AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A randomized, double-blind, placebo-controlled, parallel-group study of the safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in adult patients with primary Sjögren's syndrome (pSjS)**
Protocol number:	**ACT16618**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR441344**
Study phase:	**Phase 2**
Short title:	**Safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in primary Sjögren's syndrome (pSjS) phaethuSA**
Sponsor name:	**Global Sponsor: Sanofi-Aventis Recherche & Développement** **Local US Sponsor: Sanofi US. Services Inc**
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	[05 April 2022], version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	[28 July 2021], version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	[27 August 2020], version 1 (electronic 1.0)
Original Protocol		[29 May 2020], version 1 (electronic 1.0)

Amended protocol 03 (05 April 2022)

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the amendment is to adapt inclusion/exclusion criteria I06, E17, E18, and E22 to better account for the required characteristics of Sjögren`s syndrome (ESSDAI >5 and baseline treatment) to facilitate recruitment, without compromising safety requirements. In addition, the discontinuation due to Coronavirus Disease 2019 (COVID19) was adjusted. Further Section 9.5 (Interim analysis) was revised with an option of additional analysis. Finally, discrepancies are also being addressed in this amendment, as well as minor corrections and clarifications.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	**NCT04572841** added.	Update.
1.1. Synopsis	**"Approximately** ~~A maximum of~~ 88 participants will be randomized to study intervention such that approximately 80 participants complete the study and be evaluable for the analysis of the primary endpoint."	Adaption given the current drop-out rate is above the initial estimated 10%.
1.3. Schedule of activities	Adaption of footnote f: "[…]. ~~If the suspicion of a SARS-CoV-2 infection is confirmed~~ in the case of biologically proven COVID-19 infection, **the Investigator may permanently discontinue the IMP for the participant** ~~treatment should be~~	As different variants of COVID-19 emerge and worldwide vaccination continues, the need for permanent discontinuation of IMP due to COVID-19 infection is less certain and can be assessed on a case-by-case basis.

Section # and Name	Description of Change	Brief Rationale
	~~stopped~~ (Section 7.1.1**). If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation until the participant's COVID-19 PCR is negative (Section 7.1.2).**"	
2.3.1.1.2 Risk mitigation	**"In the case of biologically proven COVID-19 infection, the Investigator may permanently discontinue the IMP for the participant, who will be asked to continue attending the protocol scheduled visits until the EOS. If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation if the patient does not have severe or critical COVID-19 infection as defined per WHO guidelines (25). The participant must temporarily discontinue IMP until the participant's COVID-19 PCR is negative. A discontinuation of more than 30 days will be considered as permanent discontinuation. All COVID-19 infections will be reviewed by the DMC as AESI."**	As different variants of COVID-19 emerge and worldwide vaccination continues, the need for permanent discontinuation of IMP due to COVID-19 infection can be assessed on a case-by-case basis.
	Taking into account this risk, the potential risk of an increased infectious risk due to lymphopenia, and potential relevance in SARS-CoV-2 infections (34), patients with a ~~significant~~ **severe** lymphopenia will be excluded from this study (see exclusion criterion E 22 in Section 5.2).	Clarification with regards to exclusion criterion E22, to better account for characteristics of Sjogren'syndrome.
5.1 Inclusion criteria	Adaption of Inclusion criterion I06: ~~Rheumatoid factor positive and/or IgG > upper limit of normal (ULN) at Screening.~~ **IgG > lower limit of normal at Screening.**	To better account for the characteristics of Sjögren`s syndrome.
5.2 Exclusion criteria	Adaption of E17: "High dose of hydroxychloroquine or chloroquine [redacted] or **methotrexate** [redacted] or a change in hydroxychloroquine, ~~or~~ chloroquine **or methotrexate** dose within 12 weeks prior to Day 1/Randomization or expected changes during the course of the study." Adaption of E18: "[…] Previous treatment with azathioprine and other thiopurines, ~~methotrexate,~~ mycophenolate mofetil, sulfasalazine, or cyclosporine A within 3 months."	To better adapt to common baseline treatments for Sjögren`s syndrome.
5.2 Exclusion criteria	Adaption of E22: - Lymphocytes [redacted]~~/mm^3~~ [redacted]**/mm^3**	Patients with active pSjS have lymphopenia due to SjS activity with no increased risk of infection.

Section # and Name	Description of Change	Brief Rationale
5.4 Screen failures	Sentence was added: **"If a participant was re-screened once under the amended protocol 1 or 2 due to I06 or E22 (Lymphocytes [redacted]/mm^3), participant might be re-screened a second time, at the Investigator`s discretion."**	Clarification given the protocol amendment.
5.4 Screen failures	Footnote "b" was added to Table 3; I05: "**Re-testing or re-Screening is allowed once, if results in the central laboratory for anti-Ro/SSA are equivocal and no other reasons apply that prohibit re-screening."**	Clarification.
6.3 Measures to minimize bias: Randomization and blinding.	"The preliminary PK **and Biomarker** data, if needed and available during the course of the study, will refer to mean data with descriptive statistics and individual data, without revealing any individual randomization numbers or participant numbers."	Clarification.
6.5.1 Prohibited concomitant medication	• High dose of hydroxychloroquine or chloroquine [redacted], or a change in hydroxychloroquine or chloroquine dose within 12 weeks prior to Day 1/Randomization, or **expected** changes during the course of the study. **•High dose of methotrexate [redacted], or a change in methotrexate dose within 12 weeks prior to Day 1/ Randomization, or expected changes during the course of the study.** • Previous treatment with azathioprine or other thiopurines, ~~methotrexate,~~ mycophenolate mofetil, sulfasalazine, or cyclosporine A within 3 months prior to Screening and during the course of the study.	To better adapt to common baseline treatments for Sjögren`s syndrome.
6.5.2 Key authorized medications	• Low dose hydroxychloroquine or chloroquine treatment[redacted] and a stable dose within 12 weeks prior to Day1/ Randomization. No change in dose is permitted during the study **unless for the management of an AE.** Dose and any change will be recorded on the participant e CRF. Hydroxychloroquine or chloroquine cannot be started during the course of the study. **•Methotrexate up to[redacted] or equivalent and a stable dose within 12 weeks prior to Day 1/ Randomization. No change in dose is permitted during the study unless for the management of an AE. Dose and any change will be recorded on the participant eCRF. Methotrexate cannot be started during the study. Concomitant therapy with folic acid is permitted.**	To better adapt to common baseline treatments for Sjögren`s syndrome and clarification.

Section # and Name	Description of Change	Brief Rationale
7.1.1. Definitive discontinuation	~~• Diagnosed and biologically proven SARS CoV 2 infection.~~ **In the case of biologically proven COVID-19 infection, the Investigator may permanently discontinue the IMP for the participant, who will be asked to continue attending the protocol scheduled visits until EOS. If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation per Section 7.1.2. The participant cannot restart IMP until the participant's COVID-19 PCR is negative. All COVID-19 infections will be reviewed by the DMC as AESI.**	As different variants of COVID-19 emerge and worldwide vaccination continues, the need for permanent discontinuation of IMP due to COVID-19 infection can be assessed on a case-by-case basis.
7.1.2 Temporary discontinuation	[…]. ~~If the COVID-19 diagnosis is confirmed, the IMP should be discontinued definitely (Section 7.1.1).~~ **In the case of biologically proven COVID-19 infection, if according to the Investigator a permanently IMP discontinuation is not necessary or in the best interest of the participant and the participant does not have severe or critical COVID-19 as defined by WHO guidelines (25), the participant can temporarily discontinue IMP until the participant's COVID-19 PCR is negative.**	As different variants of COVID-19 emerge and worldwide vaccination continues, the need for permanent discontinuation of IMP due to COVID-19 infection is less certain and can be assessed on a case-by-case basis.
8 Study assessments and procedures	[…] Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, **this could be done locally if approved by the Sponsor.**	Clarification.
9.2 Sample size determination	**Approximately** ~~Up to~~ 88 participants are expected to be randomly assigned to the IMP, expecting a total of 80 evaluable participants with approximately 40 evaluable participants per group.	Adaption given the current drop-out rate is above the initial estimated 10%.
9.3 Populations for analyses	In Table 5, row pharmacokinetic: All **randomized and treated participants (safety population) with adequate PK results** ~~without any important deviation related to IMP administration, for whom the PK data are considered interpretable~~. Participants having received only placebo will not be part of the PK population. **Participants will be analyzed according to the intervention they received.** In Table 5, row pharmacodynamic: All **randomized and treated** participants **(safety population) with at least one post-baseline PD data.** ~~no important deviations impacting PD~~	Clarification.

