (and not secondary to localized trauma or injury). Cracks, fissures or even skin breakdown related to calcinosis should not be included. The digital ulcer count will be conducted at all visits except V1 and V3.

9.1.4.8 Scleroderma Health Assessment Questionnaire

The SHAQ, which includes the standard HAQ-DI to measure the functional disability and 5 SSc-specific VAS assessments will be completed by patients at baseline and throughout the study, except V1 and V3 (16). The SHAQ is the standard, validated, and accepted health assessment questionnaire in patients with SSc to assess the physical/functional disability related to skin and systemic fibrosis.

The HAQ DI contains 8 domains of activity (dressing, arising, eating, walking, hygiene, reach, grip, and common daily activities) each of which has at least 2 questions, for a total of 20 items. For each item, patients report the amount of difficulty experienced performing the activity. There are 4 possible responses for each item ranging from 0 (without any difficulty) to 3 (unable to do). For each of the 8 domains included in the HAQ-DI, the score is the single response within the domain with the highest score. If aids or devices are used, and if the highest score is 0 or 1, then the score is raised to 2; if the highest score is 2 or 3, the score is kept as it is. The HAQ-DI composite score is then calculated as the average of the scores of the 8 domains. If 1 or 2 of the

domains are missing, the HAQ-DI composite score is obtained by dividing the sum of the domains by the number of answered domains. If three or more of the domains are missing, then the HAQ-DI composite score is missing. The composite score is reported, falling between 0 and 3 on an ordinal scale. The scores are interpreted as 0 (no impairment in function) to 3 (maximal impairment of function).

The HAQ-DI also contains a VAS that patients use to report the amount of pain experienced in the past week. The VAS is a 10-cm line that is converted to a continuous scale from 0 to 3 where 1 cm is equivalent to 0.3 points. The anchors of the VAS are 0 (no pain) to 100 (very severe pain). To obtain the patient score, a metric ruler is used to measure the distance in centimeters from the left anchor to the patient's mark, and then multiplied by 0.3. The VAS pain score is not incorporated into the HAQ DI composite score.

For the other 5 VAS, the patients will rate breathing, vascular (Raynaud's phenomenon), gastrointestinal function, digital ulcers, and global assessment. They will be asked to make a mark on a 10 cm line to indicate the severity from 0-100 where 0 indicates no severity and 100 indicates the worst severity.

9.1.4.9 Euro-QOL-5D-5L

The EQ-5D-5L questionnaire is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L is designed for self-completion by patients.

The EQ-5D comprises 2 discrete scales: the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system has 5 items, each measuring one dimension of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension/item has a 5 level Likert-type response scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. Responses for the 5 dimensions can be combined in a single 5-digit number describing the respondent's health profile and can be converted into a single index value for the calculation of quality-adjusted life years (QALYs) to inform economic evaluations of health care interventions. The EQ VAS provides a quantitative measure of health as judged by the individual respondents on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 ("The best health you can imagine") at the top and 0 ("The worst health you can imagine") at the bottom.

In the analysis the index value will be considered as a continuous variable.

9.1.4.10 Composite response index in diffuse cutaneous systemic sclerosis

The CRISS tool summarizes the changes in the clinical and patient-reported outcomes using a single composite score that reflects the probability that the patient with dcSSc has improved (17). For an effective therapeutic agent of dcSSc, CRISS will be able to summarize the higher probability of improvement in a subject treated with the IMP versus an ineffective agent (or placebo).

CRISS is a 2-step process as described below.

Step 1: Patients who develop new or worsening of cardiopulmonary and/or renal involvement due to SSc are considered as not improved (irrespective of improvement in other core items) and assigned a probability of improving equal to 0.0. Specifically if a subject develops any of the following:

- New scleroderma renal crisis
- Decline in FVC % predicted ≥15% (relative), confirmed by another FVC% within a month, high resolution computer tomography (HRCT) to confirm ILD (if previous HRCT of chest did not show ILD) and FVC % predicted below 80% predicted*
- New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment*
- New onset of PAH on right heart catheterization requiring treatment*. PAH is defined as mean pulmonary artery pressure ≥25 mm Hg at rest and an end-expiratory pulmonary artery wedge pressure ≤15 mm Hg and a pulmonary vascular resistance >3 Wood units.

* Attributable to SSc

Step 2: For the remaining patients, Step 2 involves computing the predicted probability of improving for each subject using the following equation (equation to derive predicted probabilities from a logistic regression model):

$$\frac{\exp(-5.54-0.81*\Delta MRSS+0.21*\Delta FVC\%-0.40*\Delta Pt-glob-0.44*\Delta MD-glob-3.41*\Delta HAQ-DI)}{1+\exp(-5.54-0.81*\Delta MRSS+0.21*\Delta FVC\%-0.40*\Delta Pt-glob-0.44*\Delta MD-glob-3.41*\Delta HAQ-DI)}$$

ΔmRSS indicates the change in mRSS from baseline, ΔFVC denotes the change in FVC% predicted from baseline, ΔPt-glob indicates the change in patient global assessment, ΔMD-glob denotes the change in physician global assessment, and ΔHAQ-DI is the change in HAQ-DI. All changes are absolute change ($Time_2$–$Time_{baseline}$).

Patient and physician global assessments of overall health will be used in the Step 2 calculation of CRISS. These two assessments are based upon a Likert scale ranging from 0 (Excellent) to 10 (Extremely Poor) (see Appendix E) (17).

9.2 SAFETY ENDPOINTS

The same safety assessments will be applied across all phases of the study and across both treatment groups. Adverse events, including serious adverse events (SAEs), and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in Section 10.4.1. To ensure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.

9.2.1 Adverse events

Refer to Section 10.4 to Section 10.7 for details.

9.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including but not limited to hematology, clinical chemistry) and urinalysis. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The clinical laboratory tests will be conducted by an accredited (college of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Laboratory parameters with abnormal values that are considered to be clinically significant by the Investigator must be retested as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be retested until they return to normal, to baseline values, or to values no longer considered as clinically significant by the Investigator. If abnormalities are part of a determined disease/etiology, they should be monitored as per standard of care for the corresponding etiology/disease.

Samples will be taken at the study site before administration of the IMP. The following parameters will be measured as per study flowchart (Section 1.2) and description of study procedures in Section 10.

- Hematology
  - Hemoglobin, hematocrit, red blood cell count, erythrocyte sedimentation rate (ESR), WBC count with differential and platelet count.
- Biochemistry
  - Fasting glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, total protein, albumin, TBILI, alkaline phosphatase (ALP), ALT, AST, creatinine phosphokinase (CPK), high-sensitivity C-reactive protein (hsCRP). (Fasting is defined as a period of at least 8 hours since the last consumption of any food or liquid. Minor water intake is permitted during this fasting period).
- Urinalysis
  - Specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for protein and/or red blood cells, microscopic analysis will be performed by the central laboratory to assess for cellular casts.
- [redacted]

[redacted]

- Pregnancy Testing
  - For women of childbearing potential, a serum pregnancy test (β-human chorionic gonadotrophin) and urine pregnancy tests will be performed as per study flow chart in Section 1.2. From Visit 6, the site will dispense urine pregnancy kits to the patients who will perform the test at home on a monthly basis. If any interim urine pregnancy test performed by the patient is positive, the patient should immediately report to the investigator for appropriate follow-up and pregnancy reporting as appropriate.
- Serology and TB Testing
  - Clinical laboratory testing performed at Visit 1 will also include: hepatitis screen (HBsAg, HBsAb, HBcAb, HBV DNA [reflex testing if HBcAb is positive], hepatitis C antibody, hepatitis C RNA [reflex testing if hepatitis C antibody is positive]), HIV-1/HIV-2 antibody, and tuberculosis screen (Quantiferon®-TB gold evaluation), in addition to other testing as per the study flow chart (Section 1.2).

Decision trees for the management of some laboratory abnormalities are provided in Appendix K.

9.2.2.1 Physical examination

A complete physical examination will be performed at each site-visit as per study flow chart (Section 1.2) and description of study procedures in Section 10. Gynecological and urogenital examinations will not be done in this study unless for cause.

Specific attention will be paid to the skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. For the dermatological examination, it is recommended that the patient only wears undergarments. [redacted]

Clinically significant abnormalities should be reported in the patient's e-CRF as medical history, if observed at the screening visit (Visit 1) or as an AE if observed during subsequent visits.

9.2.2.2 Vital signs

Vital signs include blood pressure (BP) (mmHg), heart rate (beats per minute), body weight (kg) and height (cm).

Blood pressure will be measured at each study site visit in the sitting position. Both systolic and diastolic BP should be recorded. BP should be checked after 5 minutes of resting in the sitting position.

Weight should be taken with the patient wearing undergarments (or very light clothing), no shoes, and with an empty bladder. The same scale should be used throughout the study.

Height will be measured at screening (Visit 1) only.

Body mass index (BMI) will be calculated automatically at each visit.

9.2.2.3 Electrocardiogram variables

A standard 12-lead ECG will be performed at all the on-site visits (except Visit 3) as per the study flow chart (Section 1.2) and description of study procedures in Section 10. Electrocardiogram parameters will be based upon the automatic reading of the device. If the device does not provide automatic reading, then the ECG parameters will need to be determined and interpreted by the Investigator.

At Visit 1, all abnormal ECG interpretation will need to be confirmed by a local cardiologist. All findings of ischemic ECG changes will result in exclusion unless there is a left heart catheterization performed in the last year within screening that is not supportive of the current ECG finding. All other clinically significant ECG findings per guidance provided in Appendix L will result in exclusion.

At the post randomization visits, ECGs will be performed prior to IMP administration. All ECGs will be performed with the subject in a reclined position. ECG parameters include: heart rate, QRS duration, PR interval, QT interval, ST deviation, T-wave and U-wave morphology.

9.2.2.4 Hypersensitivity/Allergic or anaphylactic reactions

Assessment, categorization and treatment of systemic allergic reactions including anaphylactic reactions (18) will be specifically performed as detailed in Section 10.6.3.1 and Appendix I as appropriate.

Local injection site reactions will be assessed to determine if it is of an allergic origin as described in Section 10.6.2 and Section 10.6.3.2 (see also Appendix I and Appendix J).

9.2.2.5 Echocardiogram

A standard 2-Dimensional transthoracic echocardiogram will be obtained at Visit 1 (unless one had been previously obtained within 6 months of Visit 1) to help determine patient's eligibility with regards to Exclusion criterion 13 [E 13].

At a minimum, the echocardiogram should be able to assess for the left ventricular ejection fraction (LVEF) and the status and function of the four cardiac chambers, myocardium and valves.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics and Immunogenicity

9.3.1.1 Sampling time

Samples for PK analysis will be collected pre dose (within 2 hours before each dose administration) during Visits 2, 4, 5, 6 and 7.

Pharmacokinetics samples during Visit 8 will be collected in the morning.

Anti-SAR156597 antibodies (ADA) samples will be collected at approximately the same times as the PK samples. An additional ADA sample will be collected at Visit 1.

9.3.1.2 Pharmacokinetics and Immunogenicity handling procedure

Detailed procedures of sample preparation, storage and shipment are described in the specific laboratory manual. A total of five (5) mL blood volume is to be collected at screening for ADA samples (Table 1). A total of five (5) mL blood volume is to be collected at each subsequent visit for the PK (3 mL) and ADA (2 mL) samples combined (Table 2).

Table 1 - Plasma samples handling for immunogenicity (anti-SAR156597) at screening

Sample type	anti-SAR156597
Matrix	Plasma
Blood sample volume	5mL (4 aliquots)
Anticoagulant	CPD (Citrate Phosphate Dextrose)
Storage conditions	≤-20°C

Table 2 - Plasma samples handling for PK (SAR156597) and immunogenicity (anti-SAR156597)

Sample type	SAR156597	anti-SAR156597
Matrix	Plasma	Plasma
Blood sample volume	3mL (3 aliquots)	2mL (2 aliquots)
Anticoagulant	CPD (Citrate Phosphate Dextrose)	
Storage conditions	≤-20°C	

Abbreviation: PK = pharmacokinetics

9.3.1.3 Bioanalytical method

9.3.1.3.1 SAR156597 assay

All plasma samples to be tested for SAR156597 samples will be analyzed by Bertin Pharma (Saclay, France)

A validated enzyme-linked immunosorbent assay (ELISA) is used for the quantification of SAR156597 in human plasma. Biotinylated IL-4 coated on a streptavidin plate is used to capture SAR156597, which is then detected by SulfoTag-IL-13. This format, which uses electrochemiluminescence detection, is able to detect SAR156597 with an LLOQ of 0.05 µg/mL.

9.3.1.3.2 Anti-drug antibodies

All ADA samples will be analyzed by the Bioanalysis and Biomarkers domain in DSAR OC Montpellier (France).

For the analysis of potential ADAs in human plasma, a validated bridging qualitative ELISA using electrochemiluminescence detection will be used.

Positive samples in screening assay will then be tested in a confirmatory assay (competition with SAR156597) in order to demonstrate the presence of antibodies and eliminate false positive results generated from the initial screening assay.

Interference of SAR156597 in the ADA assay will be documented so that the highest drug concentration that does not affect the limit of ADA detection is known, and the interpretation of immunogenicity takes into account this parameter.

Additional information on the bioanalytical method for ADAs will be provided in the Laboratory Manual.

Samples that are ADA positive will be further evaluated for their potential neutralizing activity with an assay currently in development.

Placebo samples will only be analyzed at baseline, and will continue to be followed if the baseline time point results positive for ADA.

In the interim, the Sponsor will store frozen specific aliquots for neutralizing activity testing if necessary.

9.3.1.3.3 Half-arm exchange molecule assessment

If necessary, half-arm exchange of SAR156597 with endogenous hIgG4 may be assessed on specific PK sample aliquots.

9.3.1.4 Pharmacokinetics parameters

SAR156597 concentrations at selected time points after the last dose will be reported using descriptive statistics.

Additional PK parameters will be estimated using the population PK approach such as C_{max}, t_{max}, and AUC at steady state.

9.3.2 Resource utilization

To assess the economic benefit of SAR156597, health care resources will be collected retrospectively at baseline, Week 12, Week 24 and Week 35. These resources will include the following information:

- Hospitalizations (reason, number of days per ward, date of entry, date of discharge from hospital)
- Number of out-patients visits by type (gastroenterologist, pulmonologist, occupational therapist, psychiatrist, physiotherapist, other)
- Sick leaves (number of day off from work)
- Caregiver support (time spent per day to care of the patient, number of days off from work to take care of the patient).

9.3.3 Biomarkers

Blood samples will be collected for protein biomarker analyses. There will be measurement of protein biomarkers associated with the activity of the disease (COMP, CCL2) and the IL-4/IL-13 pathway (TARC, periostin, and eotaxin-3).

