AMENDED CLINICAL TRIAL PROTOCOL 2

COMPOUND: SAR156597

Efficacy and safety of SAR156597 in the treatment of Idiopathic Pulmonary Fibrosis (IPF): A randomized, double-blind, placebo-controlled, 52-week dose-ranging study

STUDY NUMBER: DRI11772

VERSION DATE / STATUS: 21-Jul-2015 / Approved

STUDY NAME: ESTAIR

NCT02345070

Protocol Amendment 10	Version number: 1	Date: 21-Jul-2015
Amended Clinical Trial Protocol 2 - Germany	Version number: 1	Date: 02-Jul-2015
Protocol Amendment 9 - Germany	Version number: 1	Date: 02-Jul-2015
Amended Clinical Trial Protocol 1 - Korea	Version number: 1	Date: 18-May-2015
Protocol Amendment 8 - Korea	Version number: 1	Date: 18-May-2015
Amended Clinical Trial Protocol 1 - France	Version number: 1	Date: 14-Apr-2015
Protocol Amendment 7 - France	Version number: 1	Date: 14-Apr-2015
Amended Clinical Trial Protocol 1 - Czech Republic	Version number: 1	Date: 27-Mar-2015
Protocol Amendment 6 - Czech Republic	Version number: 1	Date: 27-Mar-2015
Amended Clinical Trial Protocol 2 United Kingdom	Version number: 1 (electronic 2.0)	Date: 16-Mar-2015
Protocol Amendment 5 - United Kingdom	Version number: 1	Date: 16-Mar-2015
Amended Clinical Trial Protocol 1 Denmark	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015

Protocol Amendment 4 - Denmark	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015
Amended Clinical Trial Protocol 1 - United Kingdom	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015
Protocol Amendment 3 - United Kingdom	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015
Amended Clinical Trial Protocol 1 - Germany	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015
Protocol Amendment 2 - Germany	Version number: 1 (electronic 1.0)	Date: 20-Jan-2015
Amended Clinical Trial Protocol 1 - Global	Version number: 1 (electronic 1.0)	Date: 19-Dec-2014
Protocol Amendment 1	Version number: 1 (electronic 1.0)	Date: 19-Dec-2014
Clinical Trial Protocol	Version number: 1 (electronic 2.0)	Date: 14-Nov-2014

EudraCT or IND number : 2014-003933-24

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CLINICAL TRIAL SUMMARY

COMPOUND:SAR156597	**STUDY No: DRI11772**
TITLE	Efficacy and safety of SAR156597 in the treatment of Idiopathic Pulmonary Fibrosis (IPF): A randomized, double-blind, placebo-controlled, 52-week dose-ranging study.
INVESTIGATOR/TRIAL LOCATION	International
PHASE OF DEVELOPMENT	Phase 2
STUDY OBJECTIVE(S)	**Primary objective** • To evaluate, in comparison with placebo, the efficacy of 2 dose levels/regimens of SAR156597 administered subcutaneously during 52 weeks on lung function of patients with IPF **Secondary objective(s)** • To evaluate the efficacy of 2 dose levels/regimens of SAR156597 compared to placebo on IPF disease progression • To evaluate the safety of 2 dose levels/regimens of SAR156597 compared to placebo in patients with IPF • To evaluate the pharmacokinetics (trough plasma concentrations) of SAR156597 administered subcutaneously during 52 weeks • To assess the potential immunogenicity of SAR156597 • To evaluate the effect of SAR156597 on circulating biomarkers • To explore the effect of SAR156597 on quality of life
STUDY DESIGN	• Multinational, randomized, double-blind, placebo-control, 3 parallel groups • Patients will be randomized in a 1:1:1 ratio to receive SC administrations of SAR156597 or placebo in one of the following regimens: o SAR156597 200mg every week (qw) o SAR156597 200mg every 2 weeks (q2w) alternating with placebo every other week (for blind purposes) o Placebo every week (qw) • Patient stratification at baseline according to background therapy in authorized countries: o Patient with background therapy with either pirfenidone or nintedanib versus patient without background therapy • Duration of treatment: 52 weeks
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** • Consenting male or female patients

	• Documented diagnosis of IPF according to the following criteria:
	  • Exclusion of other known causes of interstitial lung disease (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)*
	  AND
	  • Combination of patterns of usual interstitial pneumonia (UIP) on HRCT images of chest, and on surgical lung biopsy (when obtained)*
	  OR
	  Presence of Possible UIP pattern* on HRCT images of chest AND additional evidence of traction bronchiectasis as assessed by an experienced chest radiologist (Central Review**)
	* As defined in the current 2011 ATS/ERS/JRS/ALAT guidelines
	** The patterns of UIP on HRCT images of chest and histopathology in surgical lung biopsy (if done) will be reviewed by central reviewers (a radiologist and a pathologist experienced in interstitial lung diseases) to confirm diagnosis of IPF for consistency.
	Exclusion criteria
	• Age ≤40 years
	• IPF disease diagnosis >5 years
	• Forced vital capacity (FVC) <40% of predicted value
	• Carbon monoxide diffusing lung capacity (DLCO) corrected for hemoglobin <30% of predicted value
	• Severe chronic obstructive bronchitis as characterized by FEV1/FVC <0.70
	• Need for 24 hrs of oxygen therapy or oxygen saturation <88% after 10 minutes breathing ambient air at rest
	• Known diagnosis of significant respiratory disorders (eg, asthma, tuberculosis, sarcoidosis, aspergillosis, or cystic fibrosis) other than IPF
	• Pulmonary artery hypertension requiring a specific treatment
	• Currently listed and/or anticipated to be listed for lung transplantation within the next 6 months (active list)
	• History of vasculitis or connective tissue disorders or ANCA positive
	• History of myocardial infarction within 6 months prior to screening

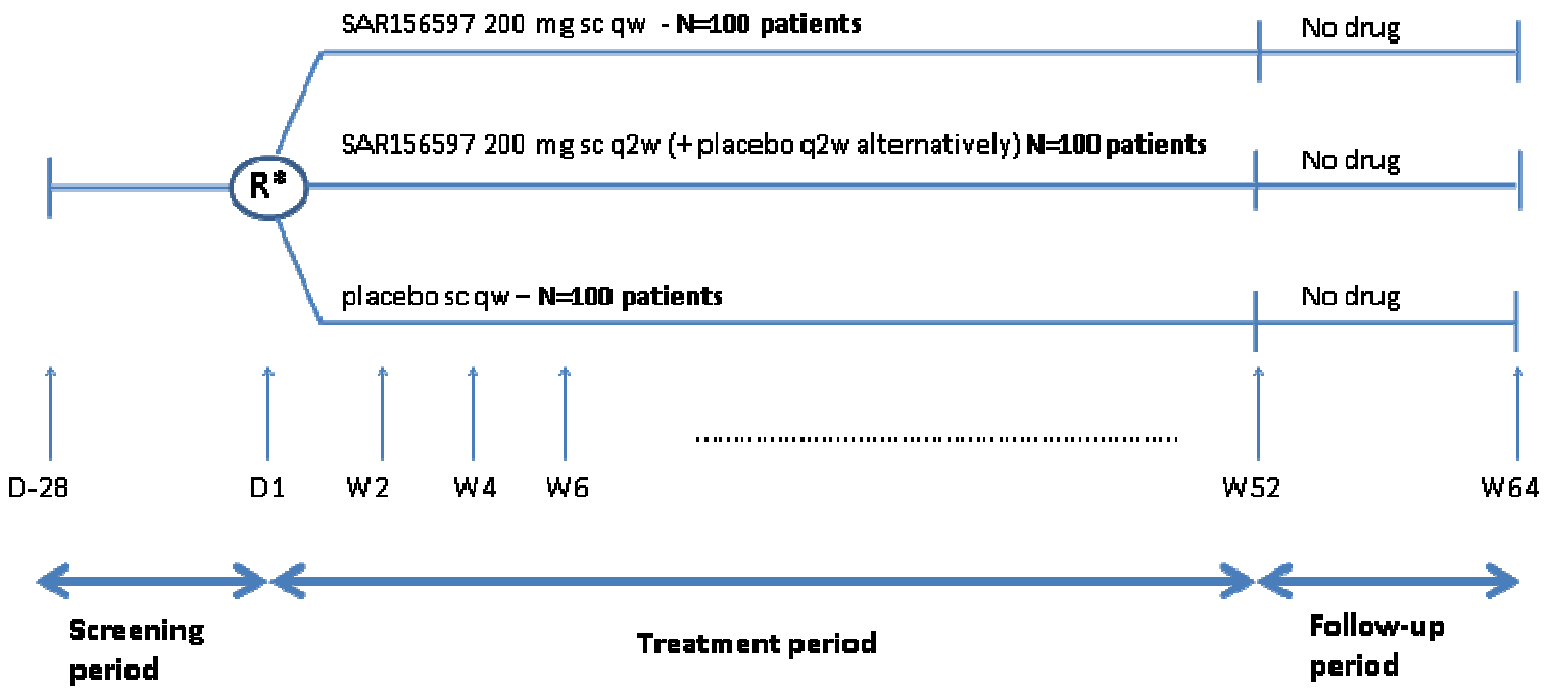
Total expected number of patients	Approximately N=300 (100 patients per group)
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	SAR156597 or placebo • SAR156597 in lyophilized form (each vial containing 125 mg total of SAR156597 plus excipients, to be reconstituted with 1.1 mL of sterile water for injection to achieve a final concentration of 100 mg/mL of SAR156597) • Placebo consisting of 1.5 mL of liquid per vial containing the same excipients at the same concentrations as for the reconstituted SAR156597 formulation
Route(s) of administration	Subcutaneous (SC)
Dose regimen	Patients will receive SC administrations of SAR156597 or placebo in one of the following regimens: • SAR156597 200mg qw • SAR156597 200mg q2w alternating with placebo every other week • Placebo qw
Noninvestigational medicinal product(s) (if applicable)	NA
ENDPOINT(S)	**Efficacy** **Primary endpoint** • Absolute change from baseline in % predicted FVC at 52 weeks **Secondary endpoint(s)** • Disease progression as defined by the number of the following events: decrease in absolute % predicted FVC ≥10%, or decrease in absolute % predicted DLCO ≥15%, or lung transplant, or death at 52 weeks • All-cause mortality at 52 weeks **Exploratory endpoint(s)** • Acute exacerbations • Respiratory hospitalizations and non-elective hospitalizations • Change in 6-Minute Walk Test distance (6-MWT) • Changes in HRCT lung interstitial evaluation score • Change on quality of life score as measured on the St George's Respiratory Questionnaire (SGRQ) and on the EuroQol questionnaire, 5 level system (EQ-5D-5L) **Safety** • Adverse events (AEs)/treatment-emergent adverse events (TEAEs) • Physical examination and body weight • Vital signs and 12-lead electrocardiogram • Clinical laboratory evaluations including hematology, biochemistry and urinalysis • [redacted]

	[redacted] • Tolerability at the investigational medicinal product (IMP) injection site: - Erythema (diameter and graded severity) - Swelling/induration/edema (diameter and graded severity) - Pain assessment **Immunogenicity** Testing for anti-drug antibodies (ADA) **Biomarker quantification** • Blood biomarkers which may predict response to drug, disease progression and provide evidence of drug action will be collected including but not limited to inter-cellular adhesion molecule 1 (ICAM1), TARC, periostin and HE4 • Archived blood samples will be performed for future assay of protein and mRNA biomarkers related to the diagnosis, progression, or therapeutic responsiveness of IPF **Pharmacokinetics** Population PK analysis of plasma SAR156597 concentrations to predict PK parameters at steady state (Cmax, tmax, AUC0-168 &/or AUC0-336) and time to reach steady state.
ASSESSMENT SCHEDULE	The study will comprise 10 on-site visits AND 9 phone calls: • Visits: - V1 screening visit between D -28 and Day -1 - V2 baseline visit at D1 (first dosing) - during the treatment period*: - visit every 2 weeks from V2 to V5 - every 6 weeks from V5 to V6 - every 12 weeks from V6 to V8 - every 16 weeks from V8 to V9 (Week 52; last dosing) - V10 follow-up visit at Week 64 - A time window of ±2 days will be allowed for each visit • Phone calls: - For safety considerations at Weeks 8, 16, 20, 28, 32, 40, 44, 48 during the treatment period and at Week 58 during the follow-up period. *IMP administration being every week.
STATISTICAL CONSIDERATIONS	**Sample size determination:** Based on prior clinical trial experience in IPF patients, it is estimated that the standard deviation (SD) of the absolute change in % predicted FVC at 52 weeks is approximately 12%. For the primary efficacy parameter of absolute change in % predicted FVC, 92 patients per treatment group will yield 80% power to detect a 5 percentage point difference between the treatment groups and placebo. Additional patients will be randomized in each regimen to allow for dropouts; therefore, approximately 100 patients

	will be randomized into each treatment group, for a total sample size of approximately 300 patients for the study. **Analysis sets:** Safety analyses will be conducted on the Safety population, which includes all randomized patients who receive at least 1 injection of investigational medicinal product. Efficacy analyses will be performed on the modified intent to treat population (primary population), which includes all patients who receive at least 1 injection of investigational medicinal product, have a valid baseline % predicted FVC measurement, and have at least 1 post-baseline % predicted FVC measurement. The primary statistical analysis will be performed once all patients have completed the Week 52 assessment and the database has been cleaned and locked. **Primary efficacy analysis** A rank-based analysis of covariance (ANCOVA) will be performed on the change from baseline in % predicted FVC. The ANCOVA model will include treatment group as the main factor and the baseline % predicted FVC as a continuous covariate. **Analysis of secondary endpoints** Analysis of time to event endpoints will be performed using the log-rank test and Cox proportional hazards regression model. **Safety analysis** TEAEs and serious AEs (SAEs) (will be summarized for each treatment group by primary system organ class (SOC), high level group term (HLGT), high level term (HLT), and preferred term (PT), as well as by severity and relationship to study treatment. The rate of potentially clinically significant abnormalities (PCSAs) will also be summarized by treatment group. Additionally, listings of all AEs, SAEs, and AEs leading to treatment discontinuation will be generated. Clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), a selected panel of biomarkers, and ADA will be tabulated by treatment group. These safety analyses will be compared qualitatively between the treatment groups.
DURATION OF STUDY PERIOD (per patient)	The study will last 68 weeks per patient as follows: • 4 weeks of screening • 52 weeks of study treatment • 12 weeks of follow-up with no study treatment

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R*: randomization
Sc: subcutaneous
D: day
W: week

1.2 STUDY FLOW CHART

Period	Screening	Baseline visit	Treatment Period															FU[m]	
Visit/phone calls	V1[a]	V2[b]	V3	V4	V5	Phone call	V6	Phone call	Phone call	V7	Phone call	Phone call	V8	Phone call	Phone call	Phone call	V9 EOT	Phone call	V10 EOS
Day/week	D-28 to D-1	D1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W58	W64
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	X	X	X	X	X	X	X
Inclusion / exclusion criteria	X	X																	
Randomization		X																	
Call IVRS[c]	X	X	X	X	X		X			X			X				X		X
Study treatment administration																			
SAR156597 or placebo[d]		←	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	→		
Safety																			
Physical examination[e]	X	X	X	X	X		X			X			X				X		X
Vital signs[f]	X	X	X	X	X		X			X			X				X		X
ECG	X	X		X			X			X			X				X		X
Hematology, biochemistry, urinalysis[g]	X	X		X			X			X			X				X		X
Serology tests[h]	X																		
ANCA, complement assays	X			X			X			X			X				X		X
[redacted]																			
Blood for archiving [redacted]							X			X			X				X		X
Tuberculosis screen[i]	X																		
β-HCG blood test[k]	X																		
Urine pregnancy test[k]		X		X			X			X			X				X		X

Period	Screening	Baseline visit	Treatment Period															FU[m]	
Visit/phone calls	V1[a]	V2[b]	V3	V4	V5	Phone call	V6	Phone call	Phone call	V7	Phone call	Phone call	V8	Phone call	Phone call	Phone call	V9 EOT	Phone call	V10 EOS
Day/week	D-28 to D-1	D1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W58	W64
Review patient booklet (Local tolerability of sc injections/ IMP compliance)[l]		X (post-dose) ----------→																	
Adverse event reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																			
Blood samples for PK[n]		X		X			X			X			X				X[p]		X
Blood samples for ADA[o]		X		X			X			X			X				X		X
Efficacy																			
PFTs [q]	X	X					X			X			X				X		X
Pulse oximetry[r]	X	X					X			X			X				X		X
HRCT [s]	X																X		
6-MWT[t]		X					X			X			X				X		X
SGRQ, EQ-5D-5L[u]		X					X			X			X				X		X
Blood samples for biomarkers analysis		X								X							X		
Archive blood samples (protein and mRNA biomarkers)[v]		X								X							X		
Blood DNA for genomics[w]		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 predose with the exception of the assessment of local tolerability of SC injections.

c Supplementary calls may be made to supply IMPs kits directly to patient's home.

d Study treatment to be administered once a week, either at the site level or at home by a nurse.

e Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic and musculoskeletal systems. [redacted] 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.

f 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.

g 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 proteins, microscopic analysis is performed by central laboratory.

h Serology testing includes hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C antibodies.

i [redacted]

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

k In women of child-bearing potential. After Visit 4 (W4) between study visits 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 at each successive visit 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 and reported in the 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.