Section # and Name	Description of Change	Brief Rationale
	~~measurements, for whom the PD data are considered sufficient and interpretable.~~ **Participants will be analyzed according to the intervention they received.**	
9.5. Interim analysis	**Beside those described interim analyses, additional analyses for internal decision making might be conducted. For those analyses, if decided to do so, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding.**	Adding the option of an additional analysis if needed for internal decision making throughout the study.

pSjS: primary Sjögren`s syndrome, SoA: Schedule of Assessments.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A randomized, double-blind, placebo-controlled, parallel-group study of the safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in adult patients with primary Sjögren's syndrome (pSjS)

Short title: Safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in primary Sjögren's syndrome (pSjS)

Rationale:

Cluster of differentiation 40 (CD40)/cluster of differentiation 40 ligand (CD40L) interaction is required for B-cell activation/maturation, dendritic cell maturation, and T-cell dependent antibody response (TDAR). Given its stimulatory role, deregulated expression of CD40L can be associated with abnormal inflammatory and autoimmune responses. Given these findings, the disruption of the CD40/CD40L pathway in autoimmune diseases (particularly those where pathogenic B-cell responses are a hallmark of the disease), would be predicted to impact both cellular and humoral responses, with therapeutic benefit.

Sjögren's syndrome (SjS) is a chronic complex autoimmune disease primarily characterized by inflammation and progressive destruction of the exocrine glands (ie, autoimmune epithelitis). Though the pathophysiology of SjS is still not fully understood, it is documented that CD40/CD40L interaction and B-cell pathology play a role. As expected, higher soluble CD40L levels can be found in patients with SjS. Indeed, an antibody against CD40 (iscalimab) recently showed promising results on clinical outcome markers in a primary SjS (pSjS) proof of concept study, further indicating that inhibition of the CD40/CD40L could be beneficial in pSjS.

SAR441344 is an antagonist monoclonal antibody (mAb) which binds to CD40L, blocking the interaction with CD40 expressed on the surface of antigen presenting cells. This study will evaluate the therapeutic efficacy of SAR441344 in adult patients with pSjS, as well as safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD).

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with primary Sjögren's syndrome (pSjS), assessed by the change of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI).	• Change in ESSDAI from Baseline to Week 12.
Secondary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI).	• Change in ESSPRI from Baseline to Week 12.
• To evaluate the therapeutic efficacy on fatigue of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the Multidimensional Fatigue Inventory (MFI).	• Change in MFI general fatigue subscale and other subscales from Baseline to Week 12.
• To evaluate the pharmacokinetic (PK) exposure of one dose level of SAR441344 over 12 weeks in adult patients with pSjS.	• Descriptive statistics of SAR441344 concentrations, including mean, median, and standard deviation. • Pharmacokinetic parameters for SAR441344 will be reported (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and terminal half-life [$t_{1/2z}$]).
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo in adult patients with pSjS as determined by adverse events (AEs).	• Incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs) from Baseline to Week 24 (End of Study [EoS]). • Incidence of study investigational medicinal product discontinuation and withdrawals due to TEAEs from Baseline to Week 24 (EoS).
• To evaluate the local tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Change in participant reported local tolerability scale. • Incidence of AEs related to local tolerability findings.
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS determined by electrocardiogram, vital signs, and laboratory evaluations.	• Participants with medically significant changes in vital signs, electrocardiogram, and/or laboratory evaluations.
• To measure the immunogenicity of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Antidrug antibodies at Baseline, Week 4, Week 8, Week 12, and Week 24.
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Overall design:

ACT16618 is a multicenter, randomized, double-blind, placebo-controlled, parallel group proof of concept Phase 2 study to assess the safety, tolerability, PK, and therapeutic efficacy of SAR441344 in pSjS. Participants included are diagnosed with pSjS, with systemic disease (European League Against Rheumatism [EULAR] Sjögren's Syndrome Disease Activity Index [ESSDAI] score ≥5) and significant biological activity. Participants will be randomized at Baseline (Day 1) to SAR441344 or placebo in a 1:1 ratio and will receive a single intravenous (IV) loading dose on Day 1, followed by 5 subcutaneous (SC) doses administered once every

2 weeks (q2w). The Screening period has a maximum duration of 30 days, followed by a treatment period for 12 weeks. The follow-up period has a 12-week duration. Randomization will be stratified by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) ≥5 versus <5.

This study will be reviewed by an independent Data Monitoring Committee (DMC).

Disclosure Statement: This is a parallel-group treatment study with 2 groups that is blinded for the participant and Investigator.

Number of participants:

Approximately 88 participants will be randomized to study intervention such that approximately 80 participants complete the study and be evaluable for the analysis of the primary endpoint.

Intervention groups and duration:

Participants will receive SAR441344, with a single IV loading dose of [redacted] mg or matching placebo on Day 1, followed by 5 doses of [redacted] mg SC q2w or matching placebo. Screening will last up to 30 days, followed by a 12-week treatment period (with the last investigational medicinal product [IMP] administration scheduled at Week 10), and a 12-week follow-up period, leading to a drug-free surveillance period of approximately 4 half-lives.

Study intervention(s)

Investigational medicinal product(s)

- Formulation: SAR441344, a humanized anti-CD40L mAb, will be supplied in single use vials containing [redacted] mg SAR441344 ([redacted] mg/mL; extractable volume: [redacted] mL). Placebo will be prepared using the same formulation as SAR441344 without the active protein and supplied in single use vials (extractable volume: [redacted] mL).
- Route(s) of administration: IV and SC.

Dose regimen: One IV loading dose of [redacted] mg or matching placebo (infusion duration: 1 hour) followed by 5 administrations of [redacted] mg or matching placebo SC q2w.

Statistical considerations:

- **Sample size considerations:**
  - The sample size was derived with respect to the primary endpoint (mean change from Baseline to Week 12 in the ESSDAI score) by applying the Quantitative Decision Making approach.
- **Main analysis populations:**
  - **Efficacy population:** all randomly assigned participants who did actually receive at least 1 complete dose of IMP with at least 1 post-IMP administration measurement, with available Baseline assessment of the ESSDAI.

    Participants will be analyzed according to the intervention they actually received.