Additionally, archived blood samples may be used for future assays of protein and mRNA biomarkers related to the disease and the response to therapy. Participation is voluntary and will require the signing of a separate Future Use of Samples informed consent form. (Refer to Section 9.4)

Of note, safety biomarkers, if any, will be analyzed as necessary.

9.4 FUTURE USE OF SAMPLES

This is a voluntary procedure which requires the patient to sign a separate informed consent document should he/she agree to participate. If agreed to participate, the patient will have blood samples collected at Visit 2, Visit 6 and Visit 8. The archived samples may be used to potentially assess for protein and mRNA biomarkers in the future. Additionally,

- Stored samples may also be used to explore safety concerns that may have arisen during or after study completion
- Stored samples may also be used for other research purposes (excluding genetic analysis) related to SSc than those defined in the present protocol. These other research purposes will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers used during the study (ie, subject ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint will be the change in mRSS from baseline to Week 24. The mRSS is a widely used endpoint in SSc clinical trials as it is the only validated measure of cutaneous involvement in patients with SSc and it correlates with patient function and mortality. Because of the challenges related to inter-rater variability, it is imperative that all raters are to be trained and certified and one rater is to be used to assess the same patient throughout the course of the study.

The secondary endpoints will assess the change from baseline to Week 24 in HAQ-DI and in respiratory function as measured by observed FVC and observed DLco (corrected for hemoglobin). Both the FVC and DLco are widely used measures of pulmonary function particularly related to the disease status of an underlying interstitial lung disease (ILD). Lastly, because it is a multisystem disease, SSc can significantly impact a patient's function and quality of life. Thus, patient reported outcomes (PROs) such as HAQ-DI (assessed with the SHAQ) which is both reliable and validated are vital information to be captured in this study (19).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

It is preferred that all study visits take place in the morning when fasting blood samples are required.

The study visits occur on the planned dates (relative to randomization date), as scheduled. The visit schedule should be adhered to within the ±2 day visit window.

If a patient is prematurely discontinued from treatment, all assessments planned at the End of Treatment visit should be performed.

Prior to all screening assessments, after discussion of participation in the study, the written informed consent form (including voluntary participation in future use of samples) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to Day 1 is respected. Patients who fail screening for certain exclusion criteria (eg, concomitant medications, required drug-specific discontinuation periods or laboratory tests), may be rescreened for study eligibility 1 additional time (refer to Section 8.4 for further instructions related to rescreening).

In general, PRO assessments should be completed at the study site as part of the visit (per study flow chart) but prior to any meaningful communication with a health care professional or any other study procedures, unless noted otherwise in the suggested order of the study procedures for each individual visit described below.

10.1.1 Visit 1: Screening/Day-28 to Day-1

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented which must precede any study procedures.

The following procedures will then be performed:

- Call IVRS to assign a patient number
- Commence AE reporting
- Record patient demographic information
- IVRS Interview to collect:
  - SSc history
    - SSc characteristics and manifestations (including SSc-ILD to be used for stratification should the patient be enrolled)

  - Disease duration from the time of the first non-Raynaud's phenomenon manifestation
  - Treatment history including current therapies
- other medical/surgical history

- Record vital signs including BP, heart rate, weight (kg) and height (cm) (collected for BMI calculation)
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Assess the mRSS
- Assess eligibility by review of Inclusion/Exclusion Criteria. This includes the review of prior and concomitant medications, SSc history and physical examination findings. Patients who fail to meet the eligibility criteria based on this preliminary review should not continue the screening process (eg, ECG or blood work) and a screen failure call should be done in the IVRS
- Perform 12-lead ECG (All abnormal ECG interpretations will need to be reviewed and confirmed by a local cardiologist)
- Perform Pulmonary function tests (PFTs): observed and % predicted FVC and observed and % predicted Carbon Monoxide DLco (corrected for hemoglobin)
- Perform echocardiogram unless one had been previously obtained within 6 months of Visit 1 (screening visit).
- Obtain blood samples for screening laboratory determinations: hematology, biochemistry, serology tests (HBsAg, HBsAb, HBcAb, HBV DNA (reflex to a positive HBcAb), hepatitis C antibody, hepatitis C RNA (reflex to a positive hepatitis C antibody), HIV-1/HIV-2 antibody), and serum beta-human chorionic gonadotropin (β-HCG) plasma test if female of childbearing potential.
- Obtain blood samples for anti-SAR156597 ADA
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for protein and/or red blood cells, microscopic analysis will be performed by central laboratory
- Complete all remaining assessments for tuberculosis screen: history and QuantiFERON-TB Gold test:
  - The QuantiFERON® TB Gold test is an in vitro TB test that measures a memory Tcell mediated response (production of interferon γ) in TB-infected patients. This test is unaffected by bacillus Calmette-Guérin (BCG) vaccination or exposure to nontuberculous mycobacteria. The test received regulatory and policy approvals in the United States of America, Japan, European Union, Canada. Blood samples are incubated within 16 hours from blood collection and sent to the central laboratory for analysis the day after collection or as soon as possible. Patients with a positive or 2 confirmed indeterminate QuantiFERON TB Gold tests are excluded.
  - Schedule a visit within a maximum of 28 days (Visit 2, Day 1)

10.1.2 Visit 2: Baseline visit/Randomization/Day 1

- Record all concomitant medication use with start date and dose in e-CRF
- Inquire about AEs/SAEs
- Record vital signs including BP, heart rate and weight
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS (confirm eligibility based upon Exclusion Criteria 03 [E 03])
  - Perform a TJC28
  - Perform a digital ulcer count
- Confirm eligibility by review of Inclusion/Exclusion Criteria

  If the patient meets all inclusion criteria and does not meet any exclusion criteria, please conduct the following procedures in the recommended order, if possible.
- Call IVRS to randomize the patient and receive a treatment kit allocation.
- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - EQ-5D-5L (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Inquire about Resource Utilization (Refer to Section 9.3.2)
- Blood and Urine Testing
  - Obtain blood samples for complete clinical laboratory determinations including hematology, biochemistry profile
  - Obtain urine for urinalysis (dipstick)
  - Perform urine pregnancy test for women of childbearing potential
  - Obtain blood samples for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
  - Obtain blood samples for protein biomarkers assessment
  - Obtain blood samples for supplementary tests for vasculitis (Refer to Section 9.2.2)
  - Obtain blood samples for archiving (potential future protein and mRNA biomarkers of interest); only for patients who signed a Future Use of Samples informed consent form.
- Other Tests and Procedures
  - Perform 12-lead ECG
  - Perform Pulmonary function tests (PFTs): observed and % predicted FVC and observed and % predicted Carbon Monoxide DLco (corrected for hemoglobin).

- Dispense and administer IMP
  - Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema/redness, swelling/induration/edema and other related observations) will be conducted
  - Provide the patient with a booklet to record information pertaining to the injections to be performed at home at Week 1 as well as the treatment kit
- Schedule an appointment for Visit 3

10.1.3 Visit 3: on treatment/Week 2

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Review patient booklet to assess local tolerability at the injection site and treatment compliance
- Record vital signs including BP, heart rate and weight

Perform a complete physical examination (Refer to Section 9.2.2.1)

- Call IVRS to dispense a 2 week treatment kit allocation
- Administer IMP for Week 2
  - Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema/redness, swelling/induration/edema and other related observations) will be conducted
- Provide treatment kit to be administered at Week 3
- Schedule an appointment for Visit 4

10.1.4 Visit 4: on treatment/Week 4

- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Record all concomitant medication use
- Inquire about AEs/SAEs

- Review patient booklet to assess local tolerability at the injection site and treatment compliance
- Record vital signs including BP, heart rate and weight
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS
  - Perform a TJC28
  - Perform a digital ulcer count
- Perform 12-lead ECG
- Blood and Urine Testing
  - Obtain blood samples for complete clinical laboratory determinations including hematology and biochemistry profile
  - Obtain urine for urinalysis (dipstick)
  - Perform urine pregnancy test for women of childbearing potential
  - Obtain blood sample for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
  - Obtain blood sample for ANCA and complements (C3, C4 and CH50)
- Call IVRS to dispense a 4 week treatment kit allocation
- Administer IMP for Week 4
  - Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema/redness, swelling/induration/edema and other related observations) will be conducted
- Provide treatment kits to be administered at Weeks 5, 6 and 7
- Schedule an appointment for phone call at Week 6
- Schedule an appointment for Visit 5 (Week 8)

10.1.5 Phone call: on treatment/Week 6, Week 16, and Week 20

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Ask about the result of urine pregnancy test (for phone calls made at Week 16 and Week 20 only)
- Assess local tolerability at the injection site by reviewing the patient booklet.

10.1.6 Visit 5: on treatment/Week 8

- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Record all concomitant medication use
- Inquire about AEs/SAEs
- Review patient booklet to assess local tolerability at the injection site and treatment compliance
- Record vital signs including BP, heart rate and weight
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS
  - Perform a TJC28
  - Perform a digital ulcer count
- Perform a 12-lead ECG
- Blood and Urine Testing
  - Obtain blood samples for evaluating laboratory determinations including hematology and biochemistry
  - Obtain a urine sample for urinalysis (dipstick)
  - Perform urine pregnancy test for women of childbearing potential
  - Obtain blood sample for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
- Call IVRS to dispense a 4 week treatment kit allocation
- Administer IMP for Week 8
  - Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema/redness, swelling/induration/edema and other related observations) will be conducted
- Provide treatment kits to be administered at Weeks 9, 10 and 11
- Schedule an appointment for the next visit, Visit 6 (Week 12)

10.1.7 Visit 6: on treatment/Week 12

- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - EQ-5D-5L (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Record all concomitant medication use
- Inquire about AEs/SAEs
- Inquire Resource Utilization (Refer to Section 9.3.2)
- Assess for Step 1 of CRISS (cardiopulmonary and/or renal involvement)
- Review patient booklet to assess local tolerability at the injection site and treatment compliance
- Record vital signs including BP, heart rate and weight
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS
  - Perform a TJC28
  - Perform a digital ulcer count
- Perform 12-lead ECG
- Blood and Urine Testing
  - Obtain blood samples for complete clinical laboratory determinations including hematology and biochemistry profile
  - Obtain urine for urinalysis (dipstick)
  - For women of childbearing potential:
    - Perform urine pregnancy test. The patients should be instructed to do the urine pregnancy test at home on a monthly basis during the intervals in between on-treatment study visits for the duration of the study. In case of a positive pregnancy test, the patient should be advised to contact immediately the investigator.
    - Dispense urine pregnancy test kits for monthly urine pregnancy tests (sufficient monthly supplies to last until the next scheduled on-site visit).
  - Obtain blood sample for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
  - Obtain blood sample for ANCA and complements (C3, C4 and CH50)
  - Obtain blood samples for protein biomarkers analysis

  - Obtain blood samples for archiving for future protein assays and mRNA analysis (only for those patients who have signed a separate Future Use of Samples informed consent form)
- Perform PFTs: observed and % predicted FVC, and observed and % predicted DLco (corrected for hemoglobin)
- Call IVRS to dispense a 6 week treatment kit allocation (Weeks 12, 13 ,14, 15, 16, and 17)
  - Reminder: Make an additional IVRS call (as per study flow chart [Section 1.2]) at Week 18 to dispense an additional 6 week supply of IMP which will be required for Weeks 18, 19, 20, 21, 22 and 23.
- Administer IMP for Week 12
  - Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema/redness, swelling/induration/edema and other related observations) will be conducted
- Provide treatment kits to be administered at Weeks 13, 14, 15, 16 and 17
- Schedule appointment for phone calls at Weeks 16 and 20 and for the End-of-Treatment (EOT) visit.

10.1.8 Visit 7: End-of-Treatment/Week 24 (or Early Termination)

The End of treatment visit is scheduled for Week 24. If a patient discontinues treatment before Week 24, a premature EOT (as noted in the e-CRF) visit will be performed employing all assessments and procedures associated with Visit 7/EOT.

- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - EQ-5D-5L (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Record all concomitant medication use
- Inquire about AEs/SAEs
- Inquire about Resource Utilization (Refer to Section 9.3.2)
- Assess for Step 1 of CRISS (cardiopulmonary and/or renal involvement)
- Review patient booklet to assess local tolerability at the injection site and treatment compliance
- Record vital signs including BP, heart rate and weight

- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS
  - Perform a TJC28
  - Perform a digital ulcer count
- Perform 12-lead ECG
- Blood and Urine Testing
  - Obtain blood samples for complete clinical laboratory determinations including hematology and biochemistry profile
  - Obtain urine for urinalysis (dipstick)
  - For women of child bearing potential:
    - Perform urine pregnancy test. The patients should be instructed to do the urine pregnancy test at home on a monthly basis during the intervals in between on-study visits for the duration of the study. In case of a positive pregnancy test, the patient should be advised to contact immediately the Investigator
    - Dispense urine pregnancy test kits for monthly urine pregnancy tests (2 months supply)
  - Obtain blood sample for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
  - Obtain blood sample for ANCA and complements (C3, C4 and CH50)
  - Obtain blood samples for protein biomarkers analysis
- Perform PFTs: observed and % predicted FVC, and observed and % predicted DLco (corrected for hemoglobin)
- Call IVRS to update the patient's status (EOT)
- Schedule an appointment for a phone call for Week 30
- Schedule an appointment for next visit, Visit 8 (EOS visit).

Post treatment, the patients will be observed for 11 weeks in a follow-up period. It will consist on one follow-up phone call at Week 30 and EOS visit at Week 35 (Visit 8).

10.1.9 Phone call: Follow-up post treatment/Week 30

The patient will be contacted over phone to:

- Record all concomitant medications
- Inquire about AEs/SAEs
- Ask about the result of pregnancy test from Week 28.

10.1.10 Visit 8: End-of-study visit/Week 35

- Questionnaires/forms to be completed:
  - SHAQ (by patient)
  - UCLA SCTC GIT 2.0 (by patient)
  - EQ-5D-5L (by patient)
  - Patient Global Assessment (by patient)
  - Physician Global Assessment (by Investigator)
- Record all concomitant medication use
- Inquire about AEs/SAEs
- Ask about the result of pregnancy test from Week 32
- Inquire about Resource Utilization (Refer to Section 9.3.2)
- Assess for Step 1 of CRISS (cardiopulmonary and/or renal involvement)
- Record vital signs including BP, heart rate and weight
- Perform a complete physical examination (Refer to Section 9.2.2.1), including:
  - Perform the mRSS
  - Perform a TJC28
  - Perform a digital ulcer count
- Perform 12-lead ECG
- Blood and Urine Testing
  - Obtain blood samples for complete clinical laboratory determinations including hematology and biochemistry profile
  - Obtain urine for urinalysis (dipstick)
  - Perform urine pregnancy test for women of childbearing potential
  - Obtain blood sample for serum SAR156597 level (PK) and for anti-SAR156597 antibody (ADA)
  - Obtain blood sample for ANCA and complements (C3, C4 and CH50)
  - Obtain blood samples for protein biomarkers analysis
  - Obtain blood samples for future protein assays and mRNA analysis (only for those patients who have signed a separate Future Use of Samples informed consent form)
- Perform PFTs: observed and % predicted FVC, and observed and % predicted DLco (corrected for hemoglobin)
- Call IVRS to update the patient's status (study completion).