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

m The follow-up period with no study treatment is due for patients who discontinue permanently the study treatment OR patients who complete the study.

n PK samples during Visits 2-9 will be collected predose (within 2 hours before each dose administration) and PK samples during Visit 10 will be collected in the morning.

o ADA samples will be collected at approximately the same times as the PK samples.

p Additional optional sampling will be performed 5 to 10 days after last dose in a subgroup of at least 30 patients per arm.

q Pulmonary function tests include DLCO, FVC, FEV1, TLC and RV. FEV1, TLC and RV will only be done at screening and at baseline. DLCO will be measured locally at the investigational site; spirometry test will be done locally but measured by a central laboratory.

r Will be measured under ambient air for all patients. For patients under oxygenotherapy, pulse oximetry will be measured under oxygenotherapy and then, after 10 minutes breathing ambient air at rest.

s Will be performed at screening unless already done within 1 year prior to screening.

t At visits 6 to 10, if oxygen saturation is less than 88% under ambient air at rest, patient should perform 6-MWT under 4L oxygen

u EQ-5D-5L will be measured at Visit 2 (baseline visit), Visit 8 (W36) and Visit 9 (W 52).

v Archive sampling requiring separate informed consent.

w Sampling for exploratory analysis of DNA requiring separate pharmacogenetics informed consent.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

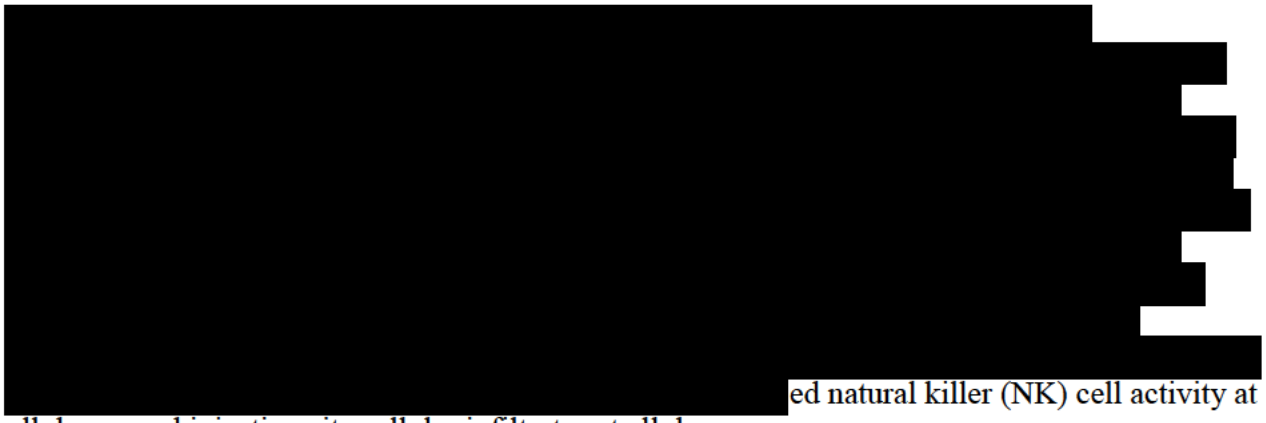
6-MWT:	6-Minute Walk Test distance (6-MWT)
ADA:	anti-drug antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALAT:	Latin American Thoracic Association
ALT:	alanine transaminase
ANCA:	anti-neutrophil cytoplasmic autoantibody
AST:	aspartate transaminase
ATS:	American Thoracic Society
CPK MB:	Creatinine Phosphokinase Muscle Brain
DLCO:	carbon monoxide diffusing lung capacity
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
e-CRF:	electronic case report form
EQ-5D-5L:	EuroQol Questionnaire, 5 level system
ERS:	European Respiratory Society
ESR:	erythrocyte sedimentation rate
FEV1:	forced expiratory volume over 1 second
FVC:	forced vital capacity
HLGT:	High-Level Group Term
HLT:	High Level Term
hsCRP:	high-sensitivity C-reactive protein
IMP:	Investigational Medicinal Product
JRS:	Japanese Respiratory Society
PCSA:	Potentially Clinically Significant Abnormalities
PFTs:	pulmonary function tests
PK:	pharmacokinetic
PT:	Preferred Term
q2w:	every 2 weeks
qw:	weekly
SAE:	serious adverse event
SC:	subcutaneous
SGRQ:	St George Respiratory Questionnaire
SOC:	System Organ Class
SpO2:	oxygen saturation by pulse oximetry
SUSAR:	suspected unexpected adverse drug reaction
TB:	Tuberculosis
ULN:	upper limit of normal range
WHO:	World Health Organization
β-HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, diffuse, and distinct chronic fibrosing interstitial pneumonia of unknown cause that is uniformly fatal with a median survival of approximately 3 years (1). The clinical course of IPF is variable and not predictable; the rate of decline and progression to death may take several clinical forms: slow physiologic deterioration with worsening severity of dyspnea, rapid deterioration, and progression to death, or periods of relative stability interposed with periods of acute respiratory decline sometimes manifested by hospitalizations for respiratory failure (2). Epidemiological data still qualify IPF as a "rare disease", even though international studies seem to report an increasing incidence, with current estimates between 4.6 and 16.3 per 100 000 person-years and a prevalence of 13 to 20 cases per 100 000 ((3), (4), (5)). There is a higher predominance of the disease in men (1.5 to 1.7:1) than in women and the frequency increases with age (5). The most important environmental risk factors are cigarette smoking, exposure to metal and wood dust(1), and infectious agents including both viruses and bacteria(6). Genetic transmission occurs in about 0.5% to 3.7% of patients with IPF (7). The diagnosis of IPF often requires a multidisciplinary approach, involving pulmonologists, radiologists, and pathologists experienced in the field of interstitial lung diseases(8). The pathogenic mechanisms are unclear, but a growing body of evidence indicates that the disease is the result of an abnormal behavior of the alveolar epithelial cells that provoke the migration, proliferation, and activation of mesenchymal cells, with the formation of fibroblast and myofibroblast foci. Activated myofibroblasts secrete exaggerated amounts of extracellular matrix molecules with the subsequent destruction of the lung architecture (9). Pirfenidone (Esbriet®, Roche), an oral drug that is hypothesized to inhibit the synthesis of transforming growth factor-beta, was approved so far in Japan, China and in the European Union for the treatment of IPF. Very recently, the FDA approved pirfenidone as well as nintedanib (Ofev®),an oral kinase inhibitor for the treatment of IPF. Per labeling information, these two drugs were shown to significantly reduce the decline of lung function as compared to placebo. No statistically significant effect on death was demonstrated. Lung transplantation is the only therapy that prolongs survival in advanced IPF, although the post-transplantation 5-year survival for patients with IPF is about 48% (10). Interleukin 4 (IL)-4 and interleukin 13 (IL-13) are structurally related cytokines expressed by T helper type 2 lymphocytes and are ligands that share in common at least 1 receptor subunit (IL-4R alpha) (11), (12). Elevations in IL-4 and IL-13 and their receptors have been linked to the pathogenesis of IPF (13), (14). In IPF patients, IL-13 and IL-4 levels in bronchial alveolar lavage fluid are elevated compared to normal controls (15). Such evidence suggests that therapies capable of suppressing or neutralizing these cytokines have the potential for delaying the progression of fibrosis in IPF patients. SAR156597 is an engineered humanized bispecific IgG4 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.

This dual simultaneous binding of IL-4 and IL-13 is unique to SAR156597, although several other monoclonal antibodies that bind individually to IL-13 have been tested in clinical trials at doses as high as 300 mg subcutaneously and 10 mg/kg intravenously (16).


ed natural killer (NK) cell activity at all doses, and injection site cellular infiltrates at all doses.

The no observed adverse effect level (NOAEL) was considered to be 10 mg/kg/week. SAR156597 is in early phase of clinical development. A placebo-controlled first in man study (TDU11325 study) has shown that single subcutaneous (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 (Cmax) 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 (t1/2z) 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 IPF to evaluate the safety, tolerability, pharmacokinetics 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 adverse events (AE) 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. Data for other pharmacodynamics i.e; lung function parameters and other biomarkers, were inconclusive probably due to the short duration of treatment and small sample size of the study.

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

4.2 RATIONALE

4.2.1 Study design

DRI11772 study will consist of the evaluation of the efficacy and safety of 2 dose levels/regimens of SAR156597 administered subcutaneously over a 52-week treatment period and, the determination of the optimal dose level/regimen for the treatment of patients with IPF.

It will be a multinational, randomized, double-blind, placebo-controlled, 3-parallel group study conducted in out-patients suffering from IPF according to the American Thoracic Society/ European Respiratory Society/ Japanese Respiratory Society/ Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guideline criteria and confirmed by a multidisciplinary panel of experts in IPF.

Patients who discontinue treatment during the study will be followed for the full planned 52 week duration of the study in order to ensure the collection of efficacy outcomes on all randomized patients and minimize the potential for bias in analyses due to missing data.

4.2.2 Design rationale

The 52-week treatment duration is based on published data from clinical trials in IPF and also from IPF natural history data that respectively showed evidence for treatment-induced changes on surrogate endpoints and significant decline in respiratory function characteristic of disease progression over a 12-month period.

The follow-up period of 12 weeks after dosing for adverse events (AEs) and pharmacokinetic (PK) analysis is appropriate taking into account the estimated half-life of about 11 to 15 days for SAR156597 from the TDU11325 and TDR11326 studies.

Dose selection

SAR156597 was safe and well tolerated at single SC doses up to 300 mg in healthy subjects as well as at repeated SC doses up to 200 mg during 6 weeks in patients with IPF, including at the injection site level.

No *in vivo* data from an appropriate animal model of IPF is available to guide the desired pharmacologically active exposure of SAR156597. However, modelling and simulation of the inhibition of Stat6 phosphorylation in monkey suggest that its inhibition will be fully achieved. Additionally, SAR156597 has been shown to reduce in a dose dependent manner (up to 200 mg once a week) the plasma level of TARC, a protein biomarker involved in the IL-4/IL-13 pathway, after 6 weeks of treatment in patients with IPF.

As the desired dose frequency for patient convenience is once every 2 weeks, the weekly dose regimen for the 200 mg dose level will be compared to the every 2 weeks dose regimen for 200 mg.

Finally, modelling and simulations based on the PK data from the multiple dose clinical study (TDR11326) have confirmed that a 200 mg dose administered once every 2 weeks and once a week give an acceptable safety margin in terms of exposure ratio (monkey AUC at NOAEL/human AUC) of ~6 and ~3 respectively.

4.2.3 Rationale for the use of outcome measures

4.2.3.1 Pulmonary Function Tests (PFTs)

Pulmonary function tests (PFTs) will be assessed during the study. Pulmonary function tests, such as spirometry and carbon monoxide diffusing lung capacity (DLCO), are standard evaluations for patients with IPF. Changes in forced vital capacity (FVC) and DLCO have been shown to be correlated with survival (17).

4.2.3.2 Six-Minute Walk Test (6MWT) and Pulse Oximetry

The 6-MWT with oximetry will be used in this study. It is a safe and reproducible procedure for patients with IPF. Baseline desaturation during a 6MWT is a powerful predictor of subsequent mortality (18)

4.2.3.3 Lung High Resolution Computed Tomography (HRCT)

A significant correlation between high-resolution computed tomography (HRCT) visual score and lung function tests both at diagnosis and at follow-up has been shown and reported in the literature. The HRCT study is able to identify and quantify anatomic IPF and also to evaluate the progression of the disease. In clinical practice, the HRCT visual score of disease extent can be used in association with function tests to monitor IPF evolution, and to evaluate prognosis and therapy (19).

4.2.3.4 St George Respiratory Questionnaire (SGRQ)

Impact of IPF on quality of life will be assessed using the SGRQ (20). This questionnaire covers the measurement of symptoms, activity, and impacts. It has good discriminative and evaluative properties and is responsive to therapeutic trials. It takes 8 to 15 minutes to complete.

4.2.3.5 EuroQol Questionnaire, 5 level system (EQ-5D-5L)

The EQ-5D is a standardized instrument for use as a measure of health outcome.

EQ-5D-5L is the 5-level system for the 5-dimensional format of the EQ-5D and covers the measurement of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

EQ-5D-5L is designed for self-completion by subjects, taking less than 5 minutes to complete.

Instructions to respondents are included in the questionnaire.

4.2.3.6 Biomarkers

Peripheral blood will be collected for measurement of protein biomarkers in serum or plasma. The protein biomarkers have been selected either based on their potential link with SAR156597 mechanism of action, based on reported association with survival in or pathogenesis of IPF or lung fibrosis. These include, but are not limited to, inter-cellular adhesion molecule 1 (ICAM1), TARC, periostin and Human Epipidymis protein 4 (HE4). In a previous observational longitudinal study (ASY12295), some of these biomarkers showed a higher circulating concentration at baseline in IPF patients compared to healthy controls, with estimated AUROC above or close to 0.8. On exploratory basis, the correlation between IPF disease biomarkers and lung function progression will be assessed at Week 24 and Week 52. Moreover, in another previous clinical study with increasing doses of SAR156597 (TDR11326) promising results were observed for some of these markers, e.g. a trend in reduced blood concentration of TARC with increasing doses of SAR156597. Drug-related protein biomarkers will be assessed at baseline, Week 24 and Week 52 to look for an effect on these proteins after 6 months and 12 months of SAR156597 treatment.

Additional blood samples will be archived for potential future assay of protein and mRNA biomarkers related to the diagnosis, progression, or therapeutic responsiveness of IPF

4.2.3.7 Genetic testing

The genetic basis of IPF is not well understood. Polymorphisms of various genes encoding for cytokines and mucins have been reported to be increased in sporadic IPF. To obtain a better understanding of IPF pathogenesis and disease course in relation to the genomic profile, blood samples will be collected to further characterize the genotype of IPF subjects by analysis of a subset of selected genes already associated to IPF including but not limited to IL4 (21), IL4R (22), STAT6 (23) and MUC5B (24).

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate, in comparison with placebo, the efficacy of 2 dose levels/regimens of SAR156597 administered subcutaneously during 52 weeks on lung function of patients with IPF.

5.2 SECONDARY

- To evaluate the efficacy of 2 dose levels/regimens of SAR156597 compared to placebo on IPF disease progression
- To evaluate the safety of 2 dose levels/regimens of SAR156597 compared to placebo in patients with IPF
- To evaluate the pharmacokinetic profile of SAR156597 200 mg administered subcutaneously every week and every two weeks during 52 weeks
- To assess the potential immunogenicity of SAR156597
- To evaluate the effect of SAR156597 on circulating biomarkers
- To explore the effect of SAR156597 on quality of life

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study will be a multinational, randomized, double-blind, placebo-controlled, 3 parallel groups study to assess the efficacy and safety of SAR156597 200 mg once a week and 200 mg once every two weeks administered subcutaneously over a 52 week period to patients with IPF.