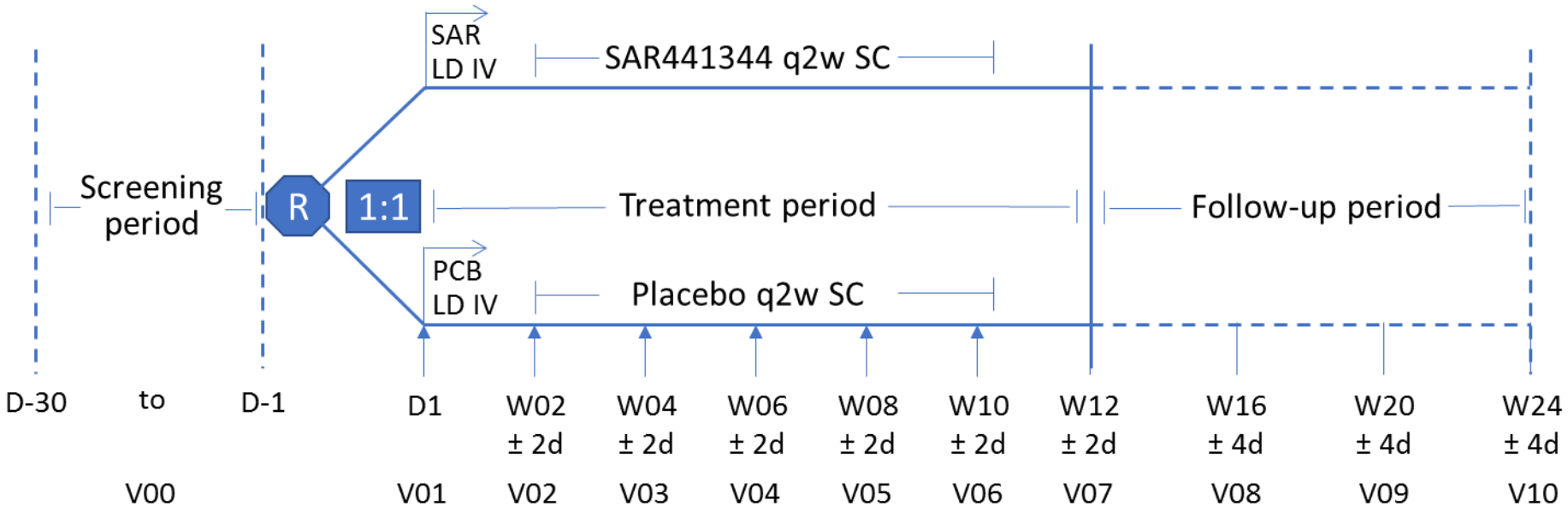
- **Safety population:** all randomized participants exposed to the IMP (regardless of the amount of treatment administered) are included in the safety population. Participants will be analyzed according to the intervention they actually received.
- **Pharmacokinetic population:** all participants without any important deviation related to IMP administration, for whom the PK data are considered interpretable. Participants having received only placebo will not be part of the PK population.

- **Analysis of primary endpoint:**
  - The difference to placebo of mean change from Baseline to Week 12 in ESSDAI score will be derived using a linear mixed model with repeated measurements over time within participant, including the fixed effects for participant-specific baseline ESSDAI, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence interval.
- **Analysis of key secondary endpoints:**
  - The difference to placebo of mean change from Baseline to Week 12 in ESSPRI will be derived using a linear mixed model with repeated measurements over time within participant, including the fixed effects for participant-specific baseline ESSPRI, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence interval.
  - The difference to placebo of mean change from Baseline to Week 12 in Multidimensional Fatigue Inventory (MFI) general fatigue subscale and other subscales will be derived using a linear mixed model with repeated measurements over time within participant, including the fixed effects for participant-specific baseline, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence intervals.
- **Analysis of safety endpoints:**
  - Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) from Baseline to Week 24 (End of Study [EoS]) will be presented.
  - Incidence of TEAEs leading to definitive treatment discontinuation will be presented.
  - Descriptive statistics of laboratory variables, electrocardiograms (ECGs), and vital signs will be presented.

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Study schema



D: Day, IV: intravenous, LD: loading dose, PCB: placebo, q2w: once every 2 weeks, R: randomization, SAR: SAR441344, SC: subcutaneous, V: Visit, W: Week.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Phase	**Screening**	**Treatment Period**							**Follow-up Period**		
Day/Week	**D-30 to D-1**	**D1 (BL)**	**W02**	**W04**	**W06**	**W08**	**W10**	**W12 (EoT[a])**	**W16[c]**	**W20[c]**	**W24 (EoS[b,c])**
Visit window			**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**
Visits	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**
Informed consent form	X										
Inclusion/exclusion criteria	X	X									
Participant demography	X										
Medical/surgical history	X										
Prior/concomitant medications[d]	<	-	-	-	-	-	-	-	-	-	>
Inclusion		X									
Randomization		X									
Phone call before visit[e]		X						X			
Phone call to evaluate potential SARS-CoV-2 infection[f]		X	X	X	X	X	X	X	X	X	X
Study treatment administration											
SAR441344 administration or placebo[g]		X	X	X	X	X	X				
Safety											
Physical examinations[h]	X	X		X		X		X			X
Height	X										
Body weight	X	X		X		X		X			X
Body temperature	X	X		X		X		X			X
Vital signs	X	X		X		X		X			X
ECG	X	X		X				X			X
Serology	X										
FSH[i]	X										
β-HCG blood test[j]	X										
Tuberculosis screening[k]	X										
Hematology	X	X	X	X		X		X			X
Coagulation	X	X	X	X		X		X			X
Clinical chemistry[l]	X	X	X	X		X		X			X

Phase	Screening	Treatment Period							Follow-up Period		
Day/Week	**D-30 to D-1**	**D1 (BL)**	**W02**	**W04**	**W06**	**W08**	**W10**	**W12 (EoT[a])**	**W16[c]**	**W20[c]**	**W24 (EoS[b,c])**
Visit window			**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**
Visits	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**
Urinalysis[m]	X	X		X		X		X			X
Urine pregnancy test, WOCBP only[n]		X	X	X	X	X	X	X	X	X	X
Local tolerability[o]			X	X	X	X	X				
Antidrug antibodies		X		X		X		X			X
Adverse event collection	<	-	-	-	-	-	-	-	-	-	>
Pharmacokinetics											
Plasma sample collection (SAR441344)		X[p]	X	X	X	X	X	X	X		X
Efficacy											
ESSDAI[q]	X[r]	X		X		X		X			X
ESSPRI[s]		X		X		X		X			X
Multidimensional Fatigue Inventory (MFI)		X						X			X
[redacted]		[redacted]									
	X[u]										
Pharmacodynamics											
[redacted]	X	[redacted]									
	X										
	X										

Phase	Screening	Treatment Period							Follow-up Period		
Day/Week	**D-30 to D-1**	**D1 (BL)**	**W02**	**W04**	**W06**	**W08**	**W10**	**W12 (EoT[a])**	**W16[c]**	**W20[c]**	**W24 (EoS[b,c])**
Visit window			**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±2 d**	**±4 d**	**±4 d**	**±4 d**
Visits	**V00**	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**
Biomarker											
Anti-Ro/SSA antibodies	X										
[redacted]		[redacted]									
Genetics											
[redacted]		[redacted]									

Note: assessments during the treatment period will be performed prior to IMP dosing, unless otherwise specified.

a If the participant discontinues the study before Week 12, the EoT visit should be performed, if possible. If the participant discontinues the IMP before Week 12, the EoT visit and the complete follow-up period should be performed.

b If the participant discontinues the study in the follow-up period, the EoS visit should be performed, if possible.

c In exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer possible or safe, one or more follow-up visits can be performed remotely (eg, via telephone call). This should be done according to local regulations and approved by the Sponsor. At least one follow-up visit should be performed on site (EoS visit), even if the visit window needs to be extended (to a maximum of 8 weeks).

d Stable background therapy with hydroxychloroquine or chloroquine, low doses of oral corticosteroids, topical therapy and pharmacological stimulants (glands), and NSAIDs are allowed; see Section 6.5 for detailed information. Participants need to be informed about restrictions on concomitant medication including nonprescription drugs as described in Section 6.5 at Screening and throughout the study.

e [redacted] (Section 6.5.2). [redacted]

f Participants will be contacted before each visit (latest on the day before the visit) by the Investigator or designee, to evaluate for signs and symptoms of a potential SARS-CoV-2 infection. In case of suspicion of such infection, the participant will be asked to not come to the study site and will be referred to a testing facility or her/his primary care physician according to local regulations. If the suspicion of a SARS-CoV-2 infection is excluded and there is no other reason to pause treatment due to the Investigator judgment, the treatment can continue. In the case of biologically proven COVID-19 infection, the Investigator may permanently discontinue the IMP for the participant (Section 7.1.1). If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation until the participant's COVID-19 PCR is negative (Section 7.1.2).

g On D1: SAR441344 [redacted] mg IV administration or placebo (infusion duration: [redacted]). On W02, W04, W06, W08, and W10: [redacted] mg SC administration of SAR441344 or placebo. See Section 6.1 for details.

h In visits where physical examinations are not scheduled, physical examinations can still be performed if participants present with any symptoms.

i Should be performed more than once, but only on postmenopausal women, where amenorrhea is present for less than 12 months (see Appendix 4 [Section 10.4]).

j To be done for all female participants.

k QuantiFERON® tuberculosis Gold test and medical history.

l Fasting is preferred. Fasting/non-fasting status will be recorded at the time of blood collection for serum glucose assessment.

m Urine dipstick analysis performed locally at the site. If positive for a pathological finding and rated clinically significant by the Investigator, the urine sample will be sent to the central laboratory for a quantitative analysis.
n If the urine pregnancy test is positive, a blood pregnancy test needs to be analyzed by the central laboratory.
o Will be assessed by a local tolerability questionnaire as described in Section 8.2.5.
p On D1, [redacted]
q Will be rated according to Seror et al (2010 and 2015]) as described in Section 8.1.1. The ESSDAI should be rated by the same Investigator per participant throughout the study, if possible.
r Study inclusion will be based on the ESSDAI score during Screening (see Section 5.1 inclusion criterion I 04 and Section 8.1.1).
s Will be rated according to Seror et al (2011 and 2015) as described in Section 8.1.2.
t Topical medication, pharmacological stimulants, and NSAIDs need to be paused at least 12 hours prior to these assessments.
u This test can be performed during the Screening period or at Baseline. The same result will be used for inclusion and Baseline.
v See Section 8.1.4.
w See Section 8.1.5.
x [redacted]
y Optional.