10.2 DEFINITION OF SOURCE DATA

All evaluations that are reported in the e-CRF and in the patient booklet (completed by the nurse) must be supported by appropriately identified source documentation.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop is temporary; permanent IMP discontinuation should be considered as the last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation may be considered by the Investigator because of suspected AE(s). Re-initiation of treatment with the IMP will be considered with close and appropriate clinical and/or laboratory monitoring after the Investigator has determined according to his/her best medical judgment that the causality of the event was unlikely related to the IMP(s) and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For example, suspicion of vasculitis should lead to a temporary discontinuation to allow for a thorough diagnostic work-up and evaluation.

A discontinuation of IMP greater than 30 days will be considered permanent and relevant e-CRF sections should be populated.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator, Sponsor or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may decide to permanently withdraw from treatment with the IMP at any time and for any reason; this decision may also rest with the Investigator or Sponsor. All efforts should be made to document the reason(s) for treatment discontinuation in the e-CRF.

IMP will be permanently discontinued in case of the following events (refer to Section 10.6 for details). The list is a guide and not intended to be exhaustive:

- [redacted]
- Symptoms of severe hypersensitivity or anaphylactic reactions (see Appendix I for definition)
- Severe skin reactions local to the site of IMP injection (see Appendix J)

- Pregnancy
- Any AEs, per Investigator's judgment, that may jeopardize the patient's safety
- Any code breaking requested by the Investigator will lead to permanent treatment discontinuation.
- Any laboratory abnormalities per the algorithms of Appendix K
- At the specific request of the Sponsor

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision regarding of possible permanent IMP discontinuation for the concerned patient. All efforts should be made to reassess in a clinically relevant timeframe (using either local or central lab), the clinical significance of lab abnormalities and corrective actions before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

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

After permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for EOT visit/Visit 7 (labeled as Premature/Early EOT in the e-CRF), and then will be asked to come for the remaining on-site visits per schedule (including Visit 7 at Week 24 and EOS at Week 35 for safety monitoring and efficacy assessments, particularly mRSS, SHAQ, FVC and DLco (corrected for hemoglobin) up to Week 24 as these are the primary and secondary endpoints. Other procedures associated with the remaining visits will also be conducted per study flow chart.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and for any reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for ongoing study participation with scheduled visits and from withdrawal of consent for non-patient contact follow-up (eg, medical records check). Patients requesting withdrawal of consent for ongoing study participation with follow-up may jeopardize the public health value of the study.

If possible, and prior to the withdrawal of consent for ongoing study participation, the patients will be assessed using the procedure normally planned for the EOS visit (Visit 8). Then, patients will receive a phone call from Investigators at Week 30 for vital status assessment.

Patients who withdraw from the study should be explicitly asked about the reason and the contribution of any possible AE(s) that led to their decision, and any AE information elicited should be documented. The patient may withdraw consent verbally or in writing. If the consent is withdrawn verbally, the site should document it appropriately. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who did not withdraw consent for ongoing study participation but fail to return to the site, the Investigator should make the best effort to contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, particularly vital status. Attempts to contact such patients must be documented in the patient's records (eg, number of attempts and dates of attempted telephone contact and receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Intensity of an AE is defined as:

- Mild: no modification of daily activities and does not require mandatory corrective/symptomatic treatment
- Moderate: hinders normal daily activities and/or requires mandatory corrective/symptomatic treatment
- Severe: prevents daily activities and requires mandatory corrective/symptomatic treatment

10.4.1.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an ER or at home for:
  - Severe hypersensitivity reactions (anaphylaxis, allergic bronchospasm [see Appendix I for the clinical criteria for diagnosing anaphylaxis])
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- ALT >3 x ULN + TBILI >2 x ULN or asymptomatic ALT increase >10 x ULN. See Appendix K.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or recurs during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

- Suspected transmission of an infectious agent via a medicinal product (eg, product contamination).

10.4.1.3 Adverse event of special interest

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

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP.

  Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).

  - 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.

- Symptomatic overdose (serious or non-serious) with IMP:
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose given during a 4 day period.

    Of note, asymptomatic overdose has to be reported as a standard AE.

- ALT > 3 x ULN: If increase in ALT >3 x ULN, see the "Increase in ALT" flow chart in Appendix K of the protocol.
  - However, if the increase in ALT is ≥ 2 x the baseline value (with baseline ALT ≥ ULN) but ≤ 3 x ULN, then ALT should be re-tested within 72 hours of initial sample to determine if the retest value meets the AESI criterion of ALT > 3 x ULN. If so, proceed as above and follow the guidelines of Appendix K. If not, monitoring of the laboratory findings will be up to the medical judgment of the Investigator.

- Other project specific AESI(s):
  - [redacted]
  - Anaphylactic reactions or acute allergic reactions that require immediate treatment (refer to Appendix I for definition of Anaphylaxis)
  - Severe injection site reactions (see Appendix J)
  - Tuberculosis or initiation of medications for suspected tuberculosis
  - Acute renal failure (see Appendix K).

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Disease progression is anticipated for the disease being treated (ie, dcSSc) and will be considered expected for the purpose of regulatory reporting. Conversely, an event more severe than the anticipated course of usual disease progression is to be considered unexpected and should be reported.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (SUSAR), the event must be reported, even if it is a component of the study endpoint.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - 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

Instructions for AE reporting are summarized in Table 3.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

Instructions for AE reporting are summarized in Table 3.

10.4.6 Guidelines for management of specific laboratory abnormalities

A decision tree for the management of laboratory abnormalities suggestive of vasculitis (including but not limited to hematuria, proteinuria, increased ESR and/or hsCRP, etc) is provided in Appendix H.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

NOTE: However, if a seriousness criterion is met, the Sponsor is informed immediately (ie, within 1 working day) using the corresponding screens in the e-CRF, following the same process as described for the SAEs.

Table 3 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Serious Adverse Event AESI	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	As applicable
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	No
		Symptomatic overdose	Yes	Yes	No
		ALT >3 x ULN	Yes	Yes	Yes
		[redacted]	[redacted]	[redacted]	[redacted]
		Anaphylactic reactions or acute allergic reactions	Yes	Yes	Yes
		Severe injection site reactions	Yes	Yes	Yes
		TB or initiation of medications for suspected TB	Yes	Yes	Yes
		Acute renal failure	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, Independent Ethics Committee/ Institutional Review Board (IECs/IRBs) as appropriate and to the Investigators.

- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Adverse events that are considered expected will be specified by the reference safety information (IB).

Unblinding of SUSARs by the Sponsor is described in this section.

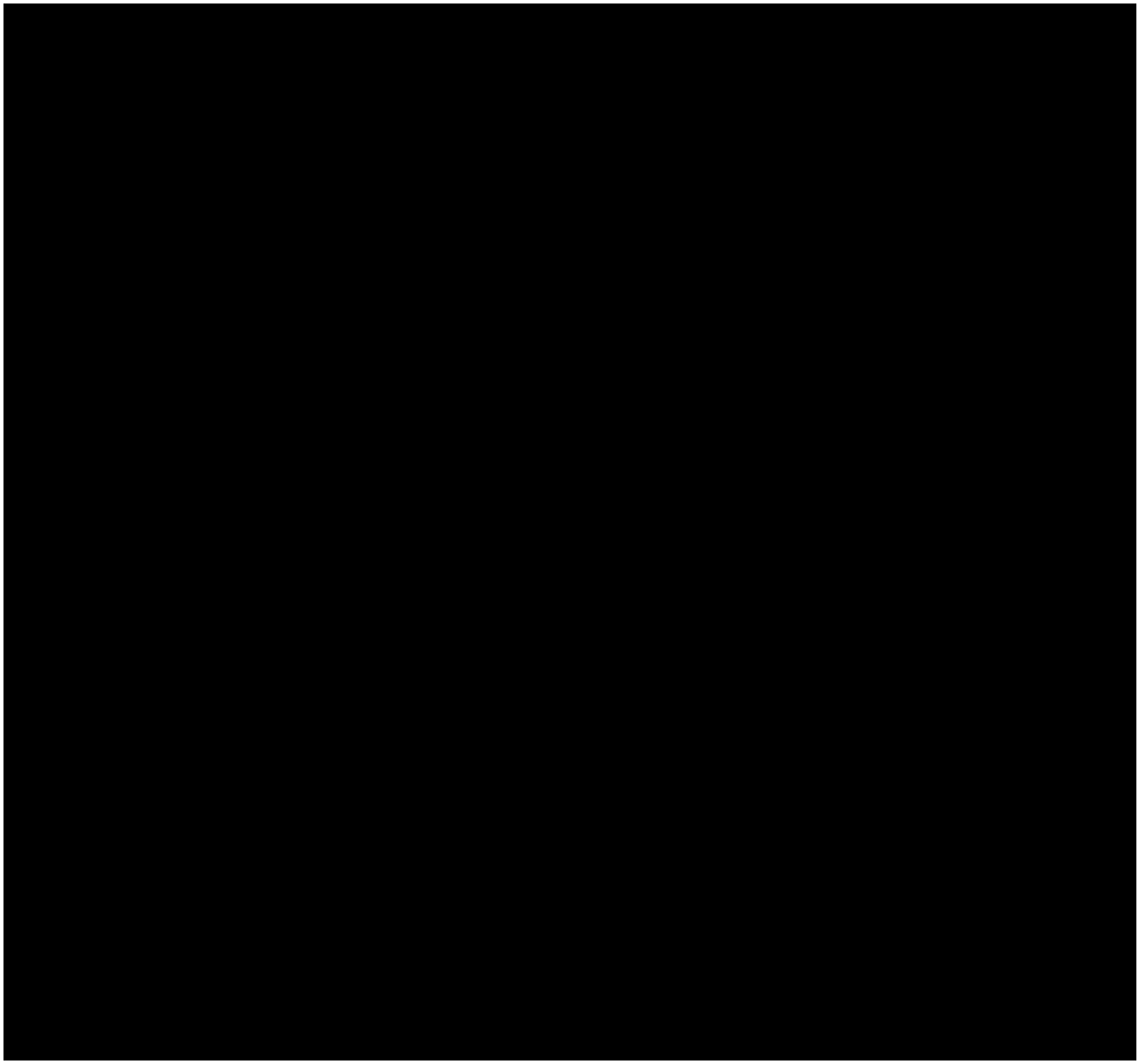
In this study, progression of the underlying condition is anticipated and thus will be considered as expected for the purpose of regulatory reporting. Please refer to the IB.

Any other AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

For regulatory purposes, the treatment code will be unblinded at Sponsor Pharmacovigilance department level for reporting to the Health Authorities of any suspected unexpected adverse drug reaction (SUSAR) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor. Apart from Sponsor Pharmacovigilance department, within the company and associated organizations, the results of this unblinding should remain undisclosed.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report and in the development safety update report.

10.6 Safety instructions



10.6.2 Tolerability at the IMP injection

10.6.2.1 Local injection site reactions

Local injection site reactions that are considered as non-allergic events should be further characterized and evaluated with the assessment of the severity grading of related symptoms such as corresponding for pain, tenderness, erythema/redness, swelling, itching or other (See Appendix J). Special e-CRF screens will need to be completed. If such an AE were to occur, then do not report the individual components of the reaction but rather the term "local injection site reaction", the individual components being described in the specific e-CRF screen.

10.6.3 Systemic allergy reaction

10.6.3.1 Anaphylaxis

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibodies.

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent is given.

These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticarial/angioedema, flushing, nausea, or vomiting.

Anaphylaxis may represent the most severe form of an allergic reaction. Allergic reactions may begin within few hours and persist up to 24 hours post dosing. Refer to Appendix I "Definition of anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored by site personnel or visiting nurse (if injection is performed at the patient's home) for at least 30 minutes or up to 2 hours as per country specific requirements after each administration of investigational product for any signs or symptoms of a hypersensitivity reaction.

Patients should be treated as medically appropriate if any AEs are observed. General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

Sometimes transient injection site reactions, irritant in nature, may occur, requiring no intervention and being of dubious significance. These reactions would not be considered to be allergic reactions, and should only be recorded on the Local Injection Site Reaction Complementary Form.

The IMP should be temporarily discontinued immediately if there is a suspicion of an allergic event related to IMP. Refer to Section 10.4.1.3 for hypersensitivity reactions to be reported as AESIs, and to Section 10.3 for hypersensitivity reactions requiring permanent treatment discontinuation.

10.6.3.2 Allergic adverse event with cutaneous involvement

Allergic AEs with cutaneous involvement or injection site reactions that progress (expand, worsen, etc.) should be evaluated by a dermatologist as soon as possible, and preferably within 1 week of the site first becoming aware of the event.

The Investigator should evaluate the patient for possible etiologies (eg, new medications) and extra-cutaneous symptoms and signs. An unscheduled Central Laboratory assessment for hematology, chemistry, liver panel, PK, and ADA should be obtained. If at all possible, the site will take pictures of the cutaneous lesions for them to be seen during the evaluation with the dermatologist. If the photos are taken, then the copies should be kept as source documents which

may later be collected by the Sponsor. The Investigator will provide a summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

A full consultation report should be sent by the dermatologist to the Investigator. The full report should contain, at a minimum, a detailed description of the skin reaction (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg, scattered, grouped, linear], distribution, color, consistency and presence of pruritus or pain, and other clinical signs). If a skin biopsy is done based on the dermatologist's or Investigator's medical judgment, the results of this investigation (including histopathology and immunofluorescence), should be reported. The Investigator will email or fax the full report and the corrected AE form if necessary, to the Monitoring Team Representative within 24 hours.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The targeted treatment benefit is a difference of 4 points between treatment groups in the mean change in mRSS from baseline to Week 24.

The impact of treatment discontinuations in the context of an ITT analysis where all mRSS data will be included in the analysis (regardless of adherence to treatment) was evaluated. Assuming that 10% of patients will discontinue the treatment, the estimated treatment effect at 24 weeks will be decreased from 4 (targeted treatment effect if all patients adhered to treatment) to 3.6 (targeted treatment effect in all randomized patients).

Ninety-four (94) patients (47 patients each in SAR156597 and placebo groups) will yield 80% power to detect a difference between SAR156597 and placebo groups of 3.6 in the mean change from baseline in mRSS at 24 weeks, assuming a SD of 7 and using a 1-sided alpha of 5% (type I error).