Approximately 300 patients will be randomized in a ratio 1:1:1 to the following three treatment arms:

- SAR156597 (qw) arm (n=100):

Patients will receive SAR156597 administered subcutaneously in 200 mg doses once every week (qw)

- SAR156597(q2w) arm (n=100):

Patients will receive SAR156597 administered subcutaneously in 200 mg doses once every 2 weeks (q2w) alternating with placebo subcutaneously once every 2 weeks

- Placebo (qw) arm (n=100):

Patients will receive placebo subcutaneously once every week.

The study population will be stratified at baseline according to a background therapy with pirfenidone or nintedanib (standard of care for IPF in authorized countries).

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 will last up to 68 weeks as follows:

- Up to 4 weeks of screening
- 52 weeks of study treatment
- 12 weeks of follow-up

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 STUDY COMMITTEES

Central review of clinical documentation

Clinical documentation such as patient history, HRCTs, and histology will be centrally reviewed by a radiologist and a pathologist specialized in interstitial lung diseases in order to confirm the diagnosis of IPF. HRCTs performed during the course of the study will also be reviewed and scored on a blinded basis to appropriately assess the changes over time.

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 that has gathered sparse safety information in patients with IPF so far [redacted]. 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

Operational Committee

An Operational Committee will be put in place for potential consultation on unexpected ethical, methodological, or technical questions that may arise during the course of the study.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Adult male or female patients.

I 02. Documented diagnosis of IPF according to the following criteria:

- Exclusion of other known causes of interstitial lung disease (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)*

AND

- Combination of patterns of usual interstitial pneumonia (UIP) on HRCT images of chest, and on surgical lung biopsy (when obtained)*

  OR

  Presence of Possible UIP pattern* on HRCT images of chest AND additional evidence of traction bronchiectasis as assessed by an experienced chest radiologist (Central Review**)

* As defined in the current 2011 ATS/ERS/JRS/ALAT guidelines

** The patterns of UIP on HRCT images of chest and histopathology in surgical lung biopsy (if done) will be reviewed by central reviewers (a radiologist and a pathologist experienced in interstitial lung diseases) to confirm diagnosis of IPF for consistency.

I 03. Signed written informed consent.

7.2 EXCLUSION CRITERIA

E 01. Age ≤40 years.

E 02. IPF disease diagnosis >5 years.

E 03. Forced vital capacity (FVC) <40% of predicted value.

E 04. Carbon monoxide diffusing lung capacity (DLCO) corrected for hemoglobin <30% of predicted value.

E 05. Severe chronic obstructive bronchitis as characterized by FEV1/FVC < 0.70.

E 06. Need for 24 hrs of oxygen therapy or oxygen saturation <88% after 10 minutes breathing ambient air at rest.

E 07. Known diagnosis of significant respiratory disorders (e.g. asthma, tuberculosis, sarcoidosis, aspergillosis, or cystic fibrosis) other than IPF.

E 08. Pulmonary artery hypertension requiring a specific treatment.

E 09. Currently listed and/or anticipated to be listed for lung transplantation within the next 6 months (on an active list).

E 10. History of vasculitis or connective tissue disorders or ANCA positive.

E 11. Known HIV or chronic viral hepatitis.

E 12. Exclusion related to tuberculosis (TB):

- Active tuberculosis (according to WHO guidelines (25) or a history of incompletely treated tuberculosis
- Incompletely treated latent tuberculosis (according to WHO guidelines)
- Positive or confirmed indeterminate (2 consecutive tests) QuantiFERON-TB Gold® test at screening (regardless of prior treatment status)

E 13. Evidence of any clinically significant, severe or unstable, acute or chronically progressive medical (other than IPF) or surgical disorder, or any condition that may affect patient safety in the judgment of the investigator.

E 14. Acute myocardial infarction within 6 months prior to screening.

E 15. Clinically significant abnormal electrocardiogram (ECG) at screening that may affect the conduct of the study in the judgement of the investigator.

E 16. Clinically significant laboratory tests 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/mm3 (except <1000/mm3 for those of African descent)
- Platelets <100 000/mm3
- Creatinine ≥150 µmol/L

E 17. Current history of substance and/or alcohol abuse.

E 18. Females who are lactating or who are pregnant.

E 19. Women who are of childbearing potential not protected by highly-effective contraceptive method(s) of birth control (as defined in the informed consent form and /or in a local protocol addendum/amendment), and/or who are unwilling or unable to be tested for pregnancy.

For Denmark only, per local requirement: *Acceptable methods of contraception include:*

- *Intra-uterine devices (IUD);*
- *Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).*

For UK only, per local requirement: *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).*

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

[For Czech Republic only, per local requirement:

E.19 Women who are of childbearing potential not protected by highly-effective contraceptive method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy.

Male participants with a female partner of childbearing potential not protected by highly effective contraceptive method(s) of birth control.

- *Acceptable methods of contraception include:*

  - Method with reliability index <1 (such as IUD, sterilization of one of the partners provided that this partner is the only one for whole duration of the clinical trial, further hormonal implants, injections, patches, oral hormonal contraception) plus one supplementary barrier method of contraception always with spermicide. Men should always use condom.

  - These methods must be used during whole study treatment duration and 3 months after the end of the investigational product administration

Note: Women of childbearing potential must have a confirmed negative pregnancy test at screening and baseline visits. Postmenopausal women must be amenorrheic for at least 12 months.]

E 20. Use of any cytotoxic/immunosuppressive agent including but not limited to azathioprine, cyclophosphamide, methotrexate, and cyclosporine within 4 weeks prior to screening.

E 21. Use of any cytokine modulators (etanercept, adalimumab, efalizumab, infliximab, golimumab, certolizumab, rituximab) within 12 weeks or 5 half-lives of screening (24 weeks for rituximab and 24 months for alefacept).

E 22. Use of any investigational drug within 1 month of screening, or 5 half-lives, if known (whichever is longer), or within 12 weeks for stem cell therapy.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

A complete description of the Investigational Medicinal Product (IMP) and its proper handling will be provided in a pharmacy manual.

- Pharmaceutical form
    - SAR156597 solution for injection at 100 mg/mL: SAR156597 is supplied as a sterile freeze-dried powder for solution for injection. Each vial is overfilled 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 water for injection, leading to an amount of 125 mg of SAR156597 drug substance in a total volume of 1.25 mL, that is a 100 mg/mL of SAR156597 solution. 1 mL of this 100 mg/mL SAR156597 solution can then be withdrawn for dose administration. 2 drug product vials are thus needed to reach a 200 mg dose.
    - Placebo consists of liquid with the same excipients as those of the reconstituted SAR156597 formulation, filled at nominal volume of 1.5 mL. Two vials are necessary, 1 mL will be taken from each vial to prepare 2 mL syringe.
- Method of preparation

At the study site, reconstitution of the IMP must be done by personnel other than those administering the drug and making clinical observations (e.g. pharmacist) to maintain the treatment blind (Refer to Section 8.4).

- At patient's home, reconstitution must be done by healthcare professionals (e.g. visiting nurse) out of view of patients and their families/caregivers.
- The IMP should be reconstituted the day of dosing (no more than 3 hours prior to SC injection), at room temperature.

- Dose of drug per administration
    - SAR156597 qw arm: one injection of SAR156597 200 mg administered subcutaneously every week
    - SAR156597 q2w arm: one injection of SAR156597 200mg administered subcutaneously once every 2 weeks alternating with one injection of placebo administered subcutaneously once every 2 weeks
    - Placebo arm: one injection of placebo administered every week

- Route and method of administration

The route and method of administration are subcutaneous in the abdomen. Subcutaneous 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. Exact site of each injection will be documented on source document.

The IMP is administered every 7 days +/- 2 days from initial IMP administration. This is permitted per protocol to accommodate special circumstances, eg. laboratory results pending, ongoing AE, patient scheduling difficulty.

If IMP administration is missed or temporarily discontinued, the initial schedule of injections should be resumed. 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 (e.g. visiting nurse service).

Patients should be monitored by site personnel/visiting nurse for at least 30 minutes after each administration for potential signs and symptoms that may suggest a hypersensitivity reaction.

[For Czech Republic only per local requirement: Patients should be monitored at the study site by site personnel for a minimum of 2 hours after the first administration of IMP and for a minimum of 1 hour after the next 5 administrations for potential signs and symptoms that may suggest a hypersensitivity reaction. For the subsequent IMP administrations, patients should be monitored by site personnel/visiting nurse for at least 30 minutes after each administration.]

For doses not given at 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.

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 randomized treatment kit number list will be generated by Sanofi.

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 (randomized treatment kit number) except under circumstances described in Section 8.3.2.

To maintain blinding, since unreconstituted placebo and SAR156597 vials are not matched for appearance, the personnel involved with dose preparation will be required to agree not to reveal to other study personnel the type of IMP solution (SAR156597 vs. placebo) in the vials/syringes.

For doses administered at patient's home, visiting nurses will be requested to reconstitute the IMP out of view of patients and their families/caregivers and to sign a confidential agreement for not disclosing the IMP box content.

Also to protect the blind, SAR156597 and placebo will be supplied in a 2 week treatment kit containing individually 2 Tamper Evident sealed treatment boxes (2 vials per box / 2 boxes per kit).

Each inner box will contain 2 vials and will be labeled as "Box 1" (week 1 treatment) and "Box 2" (week 2 treatment). Each weekly treatment box will be sealed with a tamper evident seal.

The outer kit, also tamper evident sealed will contain the 2 inner boxes and extra tamper seals.

After administration of week 1 treatment, the person preparing the dose will put the empty vials back in the original inner box 1, put the empty box 1 back in the outer kit and tamper evident sealed it until week 2 administration. After administration of week 2 treatment, the same procedure will be applied for box 2.

During monitoring visit, the unblinded monitor will break the tamper evident seal to perform IMP accountability. The monitor will tamper seal the outer box after performing IMP accountability.

The Investigator must not open the returned tamper sealed boxes.

Refer to Section 10.5 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient. If possible, contact should be initiated with the monitoring team before breaking the code.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) 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 day, and reason for code breaking.

If the blind is broken by the Investigator, for the above stated purpose, the patient must be withdrawn from treatment.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patient will be randomized following a 1:1:1 ratio to one of the three treatment arms via a centralized randomization system using IVRS/IWRS.

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

At V1 (screening) the study staff will contact the IVRS/IWRS to obtain a patient number for each patient who gives informed consent.

The result from the central reviewer on diagnosis of IPF have to be obtained to validate the inclusion of patient before randomization as per inclusion criteria (See section Section 7.1)

The population will be stratified according to background therapy at the moment of randomization:

- Patient with background therapy with either pirfenidone or nintedanib
- versus patient without background therapy
- It is planned to include a maximum of 66% of patients with background therapy.

Randomization will be performed at Visit 2 (Day 1) by a centralized randomization procedure using IVRS/IWRS.

Patients who comply with all inclusion/exclusion criteria will be assigned before the IMP administration on Visit 2 (Day 1):

- A treatment number in a preplanned order following the randomization list, and
- A patient number according to the chronological order of inclusion.

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

Patients who meet exclusion criteria may be re-screened once during the open screening period of study; a different patient identification will be issued. 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-screening date. The IVRs/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The treatment kits are sufficient for 2 weeks of treatment. As the treatment duration is 52 weeks, a patient will be allocated by the IVRS to several treatment kit numbers corresponding to the same treatment arm 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 as a treatment box. Each box will contain 2 inner boxes. Each inner box will contain 2 vials. The inner boxes will be numbered as “Box 1” and “Box 2”. Box “1” or “2” will be used for administration at the instructed time.

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 investigational Product should be stored between 2°C and 8°C (36°F and 46°F).The Investigators or other authorized persons (e.g. 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 (e.g. 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 to 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. 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 IMP 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 notified 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 IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, 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

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.
- The site unblinded 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 unblinded 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, used or unused investigational product will be destroyed on site according to the standard practices of the site after reconciliation verification by the monitor.

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

The Investigator will not destroy any investigational product 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 MEDICATIONS

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). An accurate record of all prescription medications (plus any herbal supplement or over the counter medications taken specifically for the IPF condition) must be kept on the appropriate record form, including the name of the medication (international nonproprietary name), start of administration, daily dosage, and duration for such use.

8.8.1 Prohibited medications

- Use of any cytotoxic/immunosuppressive (other than prednisone less than or equal to 10 mg/day or equivalent) including but not limited to azathioprine, cyclophosphamide, methotrexate, and cyclosporine within 4 weeks prior to screening and during the course of the study.
- Use of any cytokine modulators
    - Use of any biologic agent (such as etanercept, adalimumab, efalizumab, infliximab, golimumab, certolizumab) within 12 weeks or 5 half-lives of screening, and in the case of rituximab, use within 24 weeks of screening or no recovery of CD 19-positive B lymphocytes if the last dose of rituximab has been more than 24 weeks prior to screening. The use of these biologic agents is not authorized during the course of the study.
    - Alefacept within 24 months of screening and during the course of the study.
- Use of any investigational drug within 1 month of screening, or 5 pharmacodynamic/pharmacokinetic half-lives, if known (whichever is longer),and during the course of the study. Use of stem cell therapy within 12 weeks of screening, and during the course of the study.

8.8.2 Authorized concomitant medications

- Oral corticosteroids are permitted if ≤10 mg/day oral prednisone or equivalent and at stable dose for at least 4 weeks prior to the randomization (baseline) visit. No change is permitted unless the patient develops an AE. Dose and any change will be recorded on the patient e-CRF.
- Pirfenidone or nintedanib administered at the recommended dosage for at least 12 weeks prior to the randomization (baseline). No change is permitted unless the patient develops an AE. Dose and any change will be recorded on the patient e-CRF. Pirfenidone or nintedanib cannot be started during the course of the study.

[For Czech Republic only, per local requirement:

- *N-acetylcysteine administered at the dosage recommended by local guidelines]*

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY

9.1.1 Primary endpoint

The primary efficacy endpoint will evaluate the efficacy of SAR156597 on lung function and will be:

- The absolute change from baseline in % predicted FVC at 52 weeks

9.1.2 Secondary endpoints

Two key secondary endpoints will evaluate other aspects of the efficacy of SAR156597 in IPF:

- Patients experiencing Disease Progression as defined by the following events: decrease in absolute % predicted FVC≥10 percent or decrease in absolute percent predicted DLCO≥15 percent or lung transplant or death at 52 weeks
- Deaths (all cause) at 52 weeks

9.1.3 Exploratory endpoints

- Acute exacerbations at 52 weeks (per investigator's judgment and adjudicated cases)
- Respiratory hospitalizations and rate of non-elective hospitalizations at 52 weeks
- Change from baseline in 6-MWT distance at 52 weeks
- Change from baseline in HRCT lung interstitial score at 52 weeks
- Change from baseline in the total score of the SGRQ at 52 weeks
- Change from baseline in the total score of the EQ-5D-5L at 52 weeks

9.1.4 Assessment methods and activity parameters

9.1.4.1 Pulmonary Function Tests will include:

• DLCO: carbon monoxide diffusing capacity, corrected for hemoglobin;

• FVC: forced (expiratory) vital capacity;

• FEV1: forced expiratory volume over one second (only done at screening and at baseline)

• TLC: total lung capacity (body plethysmography) (only done at screening and at baseline)

• RV: residual volume (body plethysmography) (only done at screening and at baseline)

DLCO will be measured locally at the investigational site; spirometry test will be done locally but measured by a central laboratory.

Note: Two PFTs will be performed within 4 weeks prior to dosing one at screening and one at baseline. The first PFT will determine whether the patient qualifies for the study and the second will be averaged with the first one to establish a baseline value.

9.1.4.2 Pulse oximetry

Oxygen saturation will be assessed using pulse oximetry (SpO2).

9.1.4.3 Lung HRCT

For confirmation of diagnosis at baseline, a lung HRCT will have to be performed unless already done within 1 year prior to screening. The HRCT will be provided to the central review panel together with histology documentation if any.

A second HRCT will be performed at the end of treatment to measure the effect on lung fibrosis using a specific scoring system.

9.1.4.4 6-MWT

The distance covered by the patient over a 6 minute walk will be measured by the investigational site staff at baseline and during the treatment and reported in meters in the e-CRF. If during visits 6, 7, 8, 9 and 10, oxygen saturation is less than 88% under ambient air at rest, the patient should perform 6-MWT under 4L oxygen.

9.1.4.5 Patient Reported Outcome

The impact of the disease on patient's Quality of Life will be measured at baseline and during the treatment using the St George Respiratory Questionnaire and the EuroQol questionnaire.