[redacted] BL: Baseline, BUN: blood urea nitrogen,[redacted], D: Day, [redacted], ECG: electrocardiogram, EoT: End of Treatment, EoS: End of Study, EQ-5D-5L: EuroQoL questionnaire with 5 dimensions and 5 levels per dimension, ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index, ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index, EULAR: European League Against Rheumatism, FSH: follicle-stimulating hormone, HCG: human chorionic gonadotropin, Ig: immunoglobulin, IMP: investigational medicinal product, IV: intravenous, [redacted]A, NSAID: non-steroidal anti-inflammatory drug, [redacted], PK: pharmacokinetic(s), RF: rheumatoid factor, [redacted] SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; SC: subcutaneous, V: Visit, W: Week, WOCBP: women of childbearing potential.

2 INTRODUCTION

SAR441344 is a novel, potent CD40L inhibiting mAb that is being developed to treat several autoimmune diseases. The disruption of the CD40/CD40L pathway in autoimmune diseases, particularly those where pathogenic B-cell responses are a key hallmark of disease, would be predicted to impact both cellular and humoral responses and have therapeutic benefit, including SjS.

2.1 STUDY RATIONALE

The purpose of this proof of concept study is to obtain data on safety, tolerability, PK, and therapeutic efficacy for one dose level of SAR441344 in adult patients with pSjS.

SAR441344 is an antagonist mAb which binds to human CD40L. Binding of SAR441344 blocks interaction with CD40 expressed on the surface of antigen-presenting cells, such as B-cells, thus, disrupting the CD40/CD40L signaling pathway. Dysregulation of cellular and humoral immune responses has been clearly demonstrated as a key factor in many autoimmune disorders (1). CD40L is, therefore, identified as a target for treating a number of autoimmune diseases, including pSjS.

Although the pathophysiology of pSjS is not fully understood, it is documented that CD40/CD40L interaction and B-cell pathology play a major role (2). B-cell hyperactivity includes the production of autoantibodies like anti-Ro/SSA, anti-La/SSB, or rheumatoid factor (RF), as well as hypergammaglobulinemia and increased levels of free light chains. Autoimmune epithelitis, presented in exocrine glands (namely salivary and lacrimal glands) as part of pSjS, presents ectopic lymphoid structures (germinal-like centers) in histology. It is known that glandular epithelial cells show increased expression of CD40 (2, 3). Sjögren's syndrome patients show elevated soluble CD40L levels (4) and a recently published proof of concept study evaluating an anti-CD40 antibody (iscalimab) indicated signs of efficacy after a 12-week treatment period. Data suggest that the CD40/CD40L interaction plays a relevant role in pSjS pathomechanism and may have potential for disease modification (5).

In non-obese diabetic NOD/ShiLtJ mice (model of SjS), use of an anti-CD40L antibody after development of a SjS-like disease was able to inhibit ectopic lymphoid structure formation and autoantibody production (6). Considering these findings, targeting pSjS with SAR441344 can be justified. For this reason, the primary objective of this study is to evaluate the therapeutic efficacy of SAR441344 in adult patients with pSjS measured by the EULAR ESSDAI. Other objectives will include further assessment of efficacy by the EULAR ESSPRI, MFI, and gland function test. In addition, this study will assess the PK, PD, and safety, including antidrug antibodies, of SAR441344 in comparison with placebo.

2.2 BACKGROUND

2.2.1 Primary Sjögren's syndrome

Sjögren's syndrome is a chronic complex autoimmune disease primarily characterized by inflammation and progressive destruction of the exocrine glands (ie, autoimmune epithelitis). The main glands affected include the lacrimal and salivary glands, leading to dryness of mouth and eyes. The disease is often accompanied by severe pain and fatigue. These key manifestations are common in all phenotypes of the disease and are measured by the ESSPRI (7). However, a subset of patients (approximately 30%) develop, with variable severity, extra-glandular manifestations, including vasculitis, interstitial lung disease, kidney involvement, arthralgia, and central nervous system (CNS)/peripheral nervous system (PNS) involvement (3). These manifestations are measured by the ESSDAI (7, 8).

Thus, the spectrum of SjS can vary from a benign slowly progressive exocrinopathy to a heterogeneous potentially life-threatening systemic disorder, also characterized by an increased risk of non-Hodgkin's lymphoma (approximately 5% of the patients), based on the increased B-cell activity found in the disease. Primary SjS is the second prevalent systemic autoimmune disorder after rheumatoid arthritis and is predominant in women in a 9:1 ratio (female:male) (3, 9).

Apart from topical treatments for salivary and lacrimal glands, no treatment is approved for pSjS, revealing a significant unmet medical need.

2.2.2 SAR441344

SAR441344 is derived from the humanized mAb IDEC-131, with 2 major modifications: 1) affinity maturation of the variable region, and 2) mutations in the Fc region to inhibit binding to the FcγRIIa receptor. Similar to the first-generation IDEC-131, SAR441344 binds to CD40L and prevents binding to and signaling via CD40. Additional information on SAR441344 may be found in the Investigator's Brochure (IB). CD40L is a member of the tumor necrosis factor alpha superfamily. It is transiently expressed on the surface of cells and platelets as a homotrimer and may be released in a biologically active form into circulation (10). CD40L is expressed on a variety of cell types including T helper (Th) cells, platelets, endothelial cells, smooth muscle cells, macrophages, and antigen presenting cells.

Through its interactions with CD40, CD40L is best known for its role as an immunologic second signal expressed on Th cells and is required for B-cell activation/maturation and dendritic cell maturation (11). CD40L loss of function is associated with the development of hyper-immunoglobulin (Ig) M syndrome and is characterized by inhibition of B-cell maturation, loss of germinal center formation, absence of isotype switching, affinity maturation, somatic hypermutation, and inability to form long lived plasma cells and memory B-cells (12). In addition to its role in B-cell maturation, CD40L is thought to enhance macrophage effector function and aid in the development of CD8+ memory T-cells. Disruption of the CD40/CD40L pathway in autoimmune diseases, particularly those where pathogenic B-cell responses are a key hallmark of disease, would be predicted to impact both cellular and humoral responses and have therapeutic benefit.

Consistent with CD40L's role as a necessary second signal for B-cell maturation, isotype-switched Ig production, somatic hypermutation, germinal center formation, formation of long-lived plasma, and memory cells, anti-CD40L antibody therapies are known to be potent inhibitors of TDAR. While TDAR is often used to evaluate immunosuppression or immunomodulation, TDAR inhibition with anti-CD40L represents a downstream PD effect of anti-CD40L therapy. To evaluate the IMP effect on TDAR, keyhole limpet hemocyanin (KLH) immunization was used to characterize TDAR by inhibition of anti-KLH IgG production in the first in human (FIH) studies (see Section 2.2.2.2).