Table 4 provides power calculations depending on several assumptions for treatment effect (difference between treatment groups in the mean change in mRSS from baseline to Week 24) and SD of the response (18) (assumed to be the same in both groups) (20, 21).

Table 4 - Power calculations for mRSS, depending on treatment effect and standard deviation, using a 1-sided alpha of 0.05

Treatment effect	SD	Power
Δ=3	8	57%
	7	67%
	6	78%
Δ=3.6	8	70%
	7	80%
	6	90%
Δ=4	8	78%
	7	87%
	6	94%

Calculations were made using East 6.3 software.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all screened patients with a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

Although not permitted per the protocol, for any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The primary efficacy population will be the ITT population as defined below.

11.3.1.1 Intent–to-treat population

The ITT population is defined as all randomized patients. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

The safety population considered for the safety analyses will include all randomized patients who did actually receive at least 1 dose or part of a dose of the IMP. Patients in the safety population will be analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be the one received in the majority of injections.

11.3.3 Anti-SAR156597 antibody (ADA) population

The anti-SAR156597 antibody analysis will be performed on all randomized and treated patients (safety population) with at least 1 post dose ADA sample with a reportable result. Patients will be analyzed according to the treatment actually received.

11.3.4 Pharmacokinetics population

The PK population will include all randomized and treated patients (safety population) with at least 1 post-dose, non-missing plasma concentration value.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The duration of IMP exposure in weeks is defined as: (last dose date + 7 – first dose date)/7, regardless of intermittent discontinuations.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance <80% will be summarized. In addition, number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%), and >20% under-planned dosing administrations.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoints

The change in mRSS from baseline to Week 24 will be analyzed in the ITT population using a MMRM approach. All post-baseline data available from Week 4 to Week 24 analysis windows will be included in the analysis, regardless of adherence to treatment. Missing data will be accounted for by the MMRM. The model includes the fixed categorical effects of treatment group (placebo, SAR156597), randomization strata (SSc-ILD: Yes/No), time point (Week 4, Week 8, Week 12, Week 24), randomization strata-by-time point interaction and treatment-by-time point interaction, as well as the continuous fixed covariates of baseline mRSS value and baseline value-by-time point interaction. Model assumptions for normality will be explored prior to the analysis testing.

The repeated-measures analysis will be based on the restricted maximum likelihood method assuming an unstructured correlation matrix to model the within-patient errors. Denominator degrees of freedom will be estimated using Kenward-Roger approximation. This model will provide baseline adjusted LSmeans estimates at Week 24 for both treatment groups with their corresponding 95% confidence intervals. To compare SAR156597 to the placebo group, an appropriate contrast statement will be used to test the difference of these estimates at the 5% one-sided alpha level. The 95% and 90% confidence intervals of the difference will be provided.

Let μ_0 and μ_1 be the population means of the change from baseline in mRSS at Week 24 under placebo and SAR156597, respectively. The null hypothesis that will be tested is "$H_0 : \mu_0 = \mu_1$" versus "$H_1 : \mu_0 \neq \mu_1$".

As a sensitivity analysis, the change in mRSS from baseline to Week 24 will also be analyzed in the safety population using the same MMRM model as described above, including only post-baseline data measured during the TEAE period.

Please refer to Section 9.1.1 for the primary efficacy endpoint.

11.4.2.2 Analyses of secondary efficacy endpoints

All secondary endpoints will be analyzed using the ITT population.

Change in continuous secondary efficacy endpoints (HAQ-DI, observed FVC, observed DLco [corrected for hemoglobin]) from baseline to Week 24 will be analyzed using the same MMRM model as for the primary endpoint. Specifically, the model will contain fixed categorical effects of treatment group, randomization strata, time point (Week 4 to Week 24), randomization strata-by-time point interaction and treatment-by-time point interaction, as well as the continuous fixed covariates of corresponding baseline value and baseline-by-time point interaction. This model will provide baseline adjusted LSmeans estimates at Week 24 for both treatment groups with their corresponding 95% confidence intervals. The SAR156597 to placebo difference of these estimates will be provided with its corresponding 95% and 90% confidence intervals and p-value.

Exploratory endpoints

Responder rates (proportion of patients with an improvement from baseline in mRSS of at least 20%, 40% and 60%) at Week 24 and Week 35 will be analyzed using a logistic regression with the categorical effects of treatment group and randomization strata and the continuous covariate of corresponding baseline value. This model will provide the SAR156597 to placebo odds ratio estimate and its 95% and 90% confidence intervals. The p-value will be obtained from the Wald Chi-square test. Patients with missing value at Week 24, respectively Week 35, will be considered as non-responders.

Change in continuous efficacy endpoints from baseline to Week 24 (VAS from SHAQ, UCLA SCTC GIT 2.0, TJC28, digital ulcer count, EQ-5D-5L index) and from baseline to Week 35 (mRSS, HAQ-DI, VAS from SHAQ, observed FVC, observed DLco [corrected for hemoglobin], UCLA SCTC GIT 2.0, TJC28, digital ulcer count, EQ-5D-5L index) will be analyzed using the same MMRM model as for the primary and continuous secondary efficacy endpoints.

Due to the non-normality of the distribution of % predicted FVC and % predicted DLco (corrected for hemoglobin), their change from baseline at Week 24 and Week 35 will be analyzed using a rank-based analysis of covariance (rank analysis of covariance [ANCOVA]) model adjusted for baseline.

The distribution of the predicted probability of improving obtained using the CRISS at Week 24 and Week 35 will be compared between SAR156597 and the placebo group using a Van Elteren's test stratified on randomization strata. Methods to handle missing data will be described in the SAP. In addition, rate of patients for whom the predicted probability of improving obtained using the CRISS at Week 24 and Week 35 is ≥60% will be provided. To assist in interpreting the clinical meaningfulness of any differences in group-level mean change for SHAQ (HAQ-DI and VAS) and EQ-5D-5L (index value and VAS), individual-level change will be assessed. For this, patients will be categorized as "responders" and "non-responders" according to whether they have achieved a threshold of change considered to be meaningful (the MIC). Patients who improve by ≥ the MIC will be considered as clinically important responders (CIRs). As there is little data to support an accepted MIC value for HAQ-DI (20) and the SHAQ VAS assessments in dcSSc, estimates will be empirically-derived from within this study using both distribution-based and anchor-based methods. Distribution-based methods will include one-half a SD and 1 standard error of measurement (SEM) of the baseline score (22, 23, 24). Anchor-based methods will use the EQ-5D index value in which the magnitude of change in the HAQ-DI and the SHAQ VASs among patients who noted at least a 0.08 improvement in their current health status (0-1 scale) will define the MIC (25, 26, 27).

For the EQ-5D-5L, CIRs will be defined by an MIC of ≥0.08 in the index value. CIRs on the EQ-5D VAS will be defined using the same methods as for the HAQ-DI and SHAQ VASs (ie, 0.5SD, 1SEM, EQ-5D index value as an anchor).

The proportion of patients classified as CIRs will be assessed within the ITT sample. Patients without data at the relevant time point will be classified as non-responders. Comparison between groups on responder rates will be performed as described above using a logistic regression.

Please refer to Section 9.1.2 for the secondary efficacy endpoints.

11.4.2.3 Multiplicity considerations

No adjustment will be made. For secondary and exploratory efficacy endpoints, p-values will be provided for descriptive purpose only.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group actually received.

All safety analyses will be performed on the safety population using the following common rules:

- The baseline value is defined generally as the last available value before the first administration of the IMP.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.
- The analysis of the safety variables will be descriptive and no hypothesis testing is planned.

The following definitions will be applied to laboratory parameters, vital signs, and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the TEAE PCSA percentage.

The TEAE period is defined as the time from the first administration of the IMP up to 12 weeks (84 days) from the last dose of IMP.

Please refer to Section 9.2 for the safety endpoints.

11.4.3.1 Adverse events

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent SAEs, all TEAEs leading to permanent treatment discontinuation, treatment-emergent AESI and TEAEs leading to death.

Analysis of TEAE

Treatment emergent adverse event incidence tables will be presented by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing at least 1 TEAE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Analysis of all treatment-emergent SAEs

All treatment-emergent SAEs will be presented by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 serious TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. A listing will be provided for all SAEs by treatment group and patient with flags indicating on-treatment status.

Analysis of all TEAEs leading to permanent treatment discontinuation

TEAEs leading to treatment discontinuation will be presented by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE leading to permanent treatment discontinuation, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. A listing will be provided for all TEAE leading to permanent treatment discontinuation by treatment group and patient.

Analysis of treatment-emergent AESI

Treatment-emergent AESI will be presented by AESI category and PT, showing number (%) of patients with at least 1 treatment-emergent AESI, sorted by decreasing incidence of PT within each AESI category. The AESIs include, but are not limited to, the following categories and complete list of AESI categories will be provided in the statistical analysis plan: tuberculosis, anaphylaxis, hypersensitivity, and vasculitis.

Analysis of Deaths

The following deaths summaries will be generated:

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

11.4.3.2 Laboratory data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all laboratory variables (laboratory values and changes from baseline), will be calculated for each visit (baseline and post-baseline time points), last and worst on-treatment value assessed and presented by treatment group. Only data sampled before or on the day of the last IMP administration will be included in this analysis.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group whatever the baseline level and/or according to the baseline status.

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

11.4.3.3 Potential drug-induced liver injury

The liver function tests, namely ALT, AST, ALP and total bilirubin (TBILI), are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution of peak values of ALT versus peak values of TBILI will be presented. Note that the ALT and TBILI values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for TBILI.

The normalization (to ≤1 x ULN or return to baseline if baseline > ULN) of elevated liver function tests will be summarized by categories of elevation (3 x ULN, 5 x ULN, 10 x ULN,

20 x ULN for ALT and AST, 1.5 x ULN for ALP, and 1.5 x ULN and 2 x ULN for TBILI), with the following categories of normalization: never normalized, normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category (1-3 x ULN, 3-5 x ULN, 5-10 x ULN, 10-20 x ULN, >20 x ULN).

The incidence of liver-related AEs will be summarized by treatment group. The selection of PTs will be based on standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) Hepatic disorder.

11.4.3.4 Vital signs data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all vital signs variables (values and changes from baseline), will be calculated for each visit (baseline and post-baseline time points), last and worst on-treatment value and presented by treatment group. Only data measured before or on the day of the last IMP administration will be included in this analysis.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group whatever the baseline level and/or according to the baseline status.

11.4.3.5 ECG data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all ECG variables (values and changes from baseline), will be calculated for each visit (baseline and post-baseline time points), last and worst on-treatment value and presented by treatment group. Only data measured before or on the day of the last IMP administration will be included in this analysis.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group whatever the baseline level and/or according to the baseline status.

11.4.4 Analysis of immunogenicity

The analysis of immunogenicity will be performed on the ADA population. It will include summaries for ADA prevalence, treatment-boosted ADA incidence, treatment-induced ADA incidence and kinetics of the immune response in patients with treatment-induced ADAs. Impact on PK, efficacy and safety will be assessed. Further details will be provided in the SAP.

Please refer to Section 9.3 for the detection of ADA.

11.4.5 Analyses of pharmacokinetic and pharmacodynamic variables

The plasma concentrations of SAR156597 will be summarized by treatment group and visit using descriptive statistics, including number of available observations, arithmetic and geometric means, SD, coefficient of variation (CV%), median, minimum and maximum.

Please refer to Section 9.3 for pharmacokinetic and pharmacodynamics variables.

Further details will be provided in the SAP.

11.4.6 Analyses of patient reported outcomes (health-related quality of life/health economics variables)

Analysis of SHAQ and EQ-5D-5L is already described in Section 11.4.2.2 (Analysis of secondary efficacy endpoints).

Statistical analyses of resource use will be described in a separate dedicated health economics and outcome research (HEOR) statistical analysis plan.

Please refer to Section 9.1.4.8 and Section 9.1.4.9 for details on SHAQ and EQ-5D-5L.

11.4.7 Analyses of biomarkers

The analysis of biomarkers will be exploratory in nature, with the aim to measure the effect of SAR156597 on biomarkers of the IL-4/IL-13 pathway and biomarkers of the disease.

Please refer to Section 9.3.3 for details on biomarkers.

Details will be provided in the SAP.

11.5 INTERIM ANALYSIS

Futility analysis:

In case of major recruitment issues a futility analysis with non-binding recommendation will be performed in order to make further decisions regarding trial continuation/discontinuation.

Two-step analysis:

The analysis will be conducted in two steps:

- First step: Main efficacy and safety analyses

The first analysis will be conducted when all patients have been randomized and have at least all their data up to Week 24 collected and validated, and will consist in the final analysis of the efficacy endpoints up to Week 24. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect.

- Second step: Final analysis

The second analysis will be conducted at the end of the study and will consist in the final analysis of Week 35 efficacy endpoints and final safety analysis.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-Investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for archiving for potential future protein assays and mRNA analysis, the optional Future Use of Samples informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The informed consent form and the optional Future Use of Samples informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

The scientific justification for collection of race/ethnic origin of the patients during the clinical study is specified in Section 14.5.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, IB, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS (E-CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and Sub-Investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Sub-Investigator not to mention any information or the product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on afro American population for FDA).

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purposes of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.

- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance of the Investigator or Sub-Investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consents.