9.2 SAFETY ENDPOINTS

The same safety assessment will be applied across all arms. Adverse events will be collected at each visit from the signing of the informed consent to the end of the follow-up period. The investigator will ask the patient how he/she has felt since the last study visit/phone call. The study specific and general safety monitoring 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 6.3.

9.2.1 Adverse events

Refer to Section 10.4 to Section 10.7 for details.

9.2.2 Physical examination

A complete physical examination will be performed at each site-visit as per study flowchart (Section 1.2) and description of study procedures in Section 10.

Specific attention will be paid to skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. For the dermatological exam, it is recommended that the patient wears only undergarments. [redacted] Nail beds (periungual areas) should be examined for "splinter lesions" and digital tuft for tuft purpura or ischemia. For neurological examination, the Investigator should focus on CNS signs and refer to a neurologist if further assessments are deemed necessary.

Clinically significant abnormalities should be reported in the patient e-CRF as medical history, if observed at the screening visit (Visit1) or as an AE if observed during subsequent visits.

9.2.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including 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. Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of a persistent abnormality is determined.

Samples will be taken at the study site before administration of the IMPs. 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), white blood cell count with differential and platelet count.

- Serum chemistry

Fasting glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, CPK, high-sensitivity C-reactive protein (hsCRP).

- Urine analysis including 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 proteins, microscopic analysis is performed by central laboratory.

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 4, 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.

- Clinical laboratory testing at Visit 1 adds hepatitis screen (hepatitis B surface antigen,hepatitis B surface antibody, hepatitis B core antibody and hepatitis C antibodies) and tuberculosis screen (Quantiferon®- TB gold evaluation)
- 

Decision trees for the management of some laboratory abnormalities are provided in APPENDIX F.

9.2.4 Vital signs

Vital signs include blood pressure (mmHg), heart rate (beats per minute), body weight (kg) and height (cm).
Blood pressure will be measured at each site study visit in sitting position. Both systolic and diastolic BP should be recorded. BP should be checked after 5 minutes of resting in sitting position.

Weight should be taken with the patient wearing undergarments or very light clothing and 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.

9.2.5 Electrocardiogram variables

A standard 12-lead ECG will be performed at each on site visit as per study flowchart (Section 1.2) and description of study procedures in Section 10. ECG data will be assessed by the Investigator based on the automatic device reading.

At the post randomization visits, ECGs will be performed prior to investigational product 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 Uwave morphology.

9.2.6 Hypersensitivity/Allergic or anaphylactic reactions

Assessment, categorization and treatment of systemic allergic reactions, if any, or of anaphylactic reactions as consensually defined (26) (25) will be specifically performed as detailed in Section 10.6.3.1 and following APPENDIX D, as appropriate.

Local injection reactions will be assessed to determine if of allergic origin or not following details provided in Section 10.6.2 and Section 10.6.3.2 (see also APPENDIX D and APPENDIX E).

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

9.3.1.1 Sampling time

Samples for PK analysis will be collected at pre-dose (within 2 hours before each dose administration) during Visits 2, 4, 6, 7, 8 and 9.

Pharmacokinetics samples during Visit 10 will be collected in the morning.

An additional sample should be taken in a sub-group (at least 30 patients by cohort) between 5 and 10 days after last dose (i.e. after Visit 9). The possibility to perform this additional sample will be discussed between Investigator and patient on a case by case basis.

Anti-SAR156597 antibodies (ADA) samples will be collected at approximately the same times as the PK samples.

9.3.1.2 Pharmacokinetics handling procedure

Detailed procedure of sample preparation, storage and shipment are described in the specific laboratory manual. Five (5) ml blood volume is to be collected for each PK and ADA sample.

Table 1 – 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 (2aliquots)
Anticoagulant	CPD (Citrate Dextrose Phosphate)	
Storage conditions	≤-20°C	

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 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 0.05µg/mL.

9.3.1.3.2 Anti-drug antibodies

All anti-SAR156597 antibody samples will be analyzed by the Bioanalysis and Biomarkers domain in DSAR OC Montpellier (France).

For the analysis of potential anti-SAR156597 antibodies (ADA) 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 anti-SAR156597 antibodies 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.

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 endogeneous hIgG4 may be assessed on specific PK sample aliquots.

9.3.1.4 Pharmacokinetics parameters

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

Additional PK parameters will be estimated using the population PK approach such as Cmax, tmax and AUC at steady state.

PoP PK analysis will be presented in a separated stand alone report.

9.3.2 Biomarkers

IPF subjects will have serial peripheral blood collections for protein biomarker analyses and archival purposes (see Section 4.2.3 for detail list).

The methodology for sample preparation is described in the lab manual.

9.3.2.1 Archival serum for future biomarkers

Blood samples will be prepared and stored for future assay of laboratory protein biomarkers related to the diagnosis, progression or therapeutic responsiveness of IPF.

Peripheral whole blood will be collected and stored for future whole mRNA transcriptome analysis.

9.3.2.2 Bioanalysis methods

All the blood samples will be centralized at designated central lab. For each type of biomarker the analysis method will be detailed in the laboratory manual.

9.3.3 Pharmacogenetic

9.3.3.1 Genetic samples for DNA

At the study visit specified in the study flow chart, for those subjects who signed the specific genetic analysis informed consent form, a single blood sample will be collected to enable possible investigation of genetic variants that may affect the status and treatment of IPF.

Total blood will be collected using a 6mL vacutainer (BECTON Dickinson K2 EDTA) with HEMOGARD Closure, and gently invert tube at least 8 times permitting specimen to mix with tube's anticoagulant. Under no circumstances will the tube be centrifuged.

Special procedures for storage and shipping of genetic samples will be provided in the lab manual.

9.3.3.2 Protection of subject identity and genetic sample/data handling

The Sponsor has included safeguards for protecting subject confidentiality. The blood sample and DNA that is extracted will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This "double coding" is performed to separate a subject's medical information and DNA data. The clinical study data (coded by Subject ID) will be stored in a distinct database at a different location from the database containing the genetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and genetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

Any remaining banked blood samples and associated DNA will be discarded according to local regulations and operating procedures within 15 years of issuance of the Clinical Study Report for DRI11772.

9.3.3.3 Optional stored DNA sample

For those patients who signed the optional pharmacogenetic informed consent form, a blood sample will be collected at the study visit as specified in the study flow chart and this sample will be stored.

This sample may be used to determine a possible relationship between genes and response to treatment with SAR156597, how the body processes SAR156597 and possible side effects to SAR156597. Genes that may be studied include those for the IL4 receptor, IL4, MUC5B and additional genes that may potentially be part of the Th2 signaling pathway.

This blood sample will be transferred to a site that will, on behalf of Sanofi, extract DNA from the sample and that is managed by a contractor which can be located outside the country where the study is conducted, within or outside of the European Union.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID (deidentification code) that is different from the Subject ID. This "double coding" is performed to separate a subject's medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report.

Special procedures for storage and shipping of pharmacogenetic samples are described in detail in lab manual.

9.4 FUTURE USE OF SAMPLES

For subjects who have consented to it, 6 samples will be collected at the visit specified in the study flow chart and these samples will be stored. These samples may be used for other research purposes (excluding genetic analysis) related to IPF than those defined in the present protocol.

These other research analyses 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 than the one used during the study (i.e., 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

See also Section 4.2.3

The primary endpoint will be the mean absolute change from baseline in percent predicted FVC at 52 weeks. FVC is a widely used measure of pulmonary function and disease status in patients with IPF. Percent predicted FVC is a reliable, valid, and responsive measure of clinical status and a decline of 2-6% represents a small but clinically important difference. Regarding disease progression, a decline in % predicted FVC greater than or equal to 10% at 24 weeks was shown to be associated with a nearly five-fold increase in the risk of mortality over the subsequent year, whereas a decline of 5-10% conferred a more than twofold increase in the risk of 1-year mortality (26) (27).

Secondary and exploratory efficacy outcome measures will address other aspects of disease progression and will include rate of deaths, rate of lung transplantations, rate of hospitalizations, and rate of acute exacerbations. Finally, the extent of lung fibrosis and the effect of drug treatment on fibrosis will be measured using a specific scoring system on lung HRCT.

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 the first injection), 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 consent form (including voluntary participation in pharmacogenetic testing and for 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 that fail screening for exclusion criteria, e.g. 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).

10.1.1 Visit 1: Screening (D-28 to D-1)

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

The following procedures will then be performed:

- Call IVRS to assign a patient number
- Record patient demographic information
- Assess eligibility by review of Inclusion /Exclusion Criteria. This includes the review of prior and concomitant medications
- Commence AE reporting
- Patients who do not meet these inclusion/exclusion criteria should not continue the screening process and a screen failure call should be done in the IVRS

- Interview to collect:
    - IPF history
        - Months since IPF diagnosis;
        - IPF diagnostic algorithm (eg. diagnosis by HRCT and/or surgical biopsy);
        - History of acute exacerbation of IPF (most recent event within the past 12 months prior to randomization, in accordance with published definitions)
        - Family history of IPF
    - Other medical/surgical history and smoking habits
        - Recording of all prior significant medical conditions, and/or hospitalization history, eg. pneumonia, asthma, Choronic obstructive pulmonary disease (COPD), diabetes, hypertension, pulmonary arterial hypertension, congestive heart failure, esophageal reflux, depression, sleep apnea, myocardial infarction or arrhythmias, need for major surgery or surgical complications.
        - Recording current smoking status (current or recent smoking during the year prior to enrollment) and past smoking history (prior habitual smoking more than 1 year prior to enrollment).
- Record vital signs including blood pressure, heart rate, weight (kg) and height (cm) (collected for Body Mass Index calculation)
- Perform a complete physical examination: nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, musculoskeletal systems, and skin. Gynecological and urogenital examinations will not be done unless for cause.
    - [redacted] Nail beds (periungual areas) should be examined for "splinter lesions" and digital tuft for tuft purpura or ischemia.
- Obtain (fasting) blood samples for screening laboratory determinations: hematology, biochemistry, serology tests (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibodies), and serum β-HCG plasma test if female of childbearing potential
- Perform blood sample for ANCA
- Perform blood sample for complement (C3, C4 and CH50)
- 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 proteins, microscopic analysis is performed by central laboratory.

- Perform 12-lead electrocardiography (ECG)
- Complete all remaining assessments for tuberculosis screen: history, 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 confirmed indeterminate (by 2 consecutive tests) QuantiFERON TB Gold test are excluded.
- Perform Lung HRCT if not done within 1 year prior to screening. HRCT will be provided to the central review panel together with histology documentation if any.
- Perform Pulmonary function tests:
    - carbon monoxide diffusing capacity, corrected for hemoglobin (DLCO);
    - forced (expiratory) vital capacity (FVC)
    - forced expiratory volume over one second (FEV1)
    - total lung capacity (body plethysmography) (TLC)
    - residual volume (body plethysmography). (RV)
- Perform Pulse oximetry
- Schedule a visit within a maximum of 28 days (Visit 2, D1)

10.1.2 Visit 2: Baseline /Randomization/ Day 1

Prior to study drug administration, the Investigator or designee will:

- Record all concomitant medication use with start date and dose in e-CRF
- Inquire about AEs/SAEs
- Record vital signs including blood pressure, heart rate and weight

- Perform a complete physical examination
- Perform 12-lead ECG
- Reconfirm eligibility by review of Inclusion/Exclusion Criteria

If the patient meets all inclusion and does not meet any exclusion criteria:

- Call IVRS to randomize the patient and receive a 2 week treatment kit allocation.
- Obtain (fasting) 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
- Perform blood sample for serum SAR156597 and for anti-SAR156597 antibodies (ADA)
- Obtain blood samples for biomarkers assessment
- Obtain blood sample for genomic DNA (only for patients who signed a specific informed consent)
- [redacted]
- Obtain blood samples for archiving (potential future protein and mRNA biomarkers of interest); Only for patients who signed a specific informed consent
- Perform Pulmonary function tests: DLCO, FVC, FEV1, TLC and RV
- Perform Pulse oximetry
- Perform a 6-MWT
- Ask the patient to complete the St George Respiratory Questionnaire and the EuroQol Questionnaire (EQ-5D-5L)
- Dispense and administer IMP
    - For administration at patient's home, arrangements must be made for qualified site personnel and/or professional caregiver to administer IMPs at 1-week intervals
    - Patients will be monitored for at least 30 minutes after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema, swelling/induration/edema and other related observations) will also be conducted.

[For Czech Republic only, per local requirement:

- *Dispense and administer IMP*
    - *Patients will be monitored for at least 2 hours after dosing for any signs or symptoms of a hypersensitivity reaction. An assessment of local tolerability at the injection site (present pain, erythema,*

swelling/induration/edema and other related observations) will also be conducted.

- *Ask patients to come back to the site 1 week later to receive second IMP administration and to be monitored for at least 1 hour after dosing]*

- 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. *[For Czech Republic only, per local requirement: sentence deleted]*
- 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 *[For Czech Republic only, per local requirement: sentence deleted]*
- Record vital signs including blood pressure, heart rate and weight
- Perform a complete physical examination
- Call IVRS to register visit and obtain next treatments number
- Dispense and administer IMP

  [For Czech Republic only, per local requirement:
  - *Dispense and administer IMP*
    - *Patients will be monitored for at least 1 hour after dosing*
  - *Ask patients to come back to the site 1 week later to receive fourth IMP administration and be monitored for at least 1 hour after dosing]*
- Schedule an appointment for Visit 4

10.1.4 Visit 4: on treatment / Week 4

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Review patient booklet to assess local tolerability at the injection site and treatment compliance *[For Czech Republic only, per local requirement: sentence deleted]*
- Record vital signs including blood pressure, heart rate and weight
- Perform a complete physical examination
- Obtain (fasting) 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 kit for monthly urine pregnancy test (1 month supply)
- Perform 12-lead ECG
- Perform blood sample for serum SAR156597 and for anti-SAR156597 antibodies (ADA)
- Perform blood sample for ANCA
- Perform blood sample for complement (C3, C4 and CH50)
- Call IVRS to register visit and obtain next treatments number
- Dispense and administer IMP

  [For Czech Republic only, per local requirement:
  - *Dispense and administer IMP*
    - *Patients will be monitored for at least 1 hour after dosing*
  - *Ask patients to come back to the site 1 week later to receive sixth IMP administration and be monitored for at least 1 hour after dosing]*
- Schedule an appointment for Visit 5

10.1.5 Visit 5: on treatment / Week 6

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Review patient booklet to assess local tolerability at the injection site and treatment compliance *[For Czech Republic only, per local requirement: sentence deleted]*
- Record vital signs including blood pressure, heart rate and weight
- Perform a complete physical examination
- Call IVRS to register visit and obtain next treatments number
- Dispense and administer IMP

  [For Czech Republic only, per local requirement:
  - *Dispense and administer IMP*
    - *Patients will be monitored for at least 1 hour after dosing*
    - *For administration at patient's home, arrangements must be made for qualified site personnel and/or professional caregiver to administer IMPs at 1-week interval*
  - *Provide the patient with a booklet to record information pertaining to the injections to be performed at home as well as the treatment kit]*

- Schedule an appointment for phone call at week 8

10.1.6 Phone call: on treatment / Week 8, Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, and Week 48

- Record all concomitant medication use
- Inquire about AEs/SAEs.
- Ask about the result of urine pregnancy test
- Assess local tolerability at the injection site

10.1.7 Visit 6, Visit 7 and Visit 8: on treatment / Week 12, Week 24, and Week 36

- 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 blood pressure, heart rate and weight
- Perform a complete physical examination
- Obtain (fasting) 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.
- Perform 12-lead ECG
- Perform blood sample for serum SAR156597 and for anti-SAR156597 antibodies (ADA)
- Perform blood sample for ANCA
- Perform blood sample for complement (C3, C4 and CH50)

- **At Visit 7:** Obtain blood samples for biomarkers assessment and for archiving (potential future protein and mRNA biomarkers of interest)
- Obtain blood samples for archiving [redacted]
- Perform Pulmonary function tests: DLCO and FVC
- Perform a 6-MWT
- Perform Pulse oximetry
- Ask the patient to complete St George Respiratory Questionnaire
- **At Visit 8:** ask the patient to complete the EuroQol Questionnaire (EQ-5D-5L)
- Call IVRS to register visit and obtain next treatments number
- Dispense and administer IMP
- Schedule an appointment for next Visit

10.1.8 Visit 9: End of treatment / Week 52 (or Early termination)

- 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 blood pressure, heart rate and weight
- Perform a complete physical examination
- Obtain (fasting) 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)

- Perform 12-lead ECG
- Perform blood sample for serum SAR156597 and for anti-SAR156597 antibodies (ADA)
- Perform blood sample for ANCA
- Perform blood sample for complement (C3, C4 and CH50)
- Obtain blood samples for biomarkers assessment
- Obtain blood samples for archiving [redacted]
- Obtain blood samples for archiving (potential future protein and mRNA biomarkers of interest)
- Perform Pulmonary function tests: DLCO and FVC
- Perform Pulse oximetry
- Perform a 6-MWT
- Ask the patient to complete the St George Respiratory Questionnaire and the EuroQol Questionnaire (EQ-5D-5L)
- Perform Lung HRCT
- Call IVRS to obtain treatment number and to update the patient's status (end of treatment)
- Administer IMP
- Schedule an appointment for next Visit

10.1.9 Phone call: Follow up post treatment / Week 58

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Ask about the result of urine pregnancy test
- Assess local tolerability at the injection site and treatment compliance

10.1.10 Visit 10: End of study visit / Week 64

- Record all concomitant medication use
- Inquire about AEs/SAEs
- Assess local tolerability at the injection site
- Record vital signs including blood pressure, heart rate and weight
- Perform a complete physical examination
- Obtain (fasting) 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
- Perform 12-lead ECG
- Perform blood sample for serum SAR156597 and for anti-SAR156597 antibodies (ADA)
- Perform blood sample for ANCA
- Perform blood sample for complement (C3, C4 and CH50)
- Obtain blood samples for archiving [redacted]
- Perform Pulmonary function tests: DLCO and FVC
- Perform Pulse oximetry
- Perform a 6-MWT
- Ask the patient to complete the St George Respiratory Questionnaire
- 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 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 can be made temporarily; permanent IMP discontinuation should be a 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 product(s)

Temporary treatment discontinuation may be considered by the Investigator because of any suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that it is safe to do so (refer to Section 7.1 and 7.2).