Given the critical role of CD40L in the adaptive immune response, anti-CD40L therapies have been developed for the treatment of diseases such as immune thrombocytopenia purpura, multiple sclerosis, and systemic lupus erythematosus with some early signs of efficacy. Unfortunately, first-generation anti-CD40L therapies were associated with increased thromboembolic events in human studies and ultimately resulted in the discontinuation of their development (The term thromboembolic event or thromboembolism is used in this document to denote any arterial or venous thrombotic or embolic events). Elevated thromboembolic risk seen with first-generation anti-CD40L mAb therapies resulted from platelet activation triggered by FcγRIIa activation by higher order immune complexes containing both the anti-CD40L mAb and CD40L (membrane or soluble) which is expressed by platelets (13, 14).

Understanding Fc-mediated thromboembolic risk resulted in the engineering of second-generation anti-CD40L therapies that either did not contain an Fc or contained a modified Fc with low FcγRIIa binding, with the goal of eliminating thromboembolic risk. SAR441344 has a modified Fc region. There are at least 3 second-generation anti-CD40L mAb in clinical studies treating patients: dapirolizumab, VIB4920 (MEDI4920), and BMS-986004 (15, 16, 17). Based on trial disclosures in clinicaltrials.gov, over 400 participants have been dosed with a second-generation anti-CD40L therapy, and to the Sponsor's knowledge, no thromboembolic events have been observed in the published data as of the date of the protocol. In the first in human study with SAR441344 ([redacted] and [redacted], see Section 2.2.2.2), no thromboembolic event has occurred to the date of the protocol after treatment with SAR441344.

2.2.2.1 Preclinical data

The potential for SAR441344 to induce thromboembolic events was evaluated using an in vitro platelet activation assay and platelet rich plasma from healthy subjects, multiple sclerosis and systemic lupus erythematosus patients. The in vitro platelet activation assays demonstrated that SAR441344 in combination with recombinant human soluble CD40L (rhsCD40L) does not increase platelet activation as measured by CD62P expression as compared with first-generation anti-CD40L antibodies combined with rhsCD40L. SAR441344 effects on platelets were similar to that of the IgG1 negative control. Details on the extensive preclinical evaluation on the thromboembolic risk are described in the IB.

In summary, SAR441344 nonclinical data demonstrated that thromboembolism is not an identified hazard of the SAR441344 toxicology profile. The SAR441344 toxicology profile is consistent with its pharmacology and includes decreased cellularity in germinal centers, moderate decrease in B-cells and decreased TDAR to KLH antigen. Effects on immune system and

potential opportunistic infections are expected hazards of SAR441344. These effects on the immune system are monitorable and expected to resolve after antibody discontinuation. Antidrug antibody (ADA) formation was observed at lower doses in SAR441344 toxicology studies, but the mechanism of action of SAR441344 is expected to reduce the impact of ADA formation at higher doses. The 6-month Good Laboratory Practice (GLP) toxicity study no observed adverse effect level (NOAEL) was [redacted] mg/kg/week IV, with a Day 169 area under the curve (AUC) from hour 0 to 168 hours (AUC_{0-168}) of [redacted] µg × h/mL in cynomolgus monkeys. The maximum concentration (C_{max}) achieved was [redacted] µg/mL. For details on the non-GLP and GLP toxicity studies performed within the preclinical assessment of SAR441344, please refer to the IB.

[redacted] Details, including further nonclinical PD and PK studies, are described in the IB.

2.2.2.2 Clinical data

[redacted]

[redacted] is a completed Phase 1, double-blind, randomized, parallel design, placebo-controlled single ascending dose study to evaluate the safety, tolerability, PK, and PD of IV doses of SAR441344 in healthy adult subjects. Five sequential ascending single doses of matching SAR441344 ([redacted] mg) or matching placebo were diluted to a final volume of approximately 100 mL in 0.9% normal saline and administered on Day 1 by IV infusion over approximately 1 hour. All participants were immunized with a [redacted] (Day [redacted]). A total of 40 healthy adult subjects, including 22 (55.0%) males and 18 (45.0%) females were treated. Each cohort had 8 subjects, 6 receiving SAR441344 and 2 receiving placebo.

Overall, a single IV dose of SAR441344 between [redacted] to [redacted] mg administered in healthy male and female adult subjects was safe and well tolerated. There were no serious or severe TEAEs. No trends in vital signs, ECGs, or laboratory values were identified, including assays meant to identify potential increased thromboembolic or infectious risks.

The time to C_{max} (t_{max}) for SAR441344 was observed between 1 hour (end of infusion) to 2 hours postdose. SAR441344 exposure increased with no deviation from dose proportionality from [redacted] to [redacted] mg. The mean terminal half-lives ($t_{1/2z}$) ranged from [redacted] days over the dose range.

[redacted]

[redacted] is a completed Phase 1, double-blind, randomized, placebo-controlled multiple ascending dose study investigating 5 dose levels of SAR441344 ([redacted] and [redacted] mg) or placebo controls. Each cohort received 3 repeated [redacted] administrations of SAR441344 2 weeks apart (Days [redacted] and [redacted]). Each of the 5 dose cohorts were planned to contain 2 subjects who would receive placebo and 8 subjects who would receive SAR441344, and all subjects were to receive [redacted] on Day [redacted] and Day [redacted].

Overall, 5 dose levels of SAR441344 between [redacted] mg administered SC as 3 doses q2w in healthy male and female adult subjects appeared safe and well tolerated. There were no serious or severe TEAEs. Three subjects discontinued treatment secondary to adverse events (AEs) of elevated transaminases (leading to an AESI, judged to be unrelated to the study drug treatment by the Investigator), a presyncope in the setting of hypotension (classified as unrelated to study drug), and pityriasis rosea (placebo group). No concerning trends in vital signs, ECGs or laboratory values were identified, including assays meant to identify a potential for increased risk for thromboembolism or infection. The t_{max} for SAR441344 was observed between [redacted] days postdose after Day [redacted] dosing and between [redacted] days after Day [redacted] dosing. [redacted] SAR441344 exposure increased with no deviation from dose proportionality from [redacted] mg. The mean $t_{1/2z}$ ranged from [redacted] days over the dose range. The [redacted] induced a strong TDAR [redacted] in placebo subjects. SAR441344 treatment caused a dose-dependent inhibition of the TDAR, with partial inhibition in the [redacted] mg and [redacted] mg cohorts ([redacted] respectively), and [redacted] in the [redacted] mg, [redacted] mg, and [redacted] mg dose cohorts. The extent of inhibition at steady state would be anticipated to be more extensive than the values observed in the [redacted] study after 3 administrations.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Based on the review of the cumulative data for SAR441344, there are no important identified risks for SAR441344.

Important potential risks include:

- Thromboembolic events.
- Infections, including opportunistic infections.
- Immunogenicity/hypersensitivity.
- Injection site reactions/local tolerability at injection site.