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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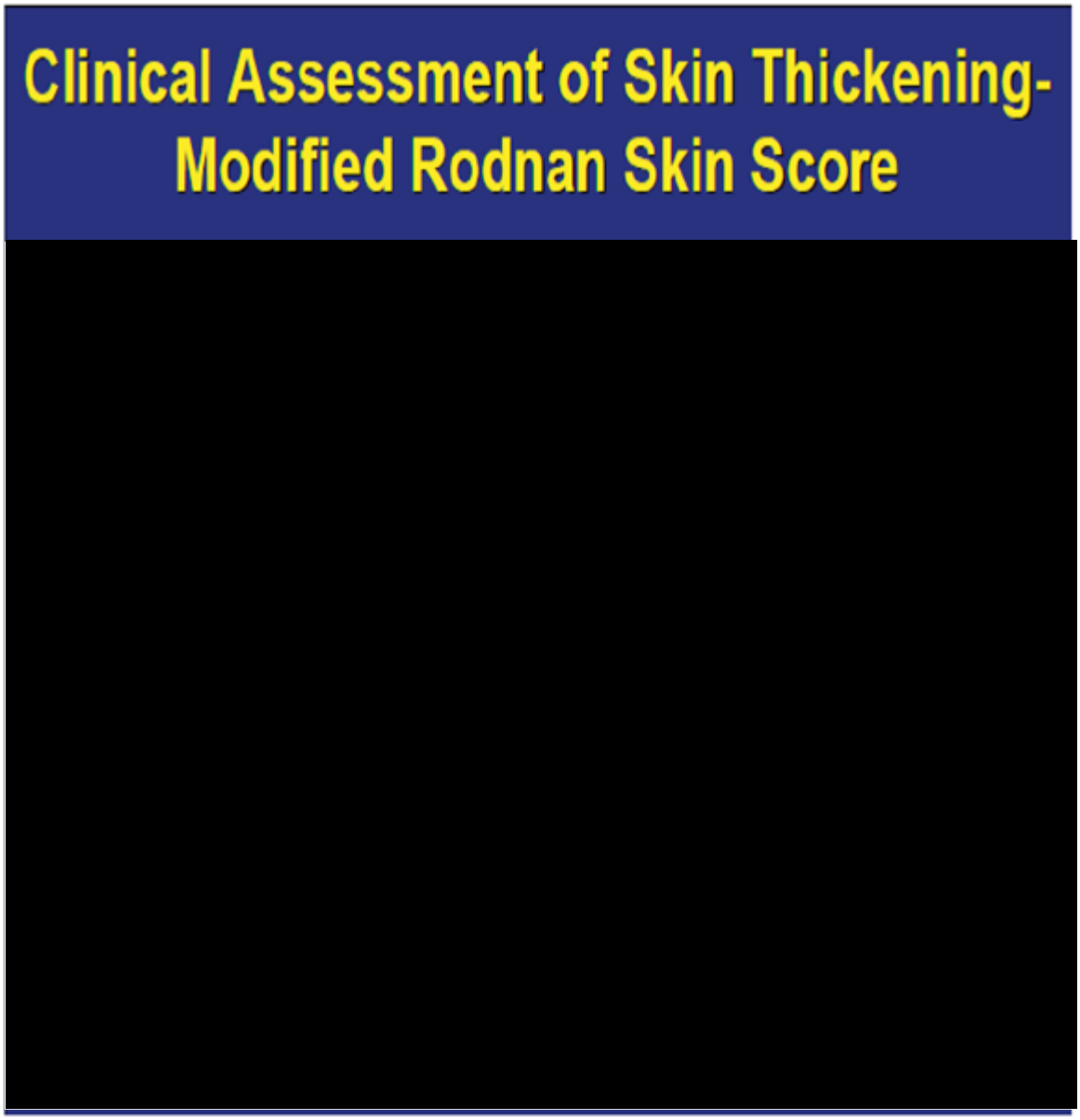
17 APPENDICES