[redacted]

For all temporary treatment discontinuations, duration and number of undelivered doses should be recorded by the Investigator in the appropriate pages of the e-CRF.

A discontinuation of IMP that is 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 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 withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented 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 not intended to be exhaustive:

- [redacted]
- Symptoms of severe hypersensitivity or anaphylactic reactions (see APPENDIX D for definition)
- Severe skin reactions local to the site of IMP injection (see APPENDIX E)
- Pregnancy
- Any adverse events, per Investigator's judgment, that may jeopardize the patient's safety

- Any laboratory abnormalities according to APPENDIX F
- 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.
- Any code breaking requested by the Investigator will lead to permanent treatment discontinuation
- At the specific request of the Sponsor

Any abnormal ECG parameter will be immediately rechecked for confirmation 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-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP (End of treatment visit/Visit 9) and then will be asked to come to the scheduled on site visits for safety monitoring and respiratory function assessment (FVC and DLCO).

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 irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit (Visit 10). Then, patients will receive a phone call from Investigators at week 52 for vital status assessment.

For patients who fail to return to the site, the Investigator should make the best effort to contact the patient (e.g. contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g. times and dates of attempted telephone contact, 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 **adverse event** (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 **serious adverse event** (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 as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Severe hypersensitivity reactions (e.g. anaphylaxis, allergic bronchospasm [see APPENDIX D for the clinical criteria for diagnosing anaphylaxis])
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN. See APPENDIX F
- Acute exacerbation of IPF
- 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 aggravated 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).
- If any suspected transmission of an infectious agent via a medicinal product (e.g. product contamination).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (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 pre-specified investigation/monitoring in order to characterize and understand them. Adverse events of special interest may be added 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 during an interval of less than 5 days.

    Of note, asymptomatic overdose has to be reported as a standard AE.
- Increase in ALT ≥ 3xULN (if baseline ALT<ULN) or ≥ 2x baseline value (if baseline ALT ≥ ULN). See the "Increase in ALT" flowchart in APPENDIX F of the protocol).
- Other project specific AESI (s):
  - [redacted]
  - Anaphylactic reactions or acute allergic reactions that require immediate treatment (refer to APPENDIX D for definition of Anaphylaxis)
  - Severe injection site reactions (see APPENDIX E)
  - Tuberculosis or initiation of medications for suspected tuberculosis
  - Acute renal failure (see APPENDIX F).

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

Disease progression is anticipated for the disease being treated (ie, IPF) and will be considered expected for the purpose of regulatory reporting. Conversely, an event more severe than anticipated usual disease progression is to be considered unexpected.
If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event [Suspected Unexpected Serious Adverse Reaction (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/NIMP, 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 page(s) or screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. Only one diagnosis (symptom if relevant) to be MedDRA coded should be reported per AE report form. 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, in order to ensure the safety of the patients, or until death. 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 2.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of a SAE, the Investigator 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 (i.e. within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in TABLE 2.

10.4.6 Guidelines for management of specific laboratory abnormalities

[redacted]

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in APPENDIX F.

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 eCRF, following the same process as described for the SAEs.

Table 2 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Comple-mentary 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 (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	No
		Symptomatic overdose	Yes	Yes	No
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT≥ULN	Yes	Yes	Yes
		[redacted]	Yes	Yes	Yes
		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, 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.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected, please refer to the Investigator's Brochure (IB).

Any other AE not listed as an expected event in the Investigator's Brochure 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 will remained 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

10.6.1 [redacted]

[redacted]

If neurological signs or symptoms are identified, the patient should be addressed to a neurologist specialized in inflammatory processes for consultation.

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 E). Special e-CRF screens will need to be completed. If such an AE was 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 infusion reaction, but these events may also occur via other immune-mediated mechanisms (e.g.cytokine-mediated). Allergic reactions may begin within few hours and persist up to 24 hours post dosing. Refer to APPENDIX D "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 performed at patient's home) for at least 30 minutes after each administration of investigational product for any signs or symptoms of a hypersensitivity reaction.

[For Czech Republic only, per local requirement: Patients should be monitored at the study site by site personnel for at least 2 hours after the first administration of IMP and at least 1 hour after the next 5 administrations for any signs or symptoms of a hypersensitivity reaction. For the subsequent IMP administrations, patients should be monitored by site personnel or visiting nurse (if injection performed at patient's home) for at least 30 minutes after each administration of IMP.]

Patients should be treated symptomatically 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 immediately interrupted (temporarily discontinued) 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

Adverse events with cutaneous involvement which are obviously of allergic origin or injection site reactions which progress/expand/worsen/etc. should be evaluated by a dermatologist as soon as possible, and preferably within one week of the site first becoming aware of the event.

The Investigator should evaluate the patient for possible etiologies (new medications, etc.) and extracutaneous symptoms and signs. An unscheduled Central Laboratory assessment for hematology, chemistry, liver panel, PK, and ADA should be obtained. If it is possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit. If the photos are obtained, then 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, the following information; a detailed description of the skin reaction (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [e.g. scattered, grouped, linear], distribution, color, consistency, presence of pruritus or pain, and other clinical signs) and, in case a skin biopsy was done based on the dermatologist's or Investigator's medical judgment, the results of this investigation (including histopathology and immunoflurosecence), with, if applicable, a specific diagnosis of the AE to be reported in the verbatim. 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

Approximately 300 patients will be randomized in this study, 100 per treatment group. Based on the enrollment in prior studies of this population approximately half of the patients are expected to be older than 65.

The sample size calculations are based on the primary efficacy variable of % predicted FVC change from baseline to week 52, with the following assumptions:

- A common standard deviation of 12% is assumed based on the data from previous trials (26)
- A 5 % mean difference between each dose and placebo in change from baseline in % predicted FVC
- A 2-sided 5% significance level with 80% power

Ninety two (92) patients per treatment group will yield 80% power to detect a 5 percentage point difference between the treatment groups and placebo. Additional patients will be randomized in each regimen to allow for dropouts; therefore, approximately 100 patients will be randomized into each treatment group, for a total sample size of approximately 300 patients for the study.

As a rank-based method will be used for analysis the actual power may differ from these calculations, however, calculations based on the ASCEND study (28), which used the same analysis method and endpoint confirm that the planned analysis should have at least 80% power. No adjustment is made for multiplicity since a hierarchical testing procedure is proposed.

Calculations were made using nQuery Advisor 7.0

11.2 DISPOSITION OF PATIENTS

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

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

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.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

The primary population for analysis will be the modified ITT (mITT) population: ITT population with an evaluable primary endpoint. This will consist of all patients who receive at least 1 injection of investigational medicinal product, have a valid baseline % predicted FVC measurement, and have at least one post-baseline % predicted FVC measurement.

11.3.2 Safety population

Safety population - the population considered for the safety analysis will be the as-treated population defined as randomized population who did actually receive at least 1 dose or part of a dose of IMP analyzed according to the treatment actually received.

In addition:

- Non randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- 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 at the majority of injections

11.3.3 Pharmacokinetic analysis population

The population for all PK and ADA analysis will be all randomized and treated patients having at least one sample.

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

Duration of IMP exposure is defined as: last dose date – first dose date + 14 days, regardless of unplanned 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 endpoint(s)

Due to the non-normality of the endpoint distribution, a two-sided rank-based analysis of covariance (rank ANCOVA) model adjusted for baseline, will be used to compare the primary efficacy variable between each active treatment group and placebo:

Change from baseline in the % predicted FVC at Week 52

The rank ANCOVA will be performed as follows:

1. The first step of the analysis is to compute the standardized ranks of the response variable (change from baseline in % predicted FVC at Week 52) and covariate (baseline % predicted FVC)

2. The second step is to perform the ANCOVA analysis based upon these ranks. Within the ANCOVA each active treatment group will be compared to placebo using a contrast.

In the primary analysis, Week 52 assessments will be used regardless of whether the patient has previously discontinued treatment. For patients with missing data at week 52, the week 52 value will be estimated based on a linear regression using all available % predicted FVC measurements. Predicted changes greater than zero (increases above baseline) will be set to zero. For patients with no Week 52 value due to the patients death (or transplant), the value for analysis will be assigned the lowest (worst) rank. Sensitivity analyses including an analysis of the on-treatment data only will be described in the statistical analysis plan.

11.4.2.2 Analyses of secondary efficacy endpoints

Disease progression, defined as decrease in absolute % predicted FVC ≥10%, or decrease in absolute % predicted DLCO ≥15%, or lung transplant, or death will be analyzed as a time to event variable. Patients not meeting the definition for disease progression will be considered censored at the time of their week 52 FVC assessment. For patients with a missing FVC assessment at week 52 the censoring time will be the time of the last measured FVC or DLCO assessment.

The time to disease progression will be compared between each active group and placebo using a log-rank test. The hazard ratio compared to placebo will be estimated from a Cox proportional hazards model.

The incidence of all-cause mortality will be calculated, but no hypothesis testing will be performed for this endpoint.

11.4.2.3 Multiplicity considerations

The overall type I error rate for this study is 5%. A hierarchical testing procedure will be used to control the type I error over the two doses. The qw dose group will be compared to placebo first, and only if this comparison is significant will the q2w dose group be compared to placebo.

The same procedure will be used for the disease progression endpoint if significance is achieved for both doses on the primary endpoint.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group on the basis of the safety population.

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 randomization.
- 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 essentially 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 on-treatment PCSA percentage.

The TEAE observation period is defined as the time from first dose of IMP up to 12 weeks after the last dose of IMP.

Analysis of the adverse event data

Treatment-emergent AEs, treatment-emergent SAEs, TEAEs leading to treatment discontinuation and treatment-emergent AESIs will be summarized for each treatment group based on MedDRA coding of verbatim terms reported by investigators.

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 one 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. Listings 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. Listings will be provided for all TEAE leading to permanent treatment discontinuation by treatment group and patient.

Analysis of treatment-emergent AESI

Treatment-emergent AESI, by AESI category and PT, will show number (%) of patients overall, sorted by decreasing incidence of PT within each AESI category. The AESIs include, but are not limited to, the following categories and details of the MedDRA coding will be provided in the statistical analysis plan: tuberculosis, anaphylaxis, hypersensitivity, vasculitis.

Analysis of Deaths

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received
- Death in nonrandomized 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.

Analysis of the laboratory data

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group. Listings will be provided with flags indicating the out of range values as well as the PCSA values.

The incidence of PCSA at any time will be summarized by treatment group for each laboratory parameter. Shift tables showing changes with respect to the baseline status will be provided.

Analysis of the vital signs data

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables will be calculated for each visit or study assessment (baseline, each post-baseline time point, endpoint) by treatment group.

The incidence of PCSA at any time will be summarized by treatment group for each vital signs variable. Shift tables showing changes with respect to the baseline status will be provided. Listings will be provided with flags indicating the out of range values as well as the PCSA values.

Assessment of potential drug-induced liver injury

The liver function tests, namely ALT, AST, alkaline phosphatase and total bilirubin, 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. The proportion of patients with PCSA values at any post-baseline visit will also be displayed by duration of exposure for each treatment group.

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

Summarize the normalization by parameter (to ≤1 ULN or return to baseline) of elevated liver function tests by categories of elevation (1-<3x, 3x, 5x, 10x, 20x ULN for ALT and AST, 1.5x ULN for Alkaline phosphatase, and 1.5x and 2x ULN for total bilirubin), with following categories of normalization: never normalized, normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category. 1-3, 3-5, 5-10, 10-20, >20

Summarize the incidence of liver related AEs by treatment group. The selection of PTs will be based on standardized MedDRA query (SMQ) for drug related hepatic disorders.

Analysis of the electrocardiogram data

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all ECG variables will be calculated for each visit or study assessment (baseline, each post baseline time point, endpoint) by treatment group.

The incidence of PCSA at any during the TEAE period will be summarized by treatment group for each ECG variable. Shift tables showing changes with respect to the baseline status will be provided. Listings will be provided with flags indicating the PCSA values.

Analysis of Immunogenicity

Anti-SAR antibody (ADA) assay results will be described categorically. Descriptive statistics will be provided for:

- Patients with any positive ADA assay response during the study.
- ADA positive patients during the TEAE period.

ADA positive patient is defined as patient with at least 1 treatment-induced or treatment-boosted ADA positive sample during the TEAE period, where

- Treatment-induced ADA positive patient is defined as a patient with non-positive assay (meaning negative or unevaluable) response at baseline but with a positive assay response during the TEAE period.
- Treatment-boosted ADA positive patient is defined as a patient with a positive ADA assay response at baseline and with at least a 4-fold increase in titer during the TEAE period

The rest will be classified as ADA negative or inconclusive patients.

Response of treatment-induced ADA positive patient is further classified as transient ADA response, persistent ADA response or indeterminate.

Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the TEAE period and at least 16 weeks before the last sample, or
- Treatment induced ADA detected at 2 or more sampling time points, where the first and last ADA positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks and the first ADA positive sample and last ADA sample are separated by a period exceeding 16 weeks or longer.

Persistent ADA response:

- Treatment-induced ADA detected at 2 or more sampling time points during the TEAE period, where the first and last ADA positive samples (irrespective of any negative samples in between) are separated by a period exceeding 16 weeks or longer

Descriptive statistics for ADA titers will be provided for patients with positive ADA assay response and selected sub-categories.

11.4.4 Analyses of pharmacokinetic, pharmacodynamics and biomarker variables

- PK data will summarized by treatment arm and timepoint using descriptive statistics (number of patients, arithmetic mean, standard deviation, geometric mean, coefficient of variation, minimum and maximum).
- Biomarkers will be summarized by treatment arm and visit using descriptive statistics. Correlation analysis may be conducted to explore the PK/PD relationship.

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. Futility analysis will be considered when at least 50% of patients have week 24 evaluation of FVC. All futility rules will be described in the statistical analysis plan.