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

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Thromboembolic events	The first-generation anti-CD40L therapies were associated with an increased risk of thromboembolic events. The SAR441344 nonclinical package did not identify thromboembolism as a hazard. No events have been publicly reported with other second-generation anti-CD40L therapies in clinical studies. Platelet count and D-dimer were monitored throughout the FIH Study [redacted] and while transient abnormal values were occasionally noted, there were no clinically significant sustained changes from baseline.	Risk assessment: • Regular monitoring of platelet counts and AEs which may suggest possible thromboembolic events. • Confirmed thromboembolic event to be reported as AESI. Risk Minimization: • Removal or modification of the Fc region is believed to have addressed the thromboembolic risk as indicated by second-generation therapies showing no elevated risk in nonclinical models or clinical studies (see Section 2.2). • Exclusion of participants with any history of thromboembolic events, as well as myocardial infarction, stroke, antiphospholipid syndrome, and/or participants requiring antithrombotic treatment.
Infection including opportunistic infections	SAR441344 inhibits CD40/CD40L interactions which plays a key role in the adaptive immune response, particularly humoral immunity. Based on the findings of the 13-week GLP toxicology study and knowledge of the CD40L loss of function phenotype in humans, inhibition of CD40L may increase the risk of upper and lower respiratory infections and gastrointestinal infections as well as opportunistic infections. In the 13-week GLP toxicology study, a moderate decrease in B-cells was noted, without a significant decrease in cell numbers and recovered after a 10-week recovery period. In the 6-month GLP toxicology study without a recovery period dose-independent slight to moderate decreases in absolute counts of B-lymphocytes were observed with statistical significance for all SAR441344 treated groups. Treatment with anti-CD40L therapies is associated with modest reductions in IgG in clinical studies. Both were not detected in the FIH study so far. Risk assessment and mitigation strategy for SARS-CoV-2 is detailed in Section 2.3.1.1.	Risk assessment: • AE reporting. Severe infections, including opportunistic infections, are considered AESI. • Baseline detection and exclusion of TB, HIV, hepatitis tests, to be repeated in case of suspicion. Risk minimization: • Exclusion of participants with active or latent tuberculosis with TB test, HIV infection, chronic viral hepatitis or other known opportunistic infection, history of severe parasitic infections, as well as active infections or chronic ongoing infections of any course. • No live vaccines/live components; vaccine policy.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Immunogenicity/hypersensitivity	Due to its mechanism of action, SAR441344 may reduce the risk of ADA formation in humans. Nevertheless, ADA may result in alterations in SAR441344 exposure and in extreme cases could result in a Type III hypersensitivity reaction. In total, only 4 subjects developed ADA [redacted]	Risk assessment: • ADA detection during the study through 4 half-lives. • Hypersensitivity reactions will be systematically monitored (eg, chills, rash, urticaria, hypotension). • Anaphylactic reaction/acute allergic as well as infusion related reaction to be reported as an AESI. Risk minimization: • IV administration of 1 hour minimum with a monitoring period of 3 hours at the study site afterwards. • Symptomatic treatment of any immunogenicity related AEs. • ADA will be checked if there is a safety concern.
Injection site reaction/local tolerability at injection site	IV administration in study [redacted] has been well tolerated up to [redacted] mg IV, there was 1 subject reported to experience an infusion site reaction. Subcutaneous administration in [redacted] up to [redacted] mL was overall well tolerated, with 3 SAR441344-treated subjects showing mild injection site reactions.	Risk assessment: • Thorough medical examination of the injection sites and implementation of assessment scale. • Severe injection and infusion site reaction will be reported as AESI. Risk minimization: • Loading dose will be administered IV to avoid large volume SC injection. • Monitoring of the injection site after IMP injection.
Study intervention: SAR441344	**Loading dose [redacted] mg IV or matching placebo Day 1** **5 doses of [redacted] mg SC or matching placebo q2w**	

ADA: antidrug antibody, AE: adverse event, AESI adverse event of special interest, CD40: cluster of differentiation 40, CD40L: cluster of differentiation 40 ligand, EOS: end of study, FIH: first in human, GLP: Good Laboratory Practice, HIV: human immunodeficiency virus, Ig: immunoglobulin, IMP: investigational medicinal product, IV: intravenous, q2w: once every 2 weeks, SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; SC: subcutaneous, TB: tuberculosis.

2.3.1.1 Risk assessment and mitigation in the context of SARS-CoV-2

2.3.1.1.1 Risk assessment

A potential risk for infections is already described for SAR441344. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a pandemic, with uncertainties regarding the epidemiology, clinical course and immunity remaining. The relevance of immunosuppression for the entire course of the disease is currently unclear but could a present a potential risk.

Assessment of the infectious risk of other anti-CD40L or CD40L compounds, which were or are in clinical development, is limited to information from early clinical trials with small sample sizes before the coronavirus infectious disease due to SARS-CoV-2 (COVID-19) pandemic. Overall,

these data showed only a slight increase of upper respiratory tract infections but did not reveal significant increased infection rates.

Although CD40L/CD40 interaction is important for B-cell differentiation, there is, based on preclinical and clinical data from the FIH study, currently no evidence that SAR441344 is B-cell depleting: a slight decrease of B-cells was noted in the 13-week GLP toxicology study, which was reversible in the recovery period. The same was seen in 6-month GLP study, which was run without a recovery period (GLP studies described in Section 2.2.2.1). Throughout the FIH, no decrease in B-cells was recorded. Therefore, the comparison with B-cell depleting drugs, such as rituximab and ocrelizumab, in terms of infectious risk is limited. However, it is important to note that although viral infections and infections of the respiratory tract are noted as very common during treatment with these compounds, severe infections remain limited.

Although the role of CD40L in immune response in general is well established, there are no detailed data available on the specific role of CD40L in the course of a SARS-CoV-2 infection/COVID-19. Currently, there is no evidence that CD40L is relevant for the viral infection with SARS-CoV-2. There is evidence that the development of viral clearance and a potential protective immunity follow the generation of an adaptive immune response, including the production of neutralizing antibodies, in which the CD40/CD40L interaction plays a key role (18, 19, 20, 21, 22, 23). Therefore, blocking CD40L may prevent antibody formation and immune response in case of an acute SARS-CoV-2 infection and may prevent long-term immunity.

Taking into account the potential risk of increased infection rates based on the mode of action of SAR441344 and knowledge of similar and related compounds, and the potential role of CD40L for adaptive immune response to a SARS-CoV-2 infection, an increased risk for study participants in the situation of the COVID-19 pandemic may be assumed, hence appropriate risk mitigation is implemented.

2.3.1.1.2 Risk mitigation

One potential risk of SAR441344 is increased rate of infections. In times of an ongoing pandemic, this risk is additionally increased. Therefore risk mitigation actions have been established to address the risk of infection for participants included in this clinical trial.

To stop spreading the SARS-CoV-2 distribution and to reduce the risk of infection, clear protective measures are described by global health agencies such as the World Health Organization (24), but also on national/local level. Study sites should ensure that before the study start and throughout the study local guidance is applied to the conduct of the study on the site level.

Stopping rules were implemented to provide guidance for Investigators:

- In case of suspicion of COVID-19 (eg, fever, cough, shortness of breath in a context of possible infected contact), temporary discontinuation of the IMP will be considered by the Investigator in accordance with Section 7.1.2, considering the following to evaluate individual benefit-risk of continuation or stop of IMP: the probability of COVID-19 disease, possibility of rapid diagnosis, severity of symptoms, and risk factors.

- In the case of biologically proven COVID-19 infection, the Investigator may permanently discontinue the IMP for the participant, who will be asked to continue attending the protocol scheduled visits until the EOS. If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation if the patient does not have severe or critical COVID-19 infection as defined per WHO guidelines (25). The participant must temporarily discontinue IMP until the participant's COVID-19 PCR is negative. A discontinuation of more than 30 days will be considered as permanent discontinuation. All COVID-19 infections will be reviewed by the DMC as AESI.
- In case of investigational site closure or complete regional or national lock-down due to a local epidemic or international pandemic, the study may be suspended completely or on selected sites or regions by the Sponsor. Every effort will be kept to continue the follow-up of already recruited patients as close to the Schedule of Activities (SoA) as possible (Section 10.1.9).

Temporary treatment discontinuations and adaptions of the follow-up period may be considered in exceptional cases as described in Section 7.1.2.

Participants will be contacted before each visit by an Investigator or designee, to evaluate for signs and symptoms of a potential SARS-CoV-2 infection. In case of suspicion of such infection, the participant will be asked to not come to the study site and will be referred to a testing facility or her/his primary care physician according to local regulations. If the suspicion of a SARS-CoV-2 infection is excluded and there is no other reason to pause treatment due to the Investigator judgment, the treatment can continue. If the suspicion of a SARS-CoV-2 infection is confirmed, treatment should be paused.

Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs in adults with underlying medical comorbidities including: chronic lung disease, cardiovascular disease, diabetes mellitus, hypertension, obesity, and cancer (26, 27, 28, 29, 30, 31, 32). High risk populations for COVID-19 are excluded due to the general selection of study participants for this proof-of-concept study, according to the inclusion/exclusion criteria I 08, E 04, E 05, E 09, and E 13 (Section 5.1 and Section 5.2). This also includes significantly immunocompromised participants, already excluded by E 06, E 07, E 09, and E 18 (Section 5.2).