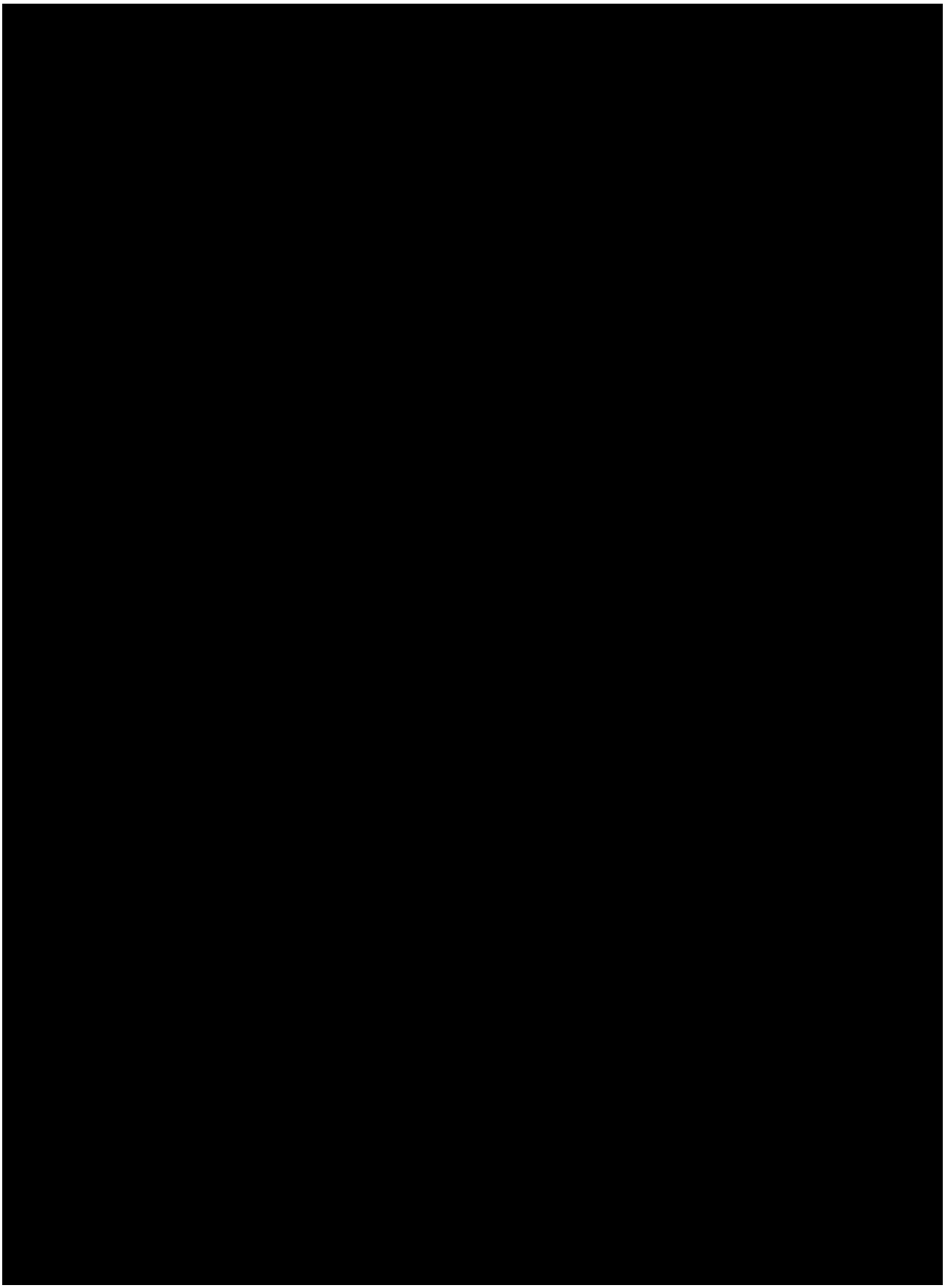
Appendix A mRSS

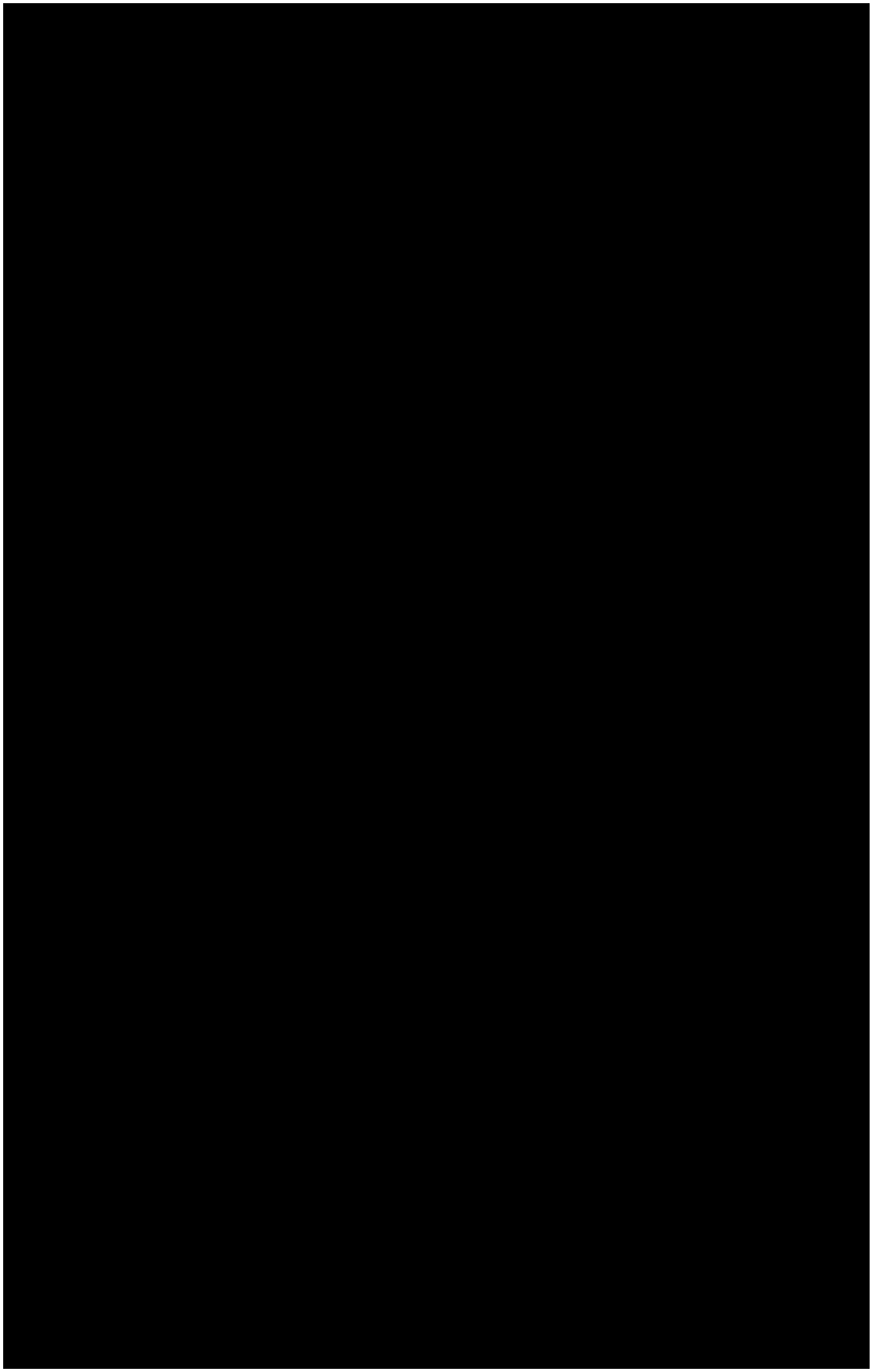


Appendix B SHAQ

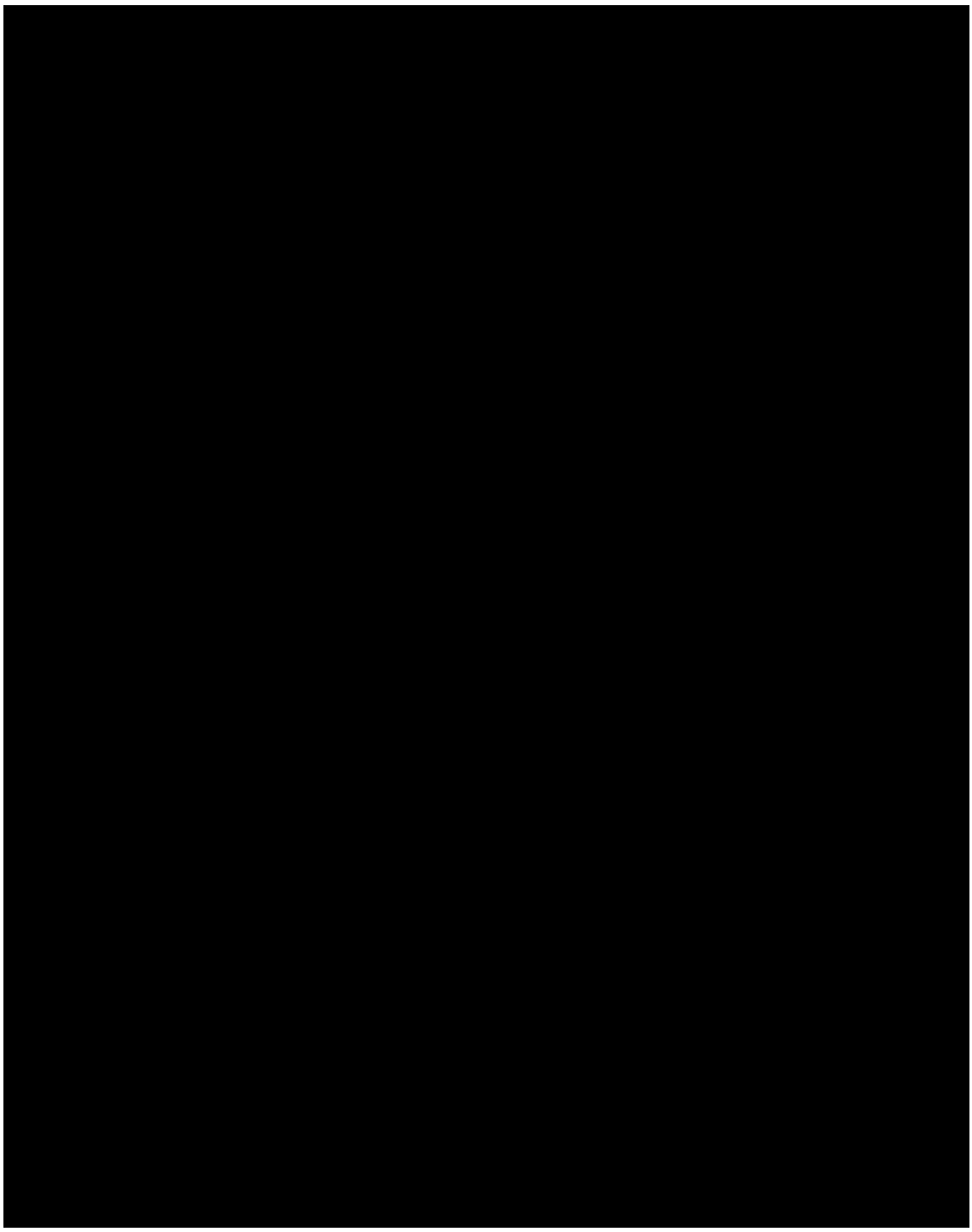
HEALTH ASSESSMENT QUESTIONNAIRE

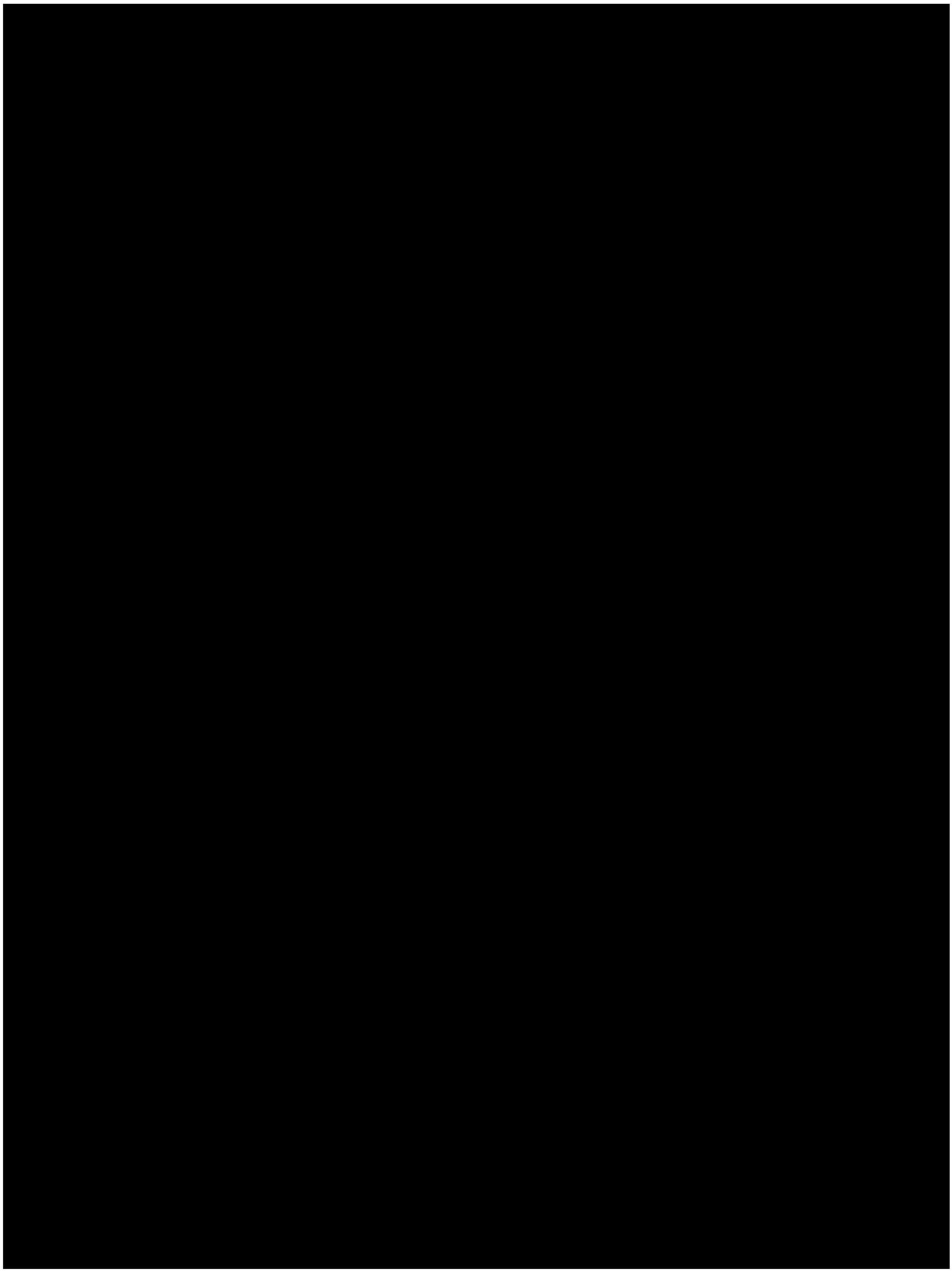
[redacted]