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 52 collected and validated, and will consist in the final analysis of the primary and secondary endpoints up to Week 52. 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 will be the final analysis:

The second analysis will be conducted at the end of the study and will consist in the final analysis of Week 64 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, delegated Investigator staff and Sub-investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, 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 ***(not applicable for this study as it is not planned to include vulnerable patients***), 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 pharmacogenetics and for potential future markers of interest, the optional pharmacogenetic informed consent form (written) and the optional informed consent form (written) for future use of samples should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative (***not applicable for this study as it is not planned to include vulnerable patients***), and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent forms will be provided to the subject.

The informed consent form, the optional pharmacogenetic informed consent form and the optional informed consent form for future use of samples, 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 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 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, Investigator's Brochure, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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 IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It 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 Investigator's Brochure will be sent to the IRB/IEC.

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 INVESTIGATOR(S)

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 CRF entries against the source documents, except for the pre-identified source data directly recorded in the 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 CRFs (e.g. patient's medical file, appointment books, original laboratory records, etc.). 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 CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate 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 CRFs should be completed to 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 curriculum vitae 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 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 (e.g. 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 purpose 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, Good Clinical Practice 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;
- Non-compliance 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(s) 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 consent(s).

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 of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 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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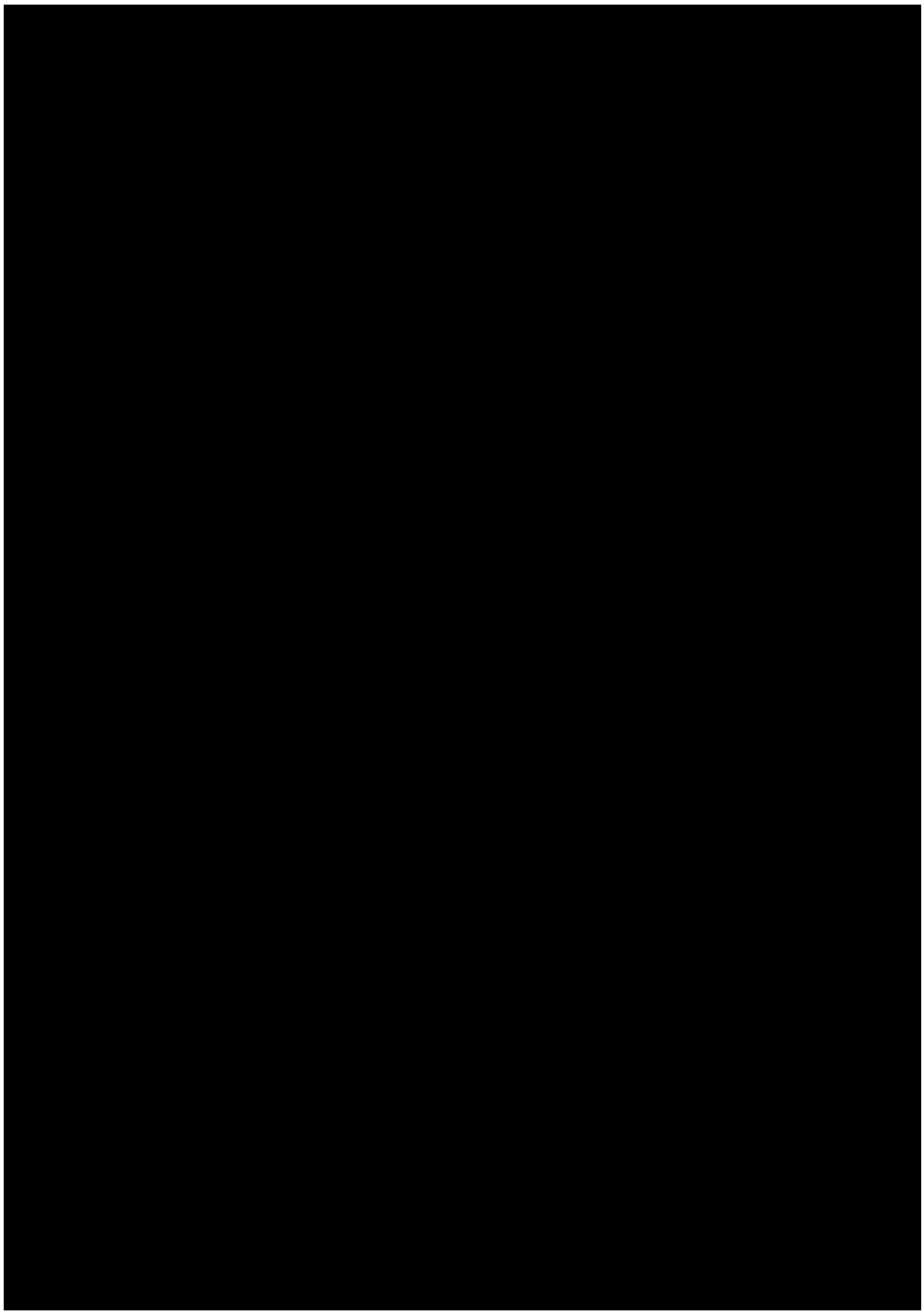
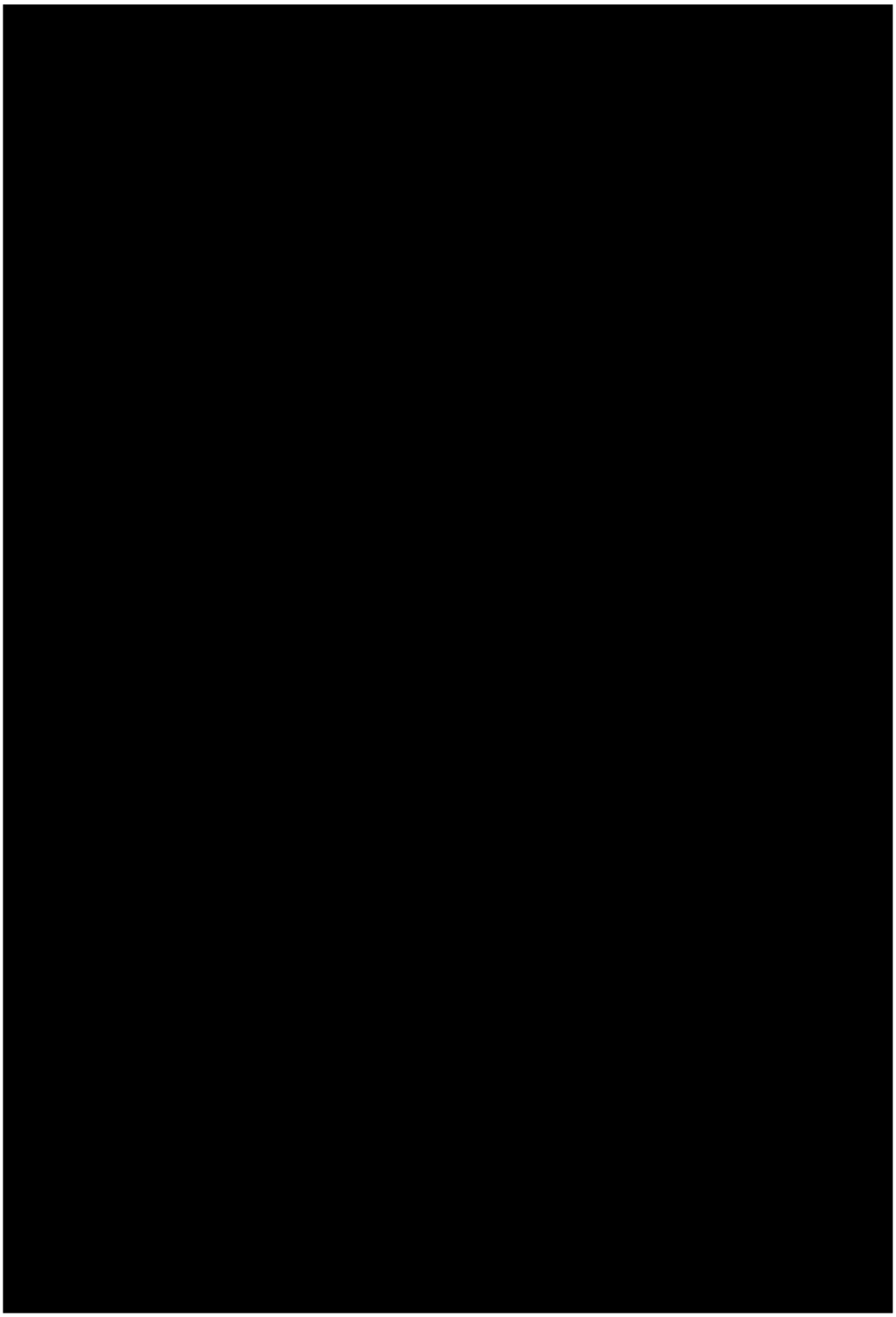
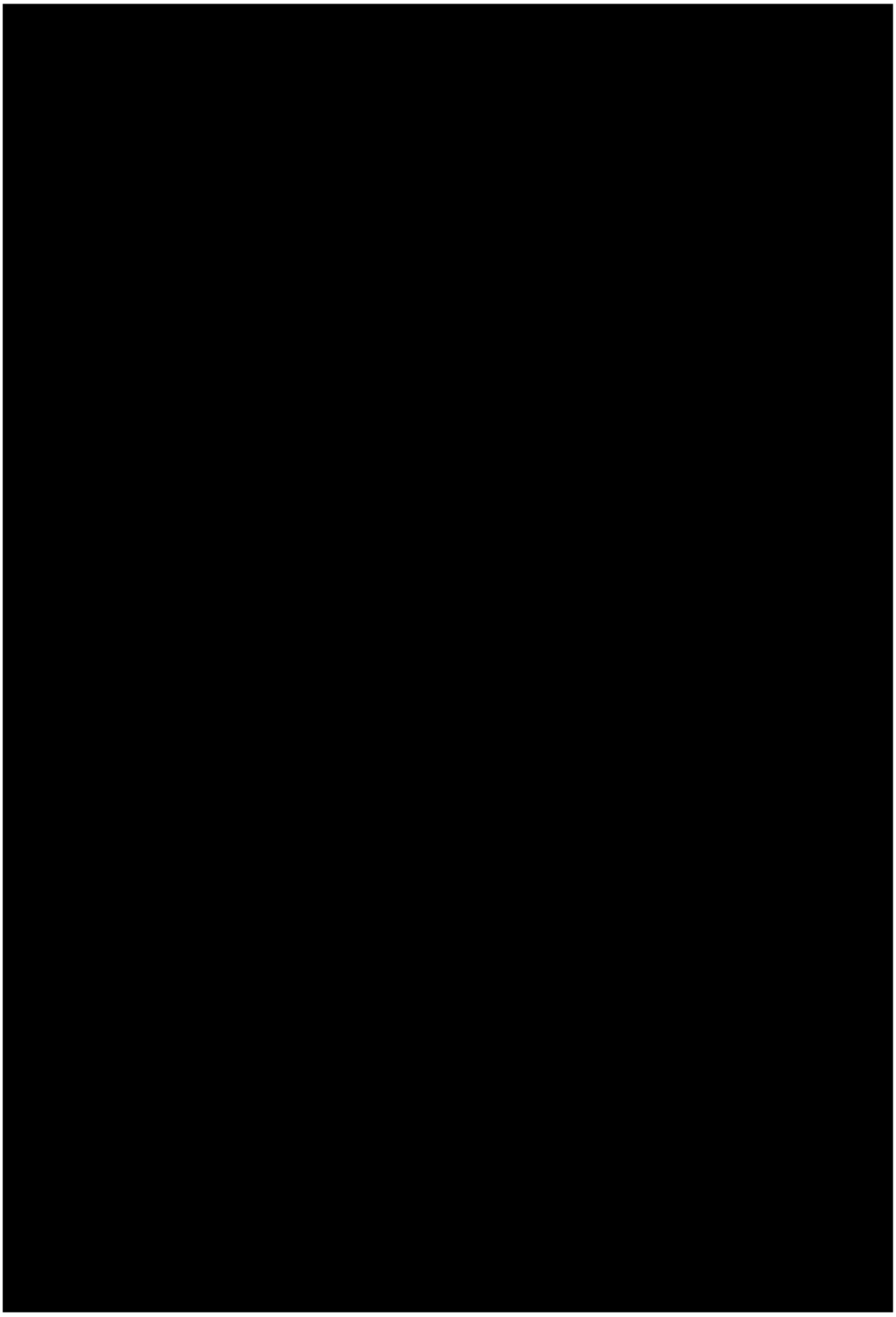
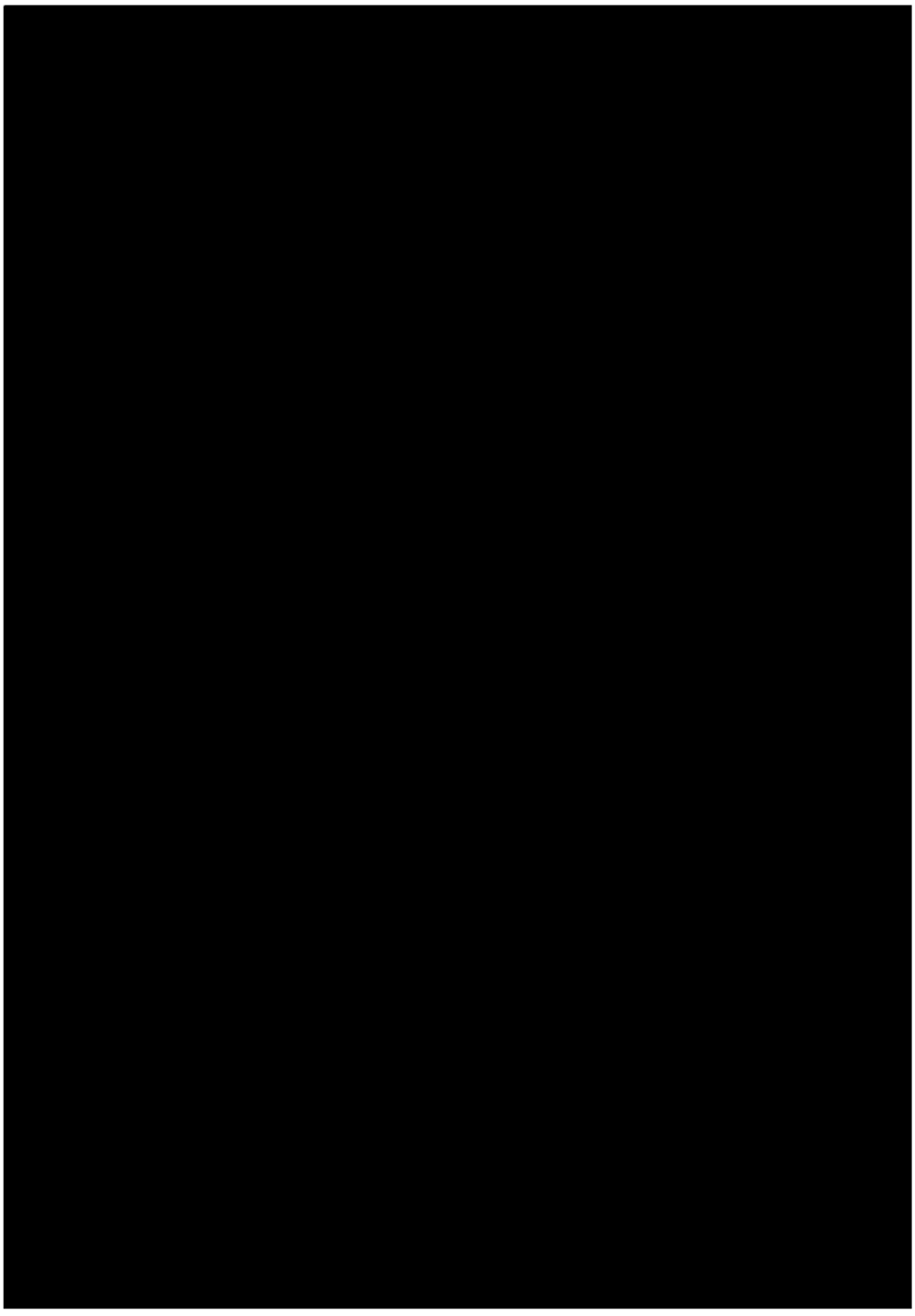
17 APPENDICES