In addition to this, patients who live in long-term care facilities and nursing homes will be excluded from study participation as they have a high risk of SARS-CoV-2 infections (33).

According to exclusion criteria E 06 and E 09 (Section 5.2), it is expected, that participants with acute infection or having a high risk for an asymptomatic SARS-CoV-2 infection (eg, living with a person that is currently infected) are not included in the study.

Taking into account this risk, the potential risk of an increased infectious risk due to lymphopenia, and potential relevance in SARS-CoV-2 infections (34), patients with a severe lymphopenia will be excluded from this study (see exclusion criterion E 22 in Section 5.2). There is even more evidence on the role of neutropenia and infectious risk within pSjS in a longitudinal follow-up of a cohort of 300 pSjS patients over 18 years: 30% showed idiopathic neutropenia and those

patients had a higher incidence of hospital admission caused by infection (35). Therefore, patients with a neutropenia will be excluded from study participation (see exclusion criterion E 22 in Section 5.2).

An extensive risk assessment on the COVID-19 pandemic has been performed. This led to a risk mitigation plan including stopping rules, which take into account the current knowledge and also potential uncertainties, including plans for lock-down situations. A participant selection that considers the risk population of COVID-19 is in place for the study. This should address and reduce the risk for participants included in this study.

2.3.2 Benefit assessment

Primary SjS comes with a high unmet medical need, as there is no approved drug for systemic treatment. This applies in particular to patients feasible for inclusion in this study (ie, ESSDAI ≥5, which implies a systemic manifestation of SjS and is associated with significant impact on wellbeing and quality of life).

Pharmacodynamic data from the [redacted] study provide a proof-of-mechanism showing a significant suppression of TDAR to KLH measured by levels of [redacted] after the administration of [redacted] in healthy subjects treated with SAR441344 or placebo, which supports the potential of clinical efficacy. Transferability of successful TDAR suppression into clinical efficacy was seen with other second-generation CD40L compounds (eg, MEDI/VIB4920 [17]).

2.3.3 Overall benefit: risk conclusion

SAR441344 was investigated in two Phase 1 first in human studies, [redacted] (single ascending dose) and [redacted] (multiple ascending dose), to assess the safety, tolerability, PK, and PD of IV and SC doses. In combination with PK, safety, and tolerability data, PD data also aided in the selection of a safe and efficacious dose for this Phase 2 study.

No safety or tolerability concerns have been identified in the Phase 1 first in human studies. In addition, results indicate that SAR441344 treatment with [redacted] mg (3 doses of [redacted] mg SC, each 2 weeks apart) leads [redacted] in healthy subjects, which supports the potential for clinical efficacy.

As there is no approved medication for systemic treatment of pSjS, the disease comes with a high unmet medical need. A treatment with SAR441344 and therefore interruption of the CD40/CD40L interaction provides a clear rationale based on what is known on the pathophysiology of pSjS (Section 2.2.1). An antibody against CD40 (iscalimab) recently showed promising results on clinical outcome markers in a 12-week pSjS proof of concept study, indicating that inhibition of the CD40/CD40L could be beneficial in pSjS (5).

To date, there is no identified risk and the important potential risks associated with SAR441344 are well defined, and appropriate risk mitigation strategies, including those for COVID-19, are in place. Therefore, the overall benefit-risk balance is favorable for further clinical development of SAR441344 in pSjS.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with primary Sjögren's syndrome (pSjS), assessed by the change of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI).	• Change in ESSDAI from Baseline to Week 12.
Secondary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI).	• Change in ESSPRI from Baseline to Week 12.
• To evaluate the therapeutic efficacy on fatigue of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the Multidimensional Fatigue Inventory (MFI).	• Change in MFI general fatigue subscale and other subscales from Baseline to Week 12.
• To evaluate the pharmacokinetic (PK) exposure of one dose level of SAR441344 over 12 weeks in adult patients with pSjS.	• Descriptive statistics of SAR441344 concentrations, including mean, median, and standard deviation. • Pharmacokinetic parameters for SAR441344 will be reported (maximum concentration [C_{max}], time to Cmax [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and terminal half-life [$t_{1/2z}$]).
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo in adult patients with pSjS as determined by adverse events (AEs).	• Incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs) from Baseline to Week 24 (End of Study [EoS]). • Incidence of study investigational medicinal product discontinuation and withdrawals due to TEAEs from Baseline to Week 24 (EoS).
• To evaluate the local tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Change in participant reported local tolerability scale. • Incidence of AEs related to local tolerability findings.
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS determined by electrocardiogram, vital signs, and laboratory evaluations.	• Participants with medically significant changes in vital signs, electrocardiogram, and/or laboratory evaluations.
• To measure the immunogenicity of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Antidrug antibodies at Baseline, Week 4, Week 8, Week 12, and Week 24.

Objectives	Endpoints
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

The ESSDAI, used for the primary endpoint, is a validated and established outcome measurement for therapeutic efficacy in SjS, evaluating disease activity mainly on extra-glandular manifestations (7, 36). It is used in clinical trials as a standard outcome measurement for efficacy, especially in similar trials using a 12-week treatment period (eg, iscalimab [5]). The ESSPRI, used as a key secondary endpoint for the measurement of therapeutic efficacy, is used as a validated and established efficacy marker in clinical trials, as well (7, 37). Another key secondary endpoint is the change in MFI rating as fatigue is one of the key symptoms of SjS, impacting the quality of life of patients significantly (38).

In terms of safety, the TEAEs, SAEs, AESIs, ECG, vital signs, and laboratory analyses will be recorded, and local tolerability will be examined. SAR441344 will be administered SC after an initial IV loading dose. Measurement of local tolerability will be done with a verbal descriptor scale (VDS) and Investigator rating, described in Section 8.2.5. Antidrug antibodies will be measured as well, although the mechanism of action of SAR441344 (prevention of CD40/CD40L interaction) is expected to decrease the risk of ADA formation (see Section 2.2.2).

4 STUDY DESIGN

4.1 OVERALL DESIGN

ACT16618 is a multicenter, randomized, double-blind, placebo-controlled, parallel group proof of concept Phase 2 study to assess the safety, tolerability, PK, and therapeutic efficacy of SAR441344 in pSjS. Participants included are diagnosed with pSjS according to the American College of Rheumatology/EULAR 2016 criteria with systemic disease (ESSDAI score ≥5) and significant biological activity. Participants will be randomized at Baseline (Day 1) to SAR441344 or placebo in a 1:1 ratio and will receive a single IV loading dose on Day 1, followed by 5 SC doses administered q2w. Randomization will be stratified by Baseline ESSPRI score ≥5 versus <5.

The safety data of this study will be reviewed by an independent DMC.

The total duration of the study will be 24 weeks (28 weeks including maximum screening duration) for each participant:

- Screening up to 30 days (Day -30 to Day -1).
- Treatment period of 12 weeks (Day 1 to Week 12).
- Follow-up period of 12 weeks (Week 12 to Week 24).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Participant population will be selected based on ESSDAI, as well as elevated markers of chronic B-cell activation, ensuring that participants will have a systemic manifestation of the disease. A stratification based on ESSPRI (score ≥5 versus <5) ensures that participants are impacted in different degrees on the key features of the disease along all phenotypes: fatigue, dryness, and pain as along with high biological activity. This will target a population with high medical need and better likelihood of clinical efficacy in a 12-week study.

The study is placebo-controlled as there is no approved systemic treatment for pSjS that could be used as an active comparator. Background therapy with low doses of steroids and/or hydroxychloroquine or chloroquine will be allowed (Section 6.5.2).

The primary objective is to compare the efficacy of SAR441344 with placebo measured by ESSDAI scoring, which is the activity index to measure the involvement of different organs in pSjS. Other measurements for therapeutic efficacy include ESSPRI and MFI, which will evaluate key features of the disease: dryness, pain, and fatigue.

Treatment duration will be 12 weeks, which should be sufficient to see a significant improvement in clinical efficacy and reach the proof-of-concept for SAR441344, based on the selection of

participants, and due to what is known from other companies working on the CD40/CD40L interaction in pSjS (eg, iscalimab, an anti-CD40 antibody [5, 39]).