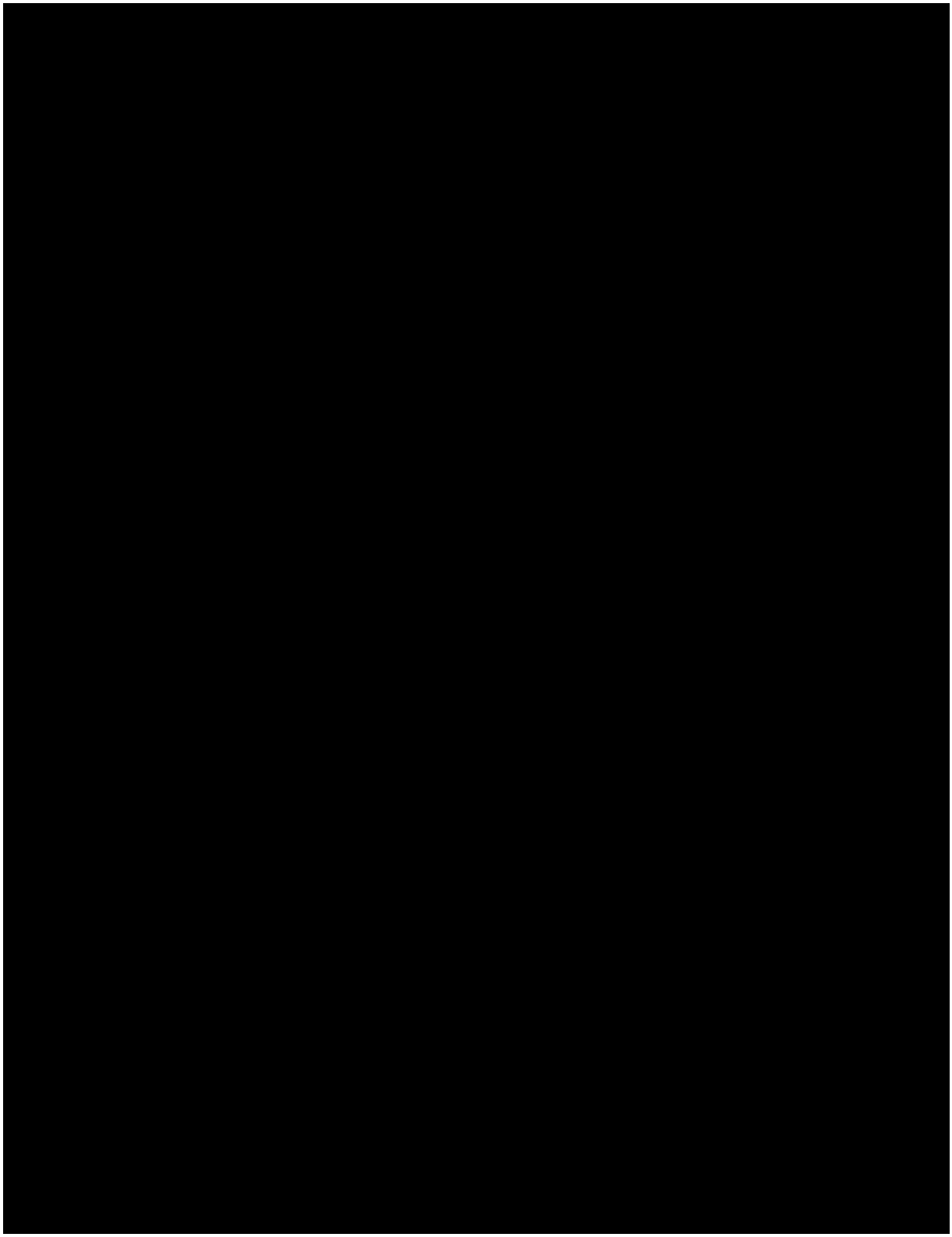


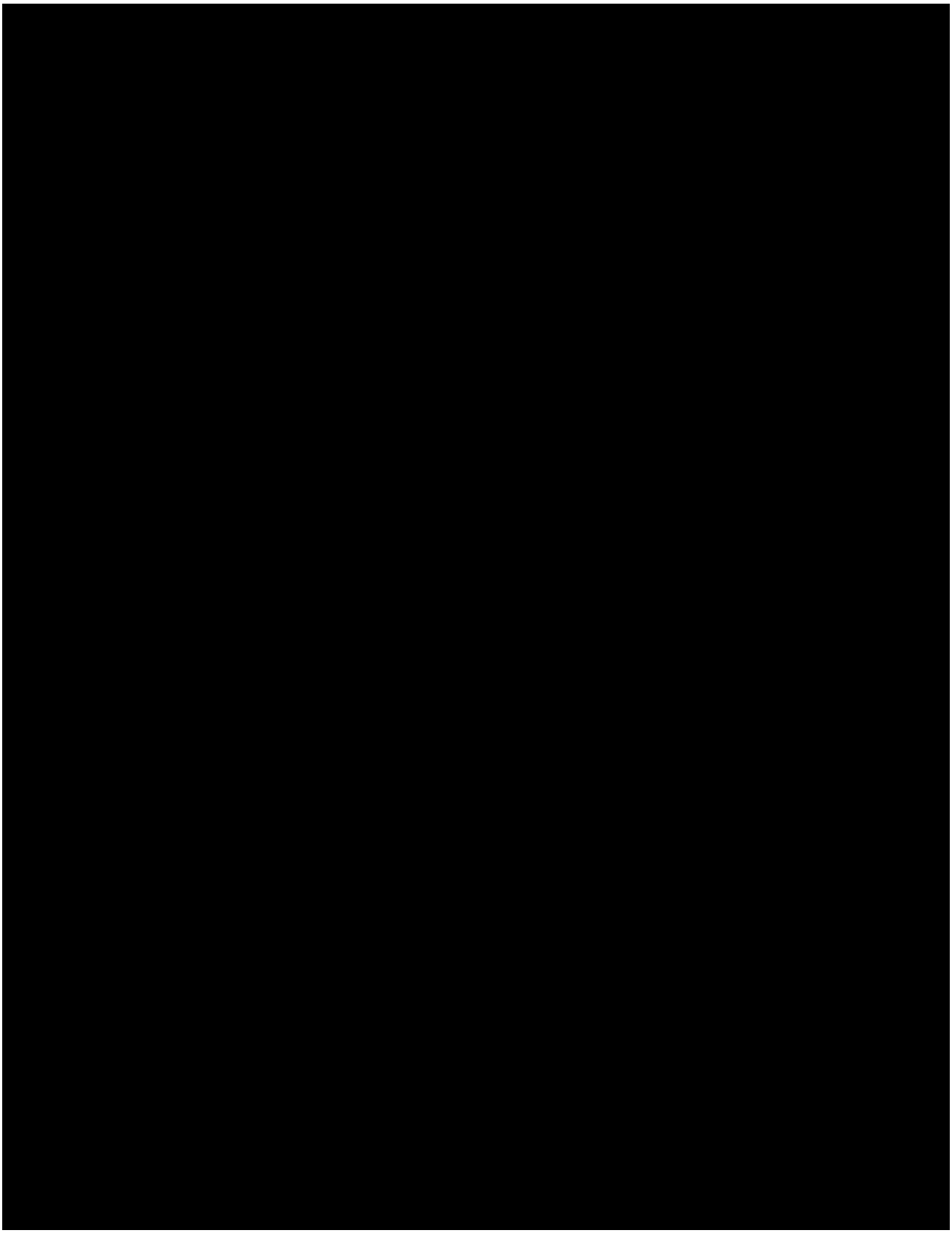


Appendix C UCLA SCTC GIT 2.0 Questionnaire



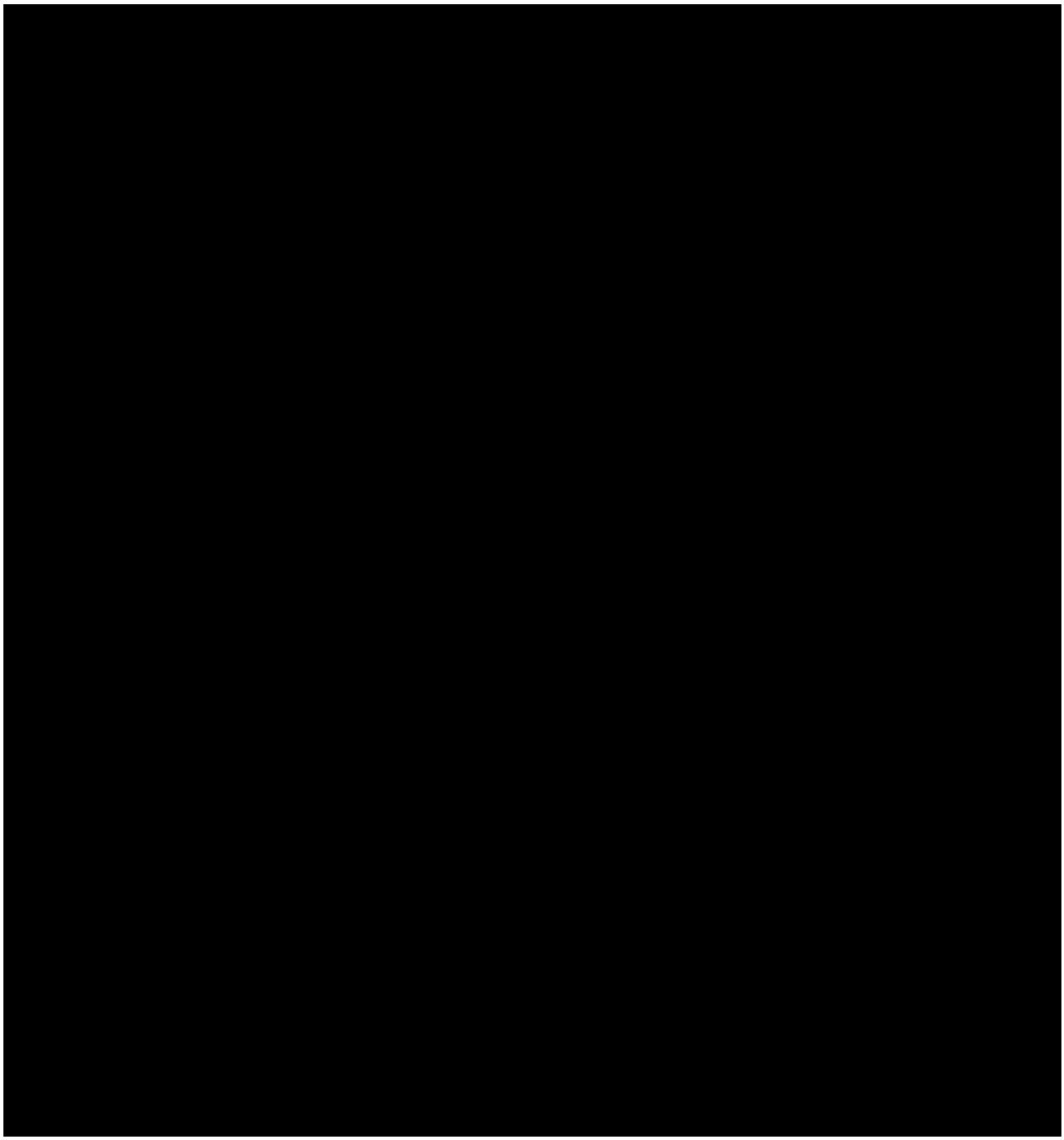


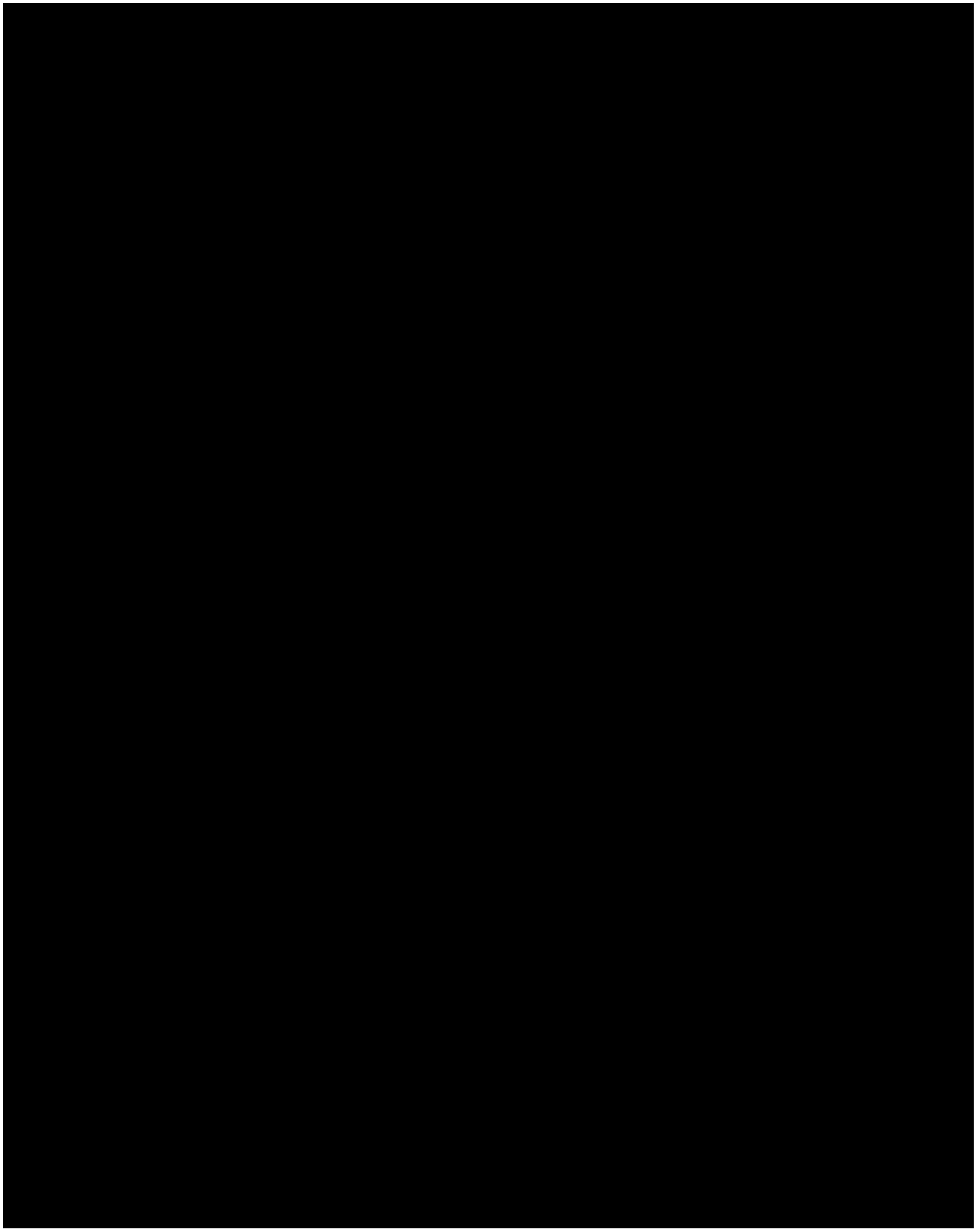




Appendix D : EQ-5D-5L

Health Questionnaire
English version for the USA

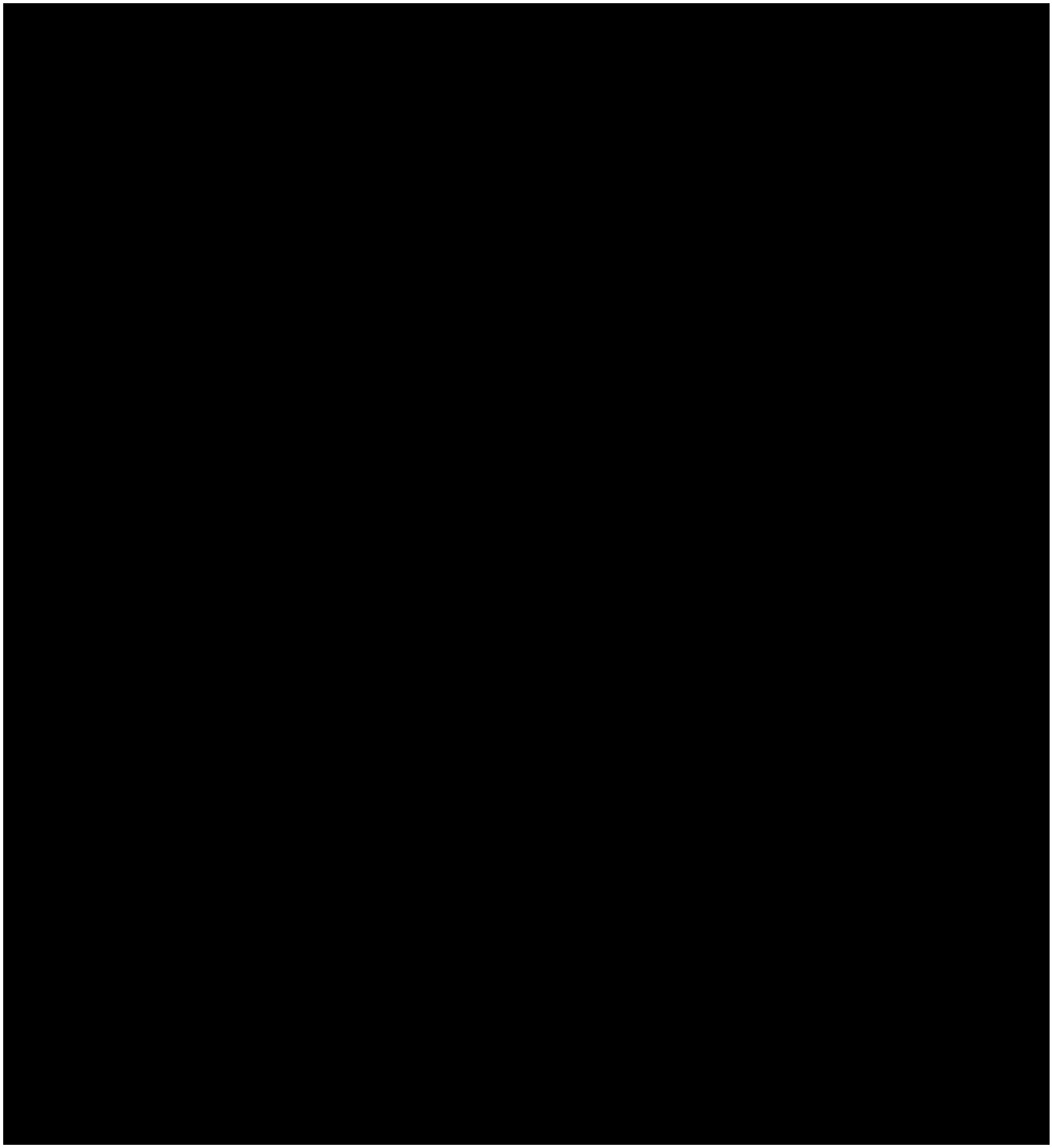




Appendix E Patient and physician global assessments of overall health using the 0-10 Likert scale

Appendix F TJC28

Tender Joint Count 28 (TJC28)

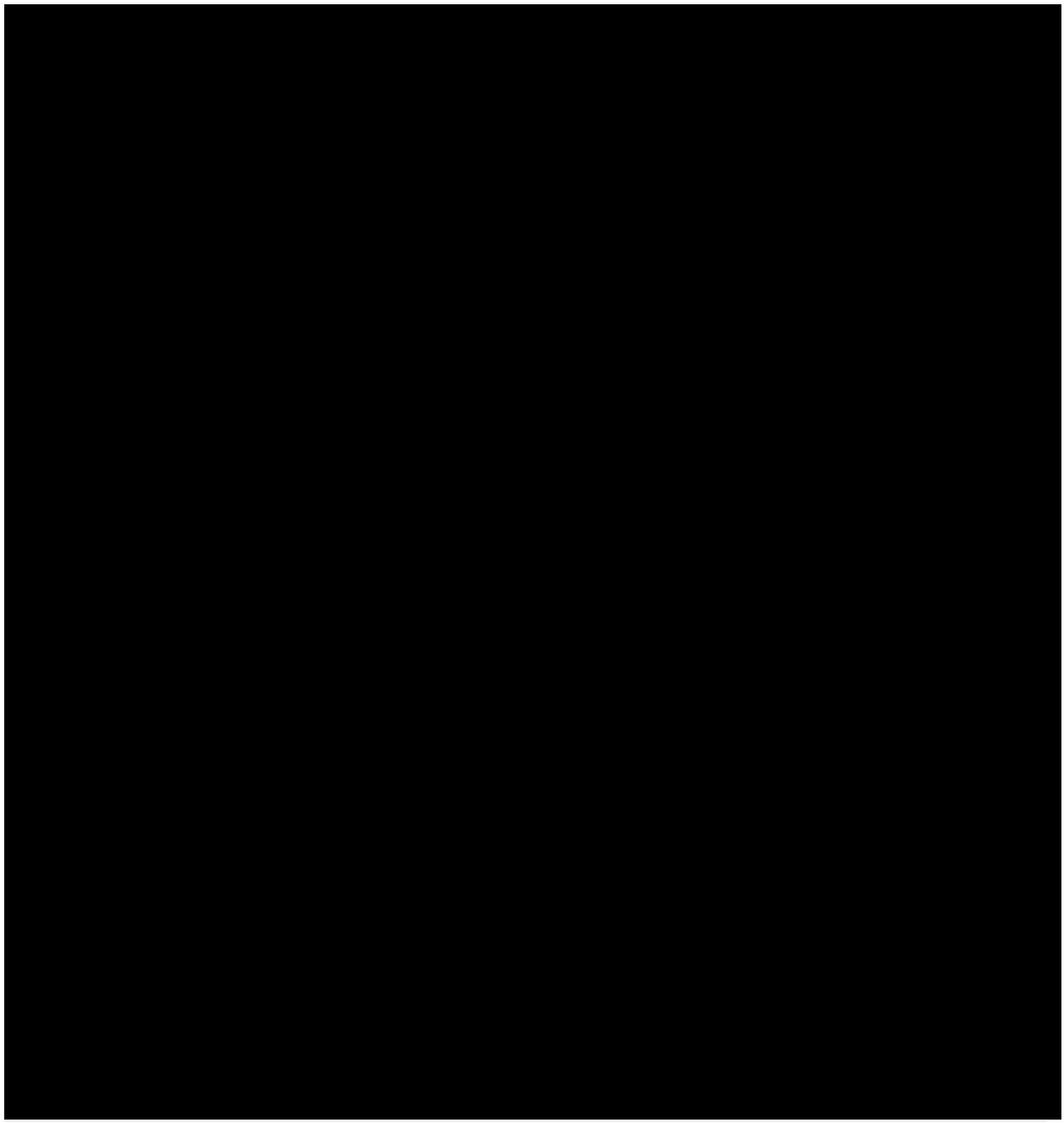


Appendix G Guidance on contraceptive methods for United Kingdom only

Acceptable forms of effective contraception include:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Male sterilisation (provided that the partner is the sole sexual partner of the woman of childbearing potential study participant and that the sterilized partner has received medical assessment of the surgical success)
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Appendix H [redacted]



Appendix I Clinical criteria for diagnosing anaphylaxis

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

Anaphylaxis is highly likely when any one of the following 3 criteria are fullfilled:

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING

A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

B) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

A) Involvement of the skin-mucosal tissue eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula

B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

C) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

D) Persistent gastrointestinal symptoms (eg, crampy, abdominal pain, vomiting)

Reduced BP after exposure to known allergen for that patient (minutes to several hours):

A) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

B) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

.
Abbreviations: PEF = peak expiratory flow; BP = blood pressure

*Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg = [2 x age]) from 1 to 10 years and less than 90 mm Hg from 11 to 17 years.

Appendix J Assessment of Local Injection Site Reactions

Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema / Redness *	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of topical or systemic treatment	Prevents daily activity or leads to other significant dermatologic conditions (such as infection, scarring, etc.)	ER visit or hospitalization
Other (Please specify)***	No modification of daily activities and/or does not require symptomatic treatment.	Hinders normal daily activities and/or requires symptomatic treatment.	Prevents daily activities and requires symptomatic treatment.	ER visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

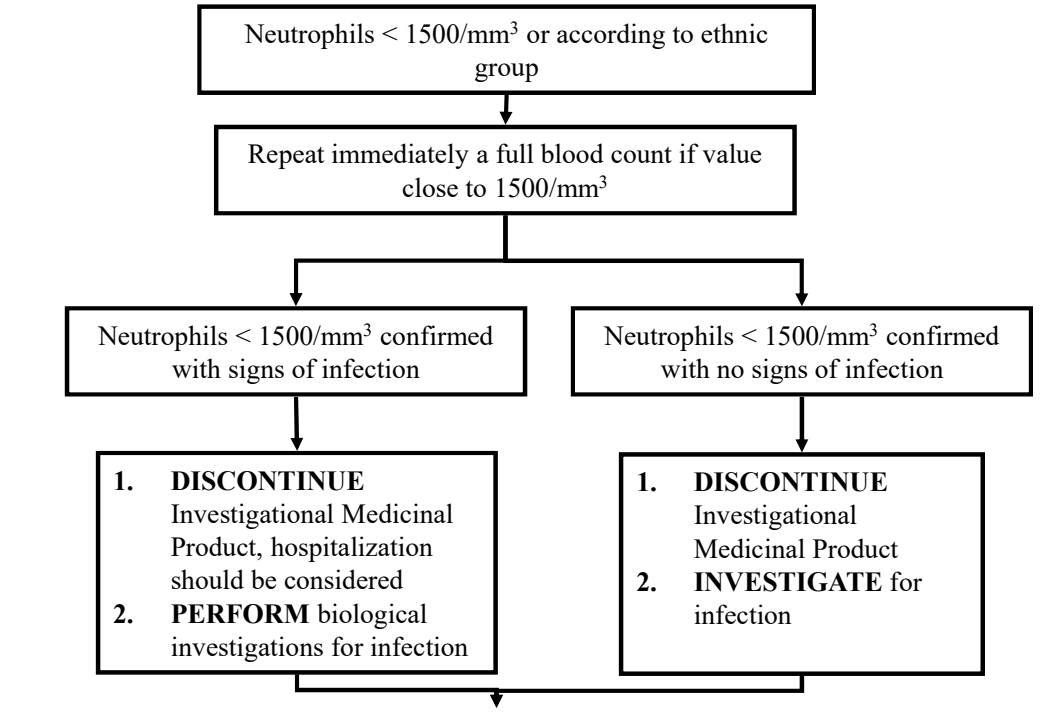
** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