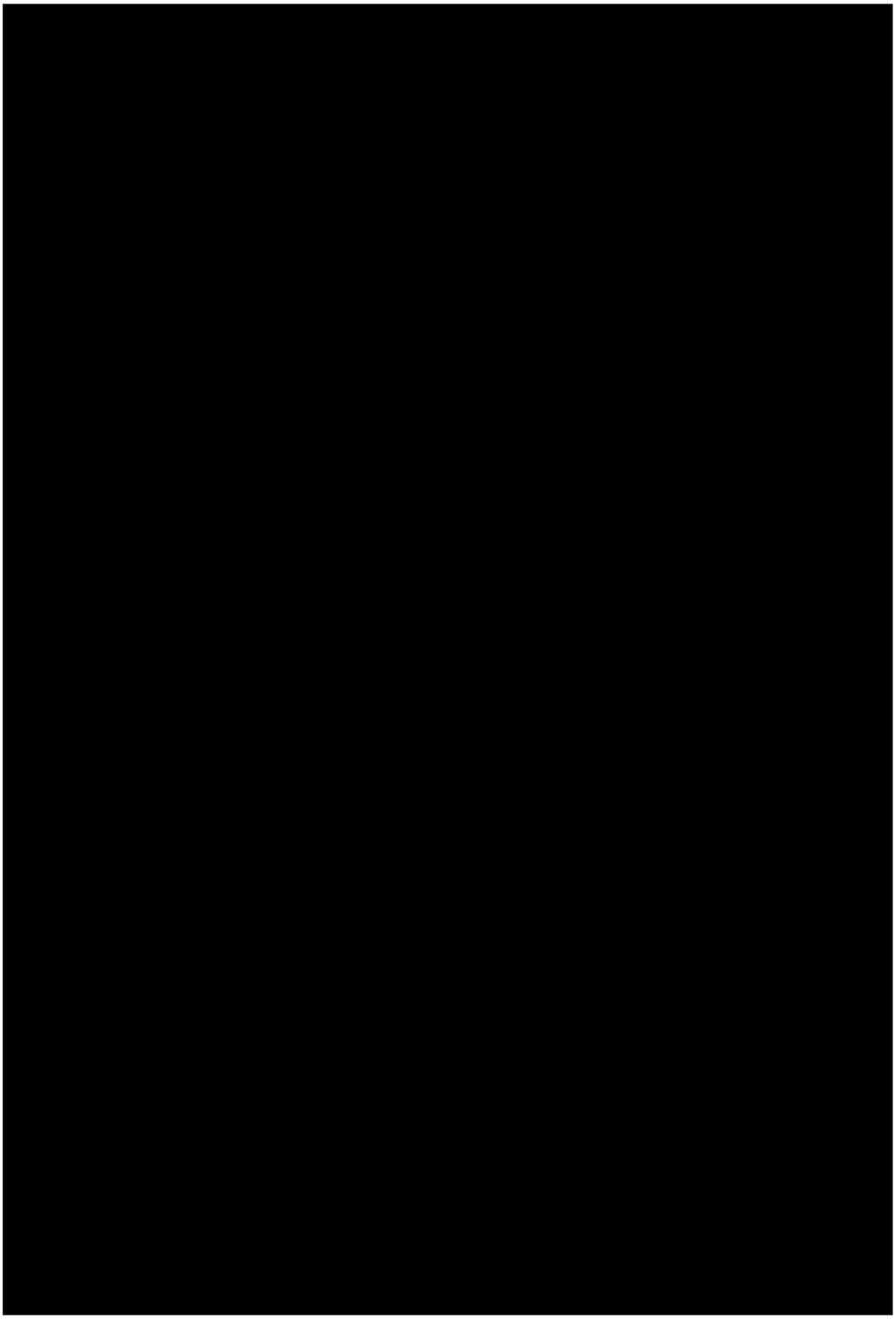
Appendix A Saint George Respiratory Questionnaire

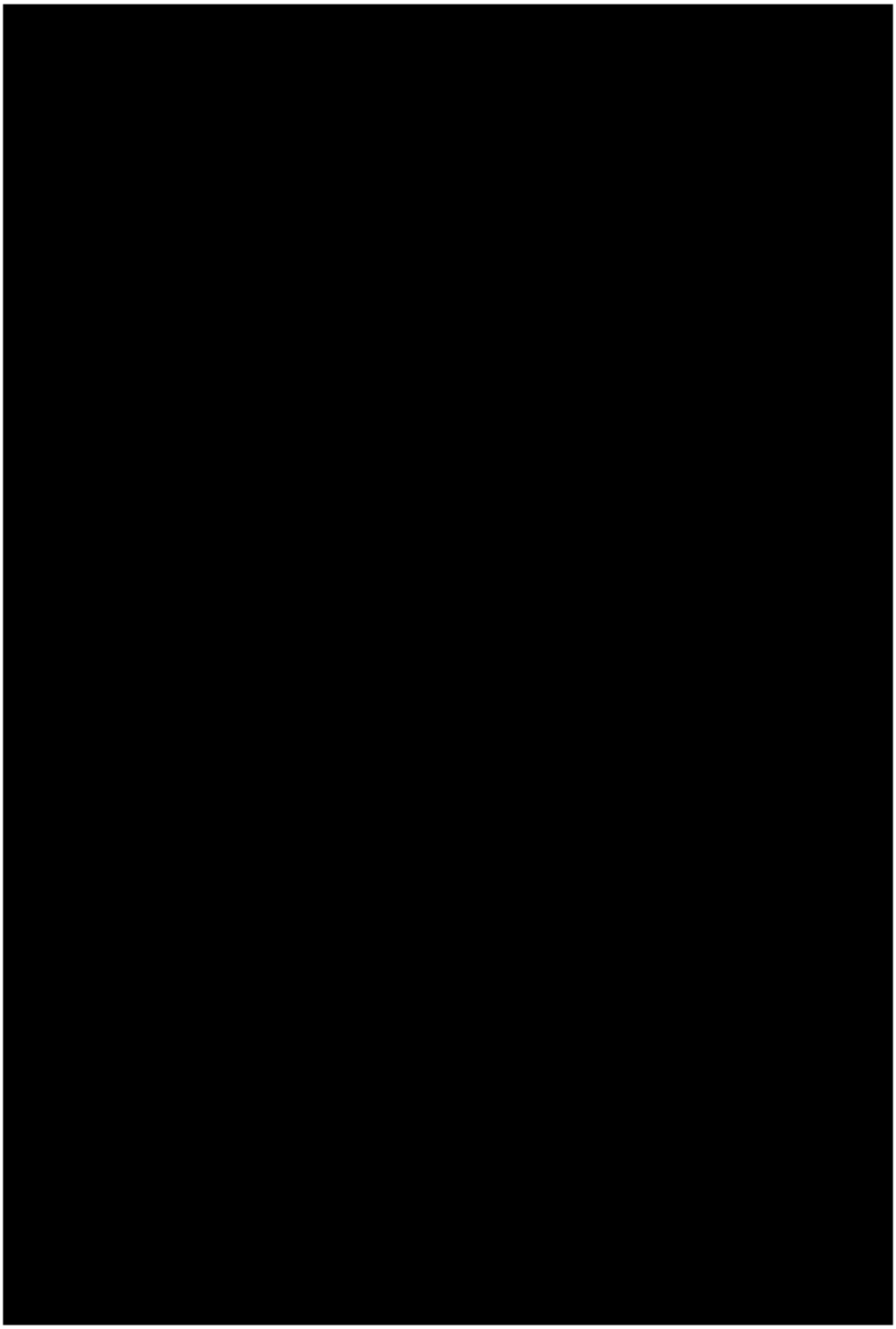




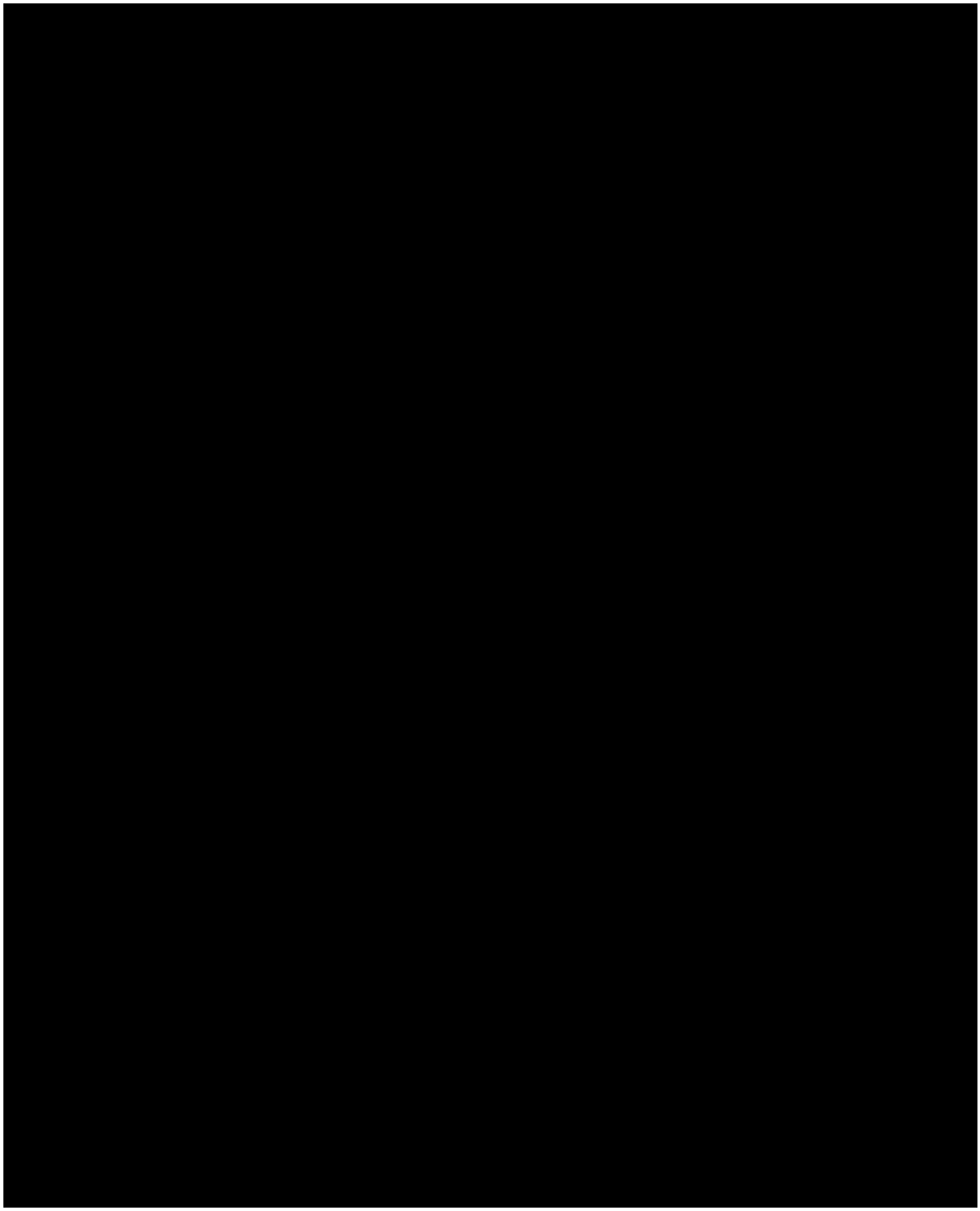


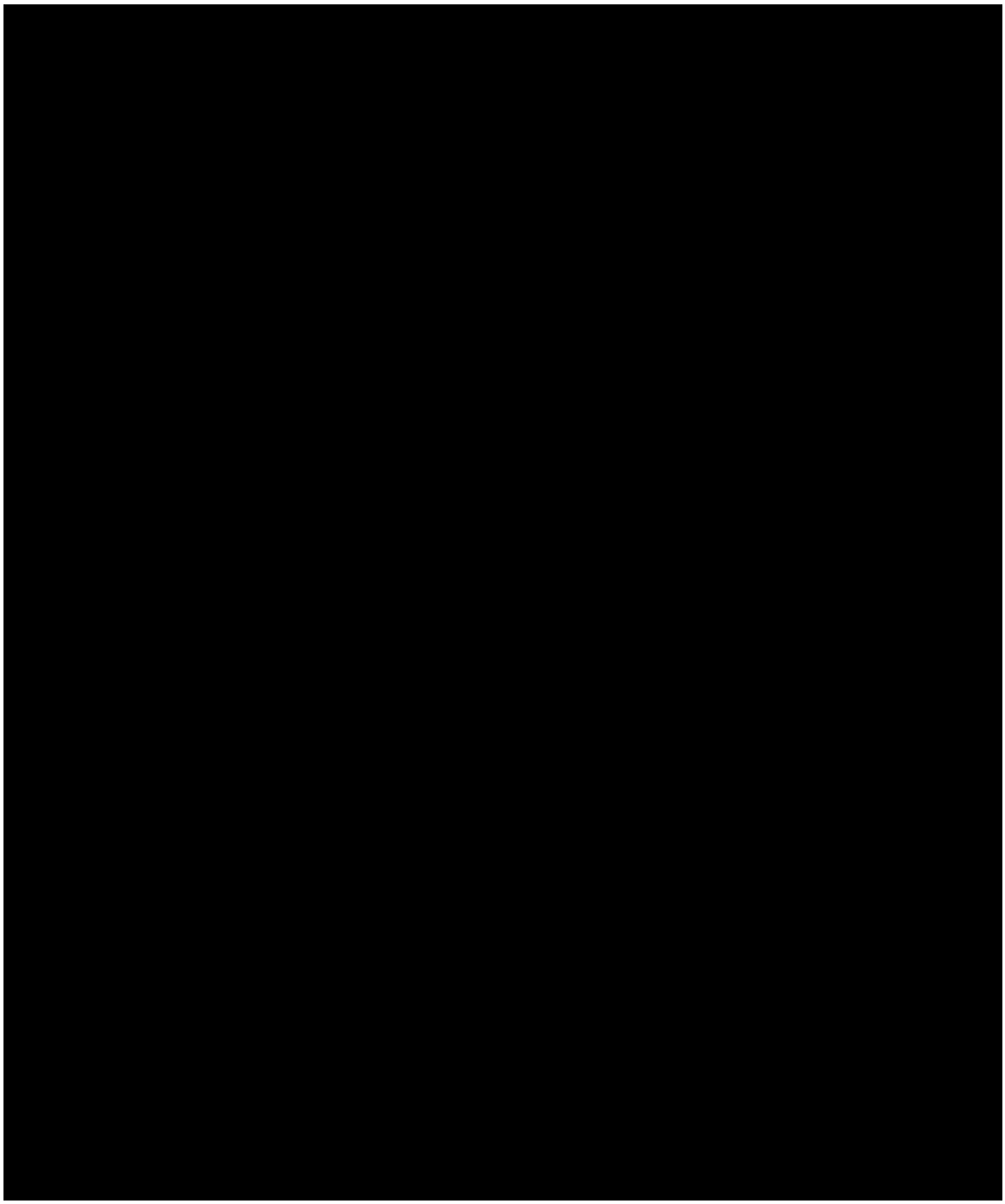






Appendix B EuroQol Questionnaire (EQ-5D-5L)





[redacted]

Appendix C [redacted]

Appendix D Clinical criteria for diagnosing anaphylaxis

H.A. Sampson et al – J Allergy Clin Immunol, 2006; vol 117, n°2: 391-7.

Anaphylaxis is highly likely when any <u>one</u> 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 (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b Reduced BP or associated symptoms of end-organ dysfunction (e.g. 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 e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula

b. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g. 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

PEF, peak expiratory flow; BP, blood pressure

*Low systolic blood pressure 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 E 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.)	Emergency Room (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.	Emergency Room (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.