*** Please specify the other signs or symptoms (for example, hematoma, discoloration, re-activation, etc).

ADAPTED from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005

Appendix K General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

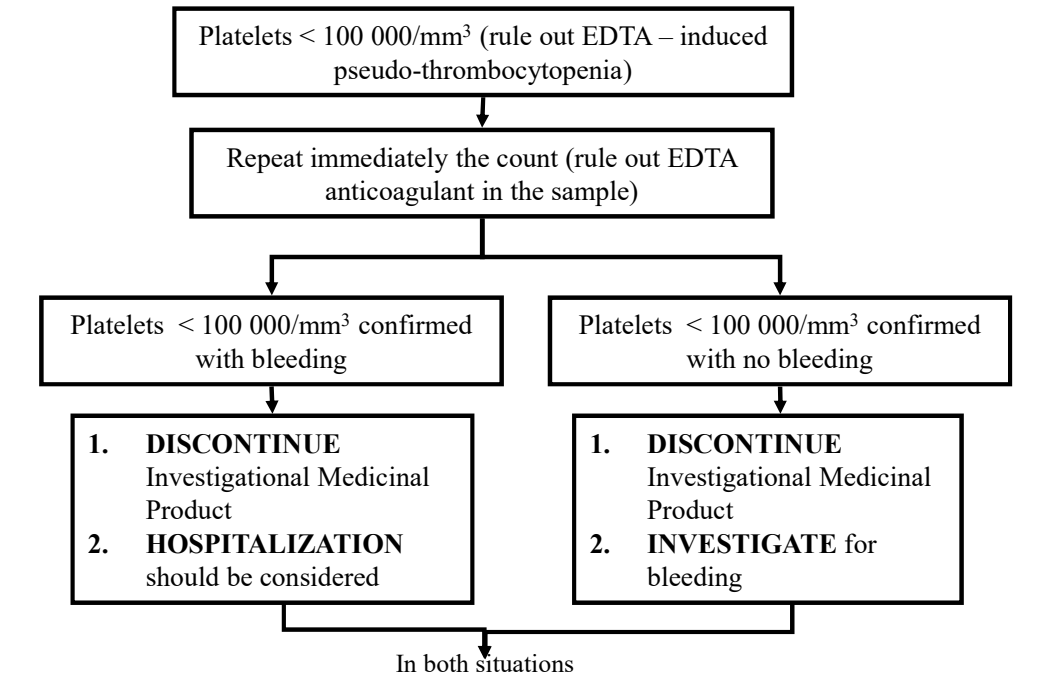


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•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 AEs in Section 10.4.3 is met.

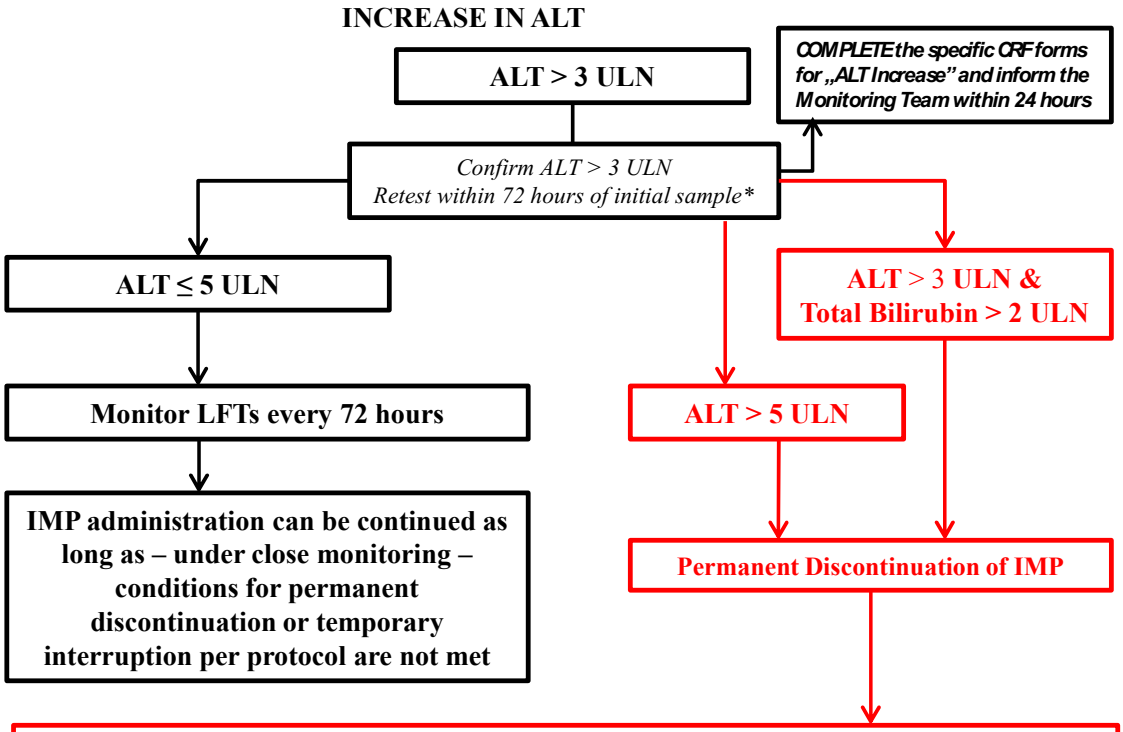
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm3
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.



In ANY CASE, FOLLOW the instructions listed in the box below:

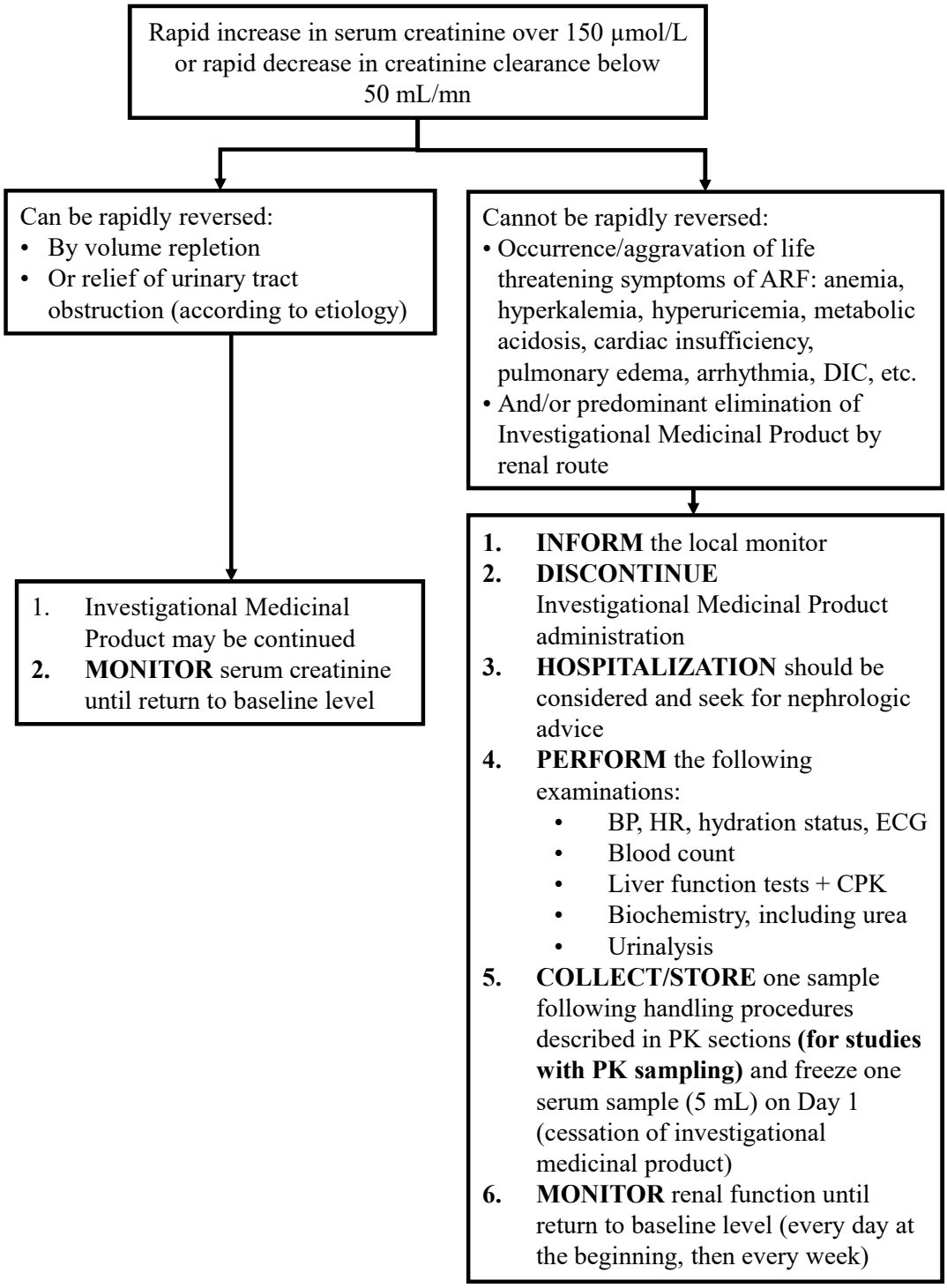
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, 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** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - A*s closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

- *If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
- Note:
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.4 for guidance on safety reporting.

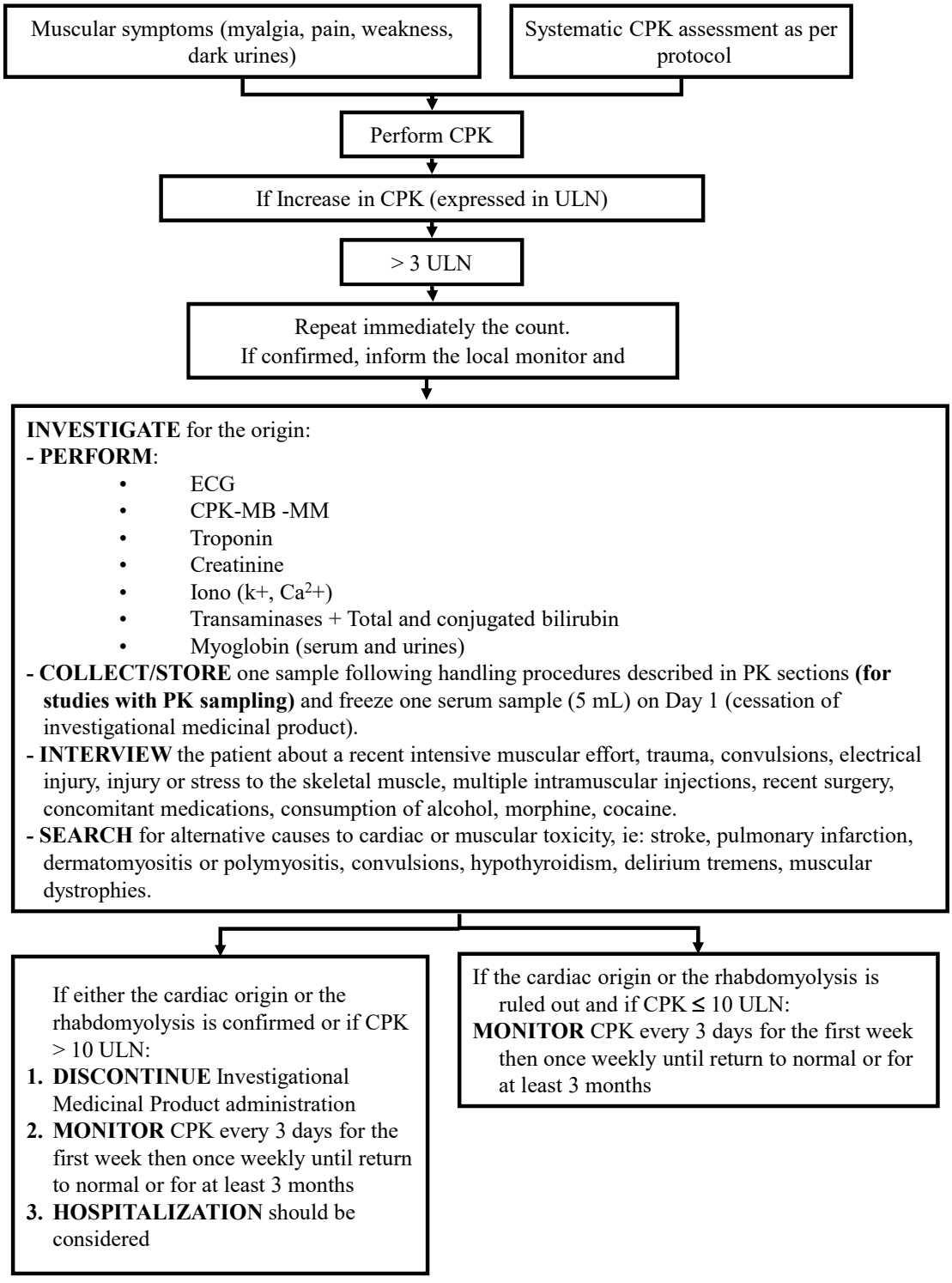
- Normalization is defined as ≤ ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.3 is met.

Appendix L Clinically significant ECG

The following list of ECG findings is considered to be clinically significant and would result in the exclusion of the patient from the study based upon Exclusion criterion 15 [E 15]. This list is not exhaustive in nature but serves as a guide to help determine clinical significance with regards to ECG for the safety of the patient who is being considered for this study.

If there is a question pertaining to another clinically significant finding not described below, it must be brought to the attention of Sanofi before consideration of enrollment. Sanofi will then provide timely recommendation after internal review regarding the patient's eligibility associated with this exclusion criterion.

Clinically significant ECG finding that would meet Exclusion criterion 15 [E 15]**:**

- Second-degree heart block
- Third-degree heart block
- QT prolongation (*symptomatic*)
- Sick sinus syndrome
- Left bundle branch block (*complete*)
- Right bundle branch block (*complete*)
- Atrial fibrillation (*uncontrolled*)
- Atrial flutter (*uncontrolled*)
- Wolff-Parkinson-White syndrome
- Atrioventricular nodal reentry tachycardia
- Ventricular Arrhythmias
  - Ventricular Tachycardia
  - Ventricular Fibrillation
  - Torsades de Pointes
  - Bradyarrhythmias

ACT14604 Amended Protocol01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	09-Aug-2017 13:53 GMT+0200
[redacted]	Clinical Approval	09-Aug-2017 16:48 GMT+0200