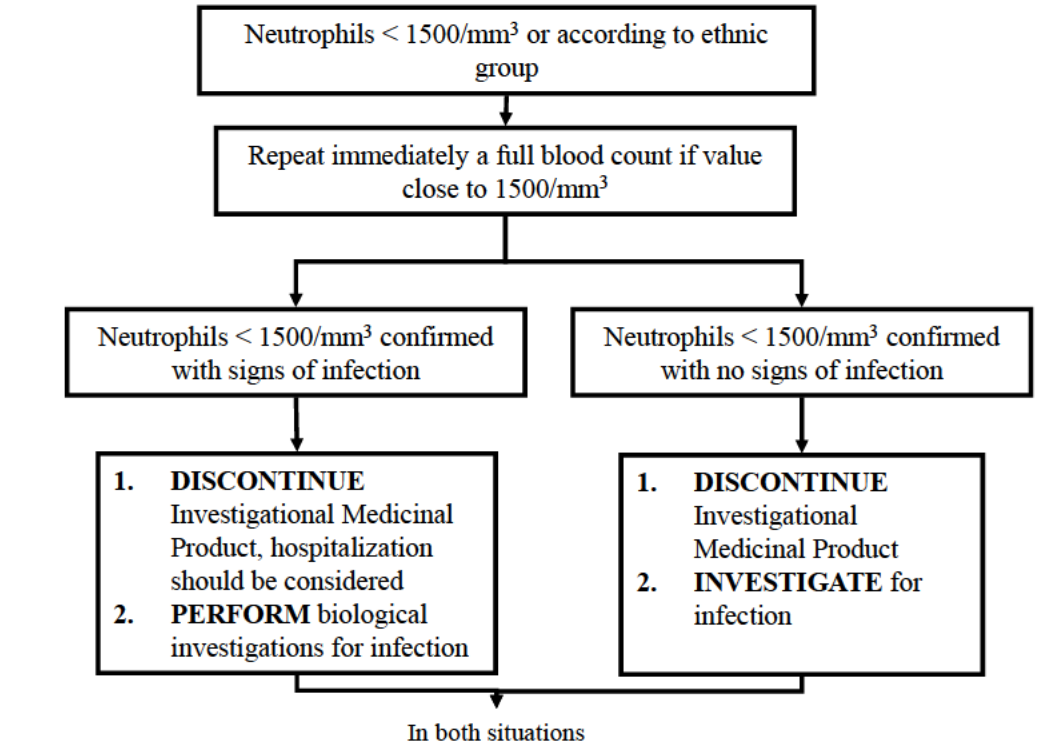
** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

*** 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 F General Guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

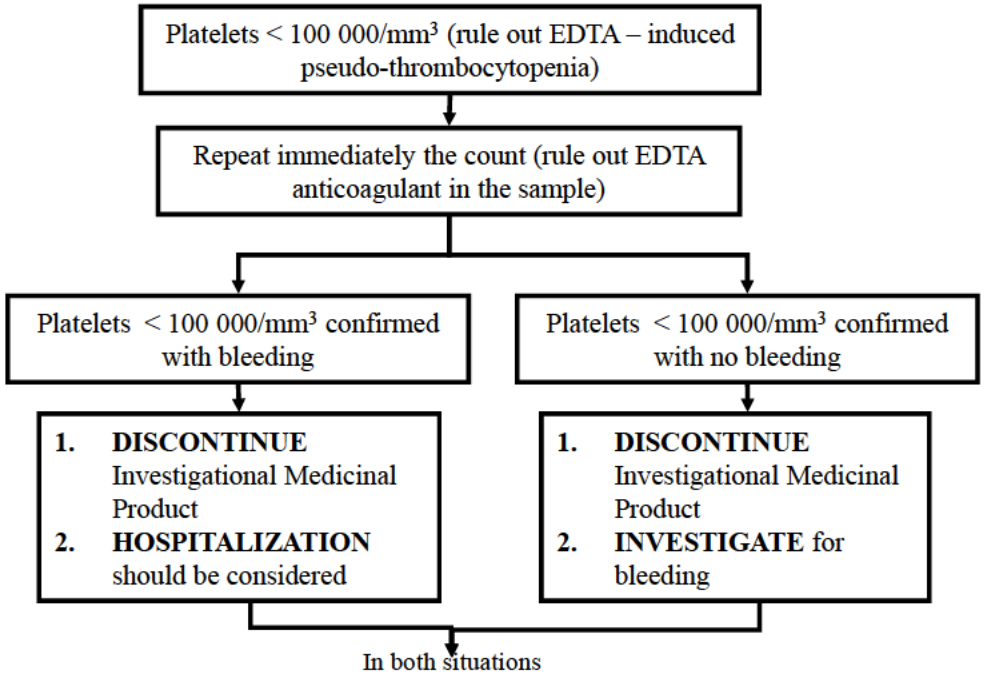


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, 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 AE only if at least one of the criteria listed in Section 10.4.3 is met

THROMBOCYTOPENIA

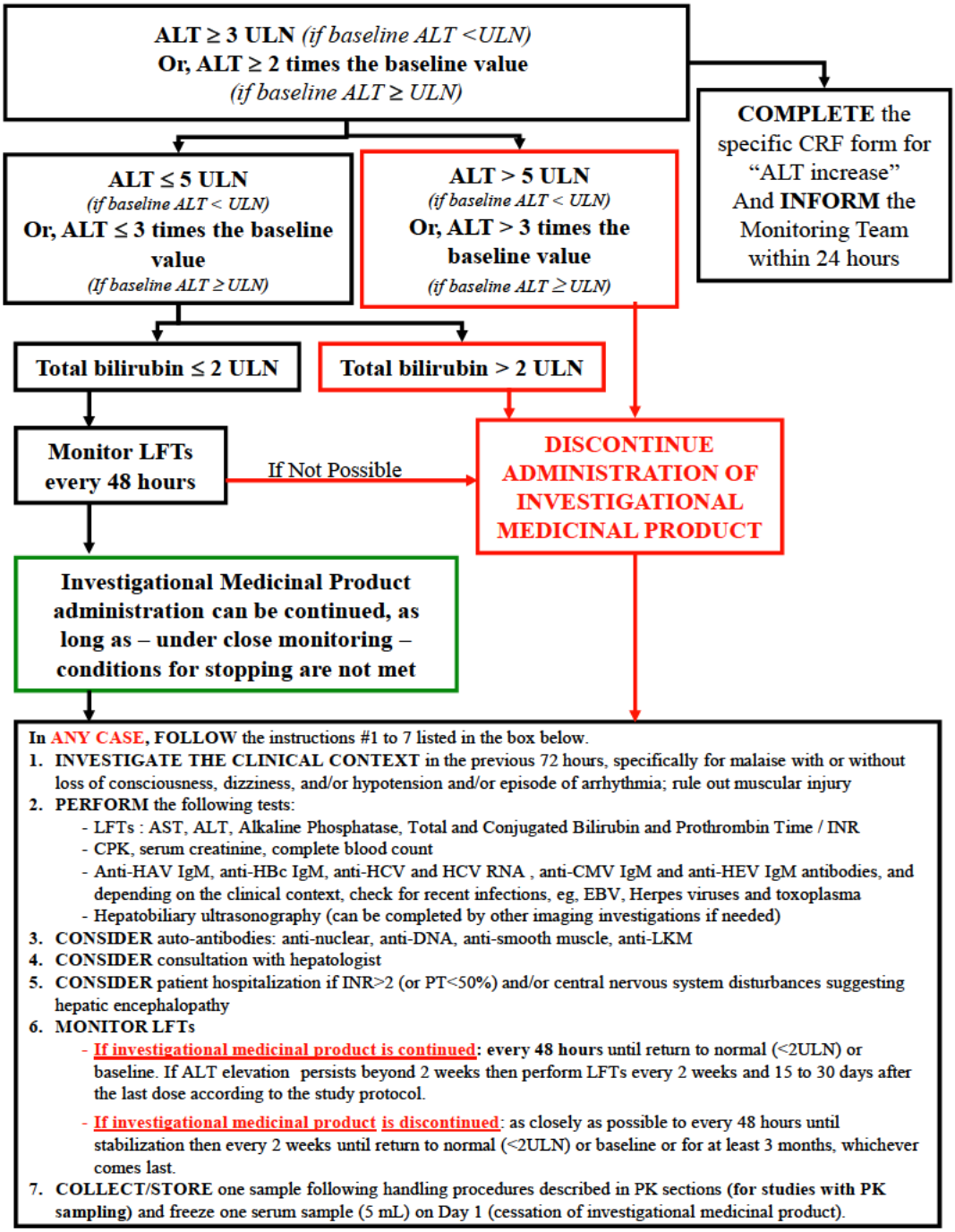


3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin 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.

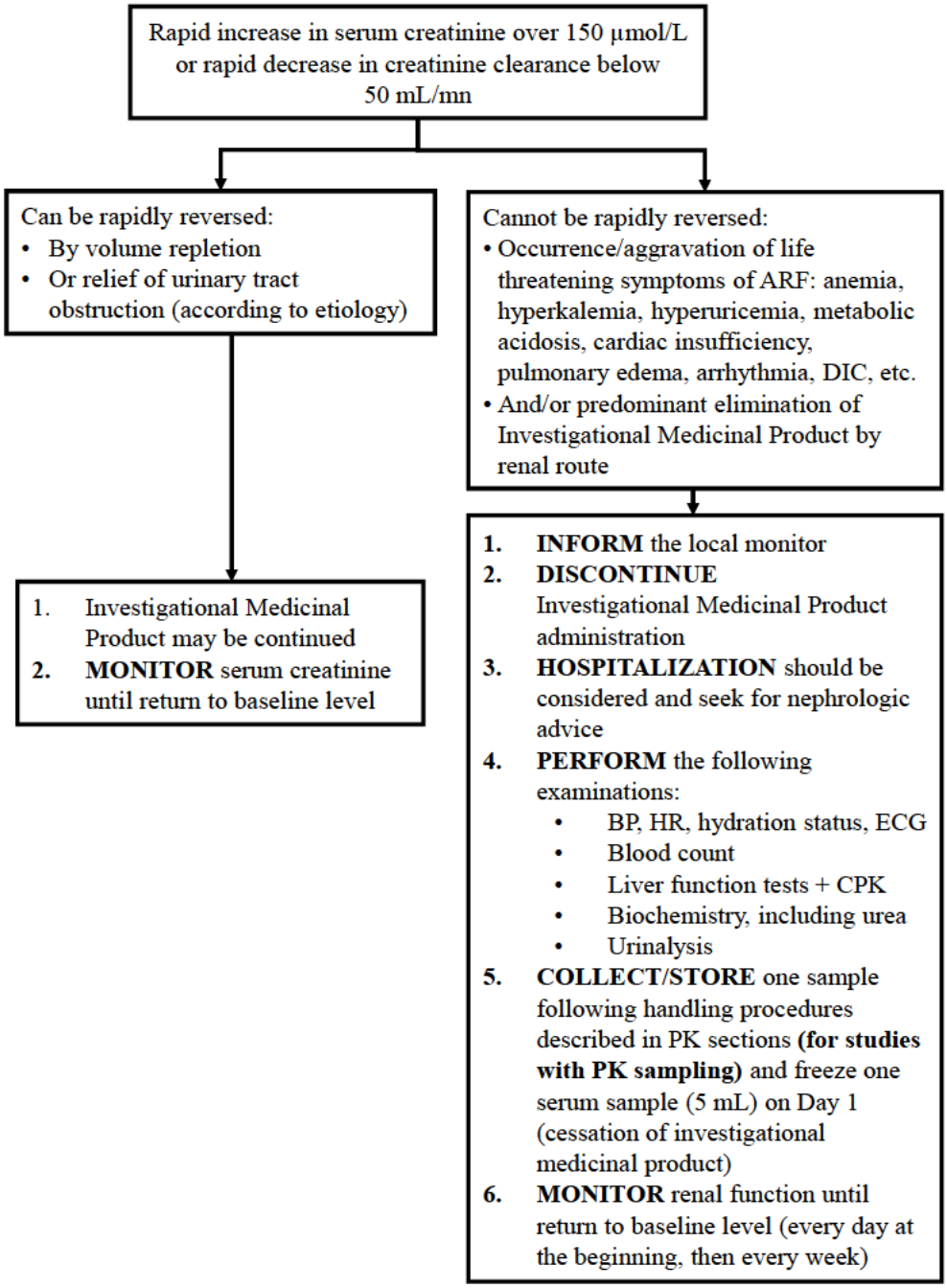
Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

INCREASE IN ALT



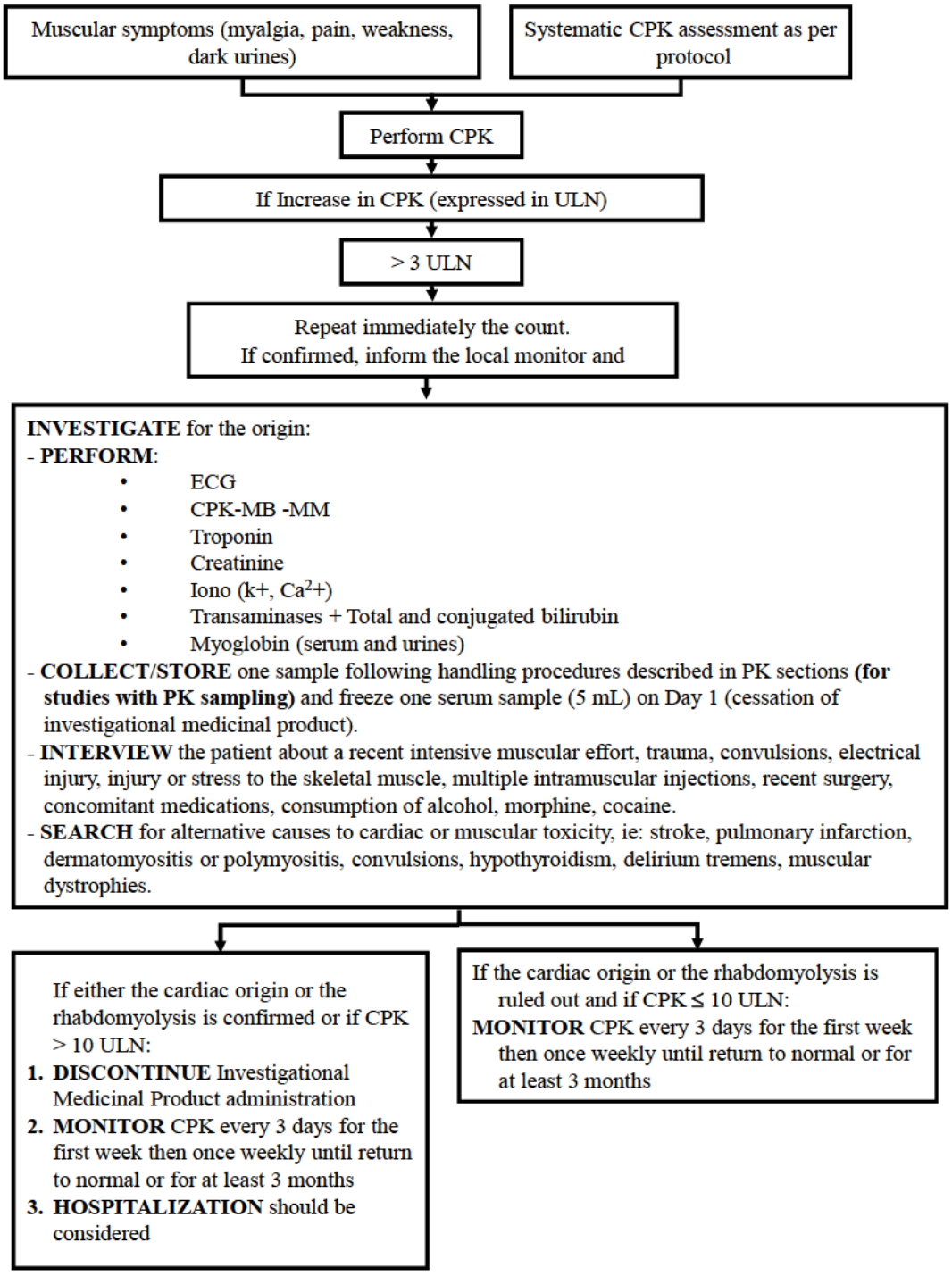
NOTE: ALT ≥ 3 ULN (IF BASELINE ALT < ULN) OR ALT ≥ 2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTIONS 10.4.1.3, 10.4.5, AND 10.4.6). IN ADDITION, IF ALT < 3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

DRI11772 Amended Protocol 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	29-Jul-2015 13:32 GMT+020
[redacted]	Clinical Approval	29-Jul-2015 17:02 GMT+020
[redacted]	Clinical Approval	29-Jul-2015 21:32 GMT+020