A Screening period is planned for up to 30 days, to ensure that all laboratory and score results are evaluated for Baseline. The follow-up period will have a duration of 12 weeks (up to Week 24), to ensure an approximate 4-half-life period surveillance after the last drug administration (on Week 10).

One optional sub-study is planned:

[redacted] (Section 1.3).

These samples will be used for research purposes related to inflammation and immunity in the context of CD40L-targeted treatment. In addition, research may be performed to help understand disease subtypes and drug response, to develop and validate bioassay methods, or to identify new drug targets or biomarkers.

4.2.1 Participant input into design

Participants were involved in the design of the study as a patient panel review of the abbreviated protocol has taken place. There was general agreement with the study design. Feedback of the patient panel was taken into account for the design of the visits, learning about the burden of certain assessments, and concomitant therapy.

4.3 JUSTIFICATION FOR DOSE

A loading dose of [redacted] mg IV or matching placebo is planned on Day 1. Afterwards, IMP administration will be continued with [redacted] mg SC or matching placebo q2w for 5 doses. The last IMP administration will take place on Week 10.

SAR441344 was safe and well tolerated at single IV doses up to [redacted] mg and at multiple doses SC (3 × q2w) up to [redacted] mg in healthy subjects. Of note, a maximal tolerated dose has not been reached in either of these clinical studies (see Section 2.2.2.2).

In the multiple ascending dose study in healthy subjects [redacted], SAR441344 inhibited KLH-TDAR in a dose dependent manner after SC 3 × q2w and the sequential administration of [redacted] (Day [redacted] and Day [redacted]). A dose of [redacted] mg SC 3 × q2w in healthy subjects [redacted] Hence, high probability of clinical efficacy for this dose is expected. During the [redacted] study, no ADAs were detected in the dose level of [redacted] mg SC 3 × q2w. A dose of [redacted] mg q2w SC will be given with a [redacted] mL syringe injection throughout this study.

The rationale of choosing a loading dose is that steady state is predicted to be reached only after 12 weeks of q2w dosing. An IV loading dose of double the SC maintenance dose on Day 1 would assure that plasma concentration close to steady state would be reached after the second administration.

Finally, predicted exposure for a [redacted] mg dose administered q2w for 12 weeks (predicted AUC over the dosing interval [$AUC_{0\text{-}tau}$]: [redacted] µg × h/mL) gives an acceptable safety margin of [redacted]. The predicted C_{max} after the IV loading dose [redacted] mg is [redacted] µg/mL, which is [redacted] than the C_{max} at NOAEL (for the definition of NOAEL, see Section 2.2.2.1).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (EoS visit).

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

I 01. Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Diagnosis of pSjS according to the American College of Rheumatology/EULAR 2016 criteria (40) with a score of ≥4 at Screening. For the following criteria, historical data can be used:

- Labial salivary gland with lymphocytic sialadenitis and focus sore of ≥1 foci/4 mm^2,
- Ocular staining score ≥5 (or van Bijsterveld score ≥4) in at least 1 eye,
- Schirmer test ≤5 mm/5 minutes in at least 1 eye,
- Unstimulated whole saliva flow rate ≤0.1 mL/min.

I 03. Disease duration since first diagnosis of pSjS ≤ 15 years based on medical history.

I 04. Participants with moderate to severe disease activity set with ESSDAI total score ≥5, based on the following domains at Screening: glandular, articular, muscular, hematological, biological, and constitutional, lymphadenopathy.

I 05. Seropositive for anti-Ro/SSA antibodies.

I 06. IgG > lower limit of normal at Screening.

I 07. Stimulated salivary flow rate of ≥0.1 mL/min at Screening or Baseline.

Weight

I 08. Body weight within 45 to 120 kg (inclusive) and body mass index within the range of 18.0 to 35.0 kg/m^2 (inclusive) at Screening.

Sex

I 09. Male or female.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants must follow the guidance for contraceptive use:

- Male participants, whose partners are of childbearing potential (including lactating women), must accept to use, during sexual intercourse, a double contraception method according to the following algorithm: eg, condom plus intra-uterine device from the inclusion until completion of EoS visit (see contraceptive guidance in Appendix 4 [Section 10.4]). Condom with spermicide may be used as a valid double contraception method for this study.
- Male participants, whose partners are pregnant, must use, during sexual intercourse, a condom from inclusion until completion of the EoS visit (see contraceptive guidance in Appendix 4 [Section 10.4]).
- Male participants have agreed not to donate sperm from inclusion in the study up to 6 months after the last dose. (see contraceptive guidance in Appendix 4 [Section 10.4]).

b) A female participant is eligible to participate if she is not pregnant or breast-feeding, and follows the following guidance for contraceptive use:

- Female participant must use a double contraception method including one highly effective method of birth control (as defined in Appendix 4 [Section 10.4]), except if she has undergone sterilization at least 6 months earlier or is postmenopausal. Menopause is defined as being amenorrheic for at least 12 months or, in the absence of 12 months of amenorrhea, a plasma follicle-stimulating hormone (FSH) level >ULN as defined by central laboratory readout (more than 1 measurement, see contraceptive guidance in Appendix 4 [Section 10.4]). Contraception as described is required from signing of the informed consent until completion of the EoS visit. Use of hormonal contraception is permitted in this study.

Informed Consent

I 10. Having signed a written informed consent prior to any procedure related to the study.

I 11. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Any autoimmune disease (except pSjS and Hashimoto thyroiditis) with or without secondary SjS.

E 02. History, clinical evidence, suspicion or significant risk for thromboembolic events, as well as myocardial infarction, stroke, and/or antiphospholipid syndrome and any participants requiring antithrombotic treatment.

E 03. Active life-threatening or organ-threatening complications of SjS disease at the time of Screening based on treating physician evaluation including but not restricted to:

- Vasculitis with renal, digestive, cardiac, pulmonary, or CNS involvement characterized as severe,
- Active CNS or PNS involvement requiring high dose steroids,
- Severe renal involvement defined by objective measures,
- Lymphoma.

E 04. Cardiac heart failure stage III or IV according to the New York Heart Association.

E 05. Severe pulmonary impairment documented by an abnormal pulmonary function test: diffusing capacity for carbon monoxide (DL_{CO}) <40% of predicted or forced vital capacity (FCV) <60% of predicted within the last 6 months before Screening.

E 06. Serious systemic viral, bacterial or fungal infection (eg, pneumonia, pyelonephritis), infection requiring hospitalization or IV antibiotics or significant chronic viral (including history of recurrent or active herpes zoster), bacterial, or fungal infection (eg, osteomyelitis) 30 days before and during Screening.

E 07. Participants with a history of invasive opportunistic infections, such as, but not limited to histoplasmosis, listeriosis, coccidioidomycosis, candidiasis, pneumocystis jirovecii, and aspergillosis, regardless of resolution.

E 08. Evidence of active or latent tuberculosis (TB) as documented by medical history (eg, chest X-rays) and examination, and TB testing: A positive or 2 indeterminate QuantiFERON®-TB Gold tests at Screening (regardless of prior treatment status).

E 09. Evidence of any clinically significant, severe or unstable, acute or chronically progressive, uncontrolled infection or medical condition (eg, cerebral, cardiac, pulmonary, renal, hepatic, gastrointestinal, neurologic, or any known immune deficiency) or previous, active or pending surgical disorder, or any condition that may affect participant safety in the judgment of the Investigator (including vaccinations which are not updated based on local regulation).

E 10. History or presence of diseases which exclude diagnosis of SjS as per the American College of Rheumatology/EULAR 2016 criteria (40) including, but not limited to, sarcoidosis, amyloidosis, graft-versus-host disease, IgG4-related disease, and history of head and neck radiation treatment.

E 11. History of a systemic hypersensitivity reaction or significant allergies, other than localized injection site reaction, to any humanized mAb.

E 12. Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

E 13. Any prior history of malignancy or active malignancy, including lymphoproliferative diseases and lymphoma (except successfully treated carcinoma in situ of the cervix, nonmetastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to Baseline.

E 14. Substance abuse (including cannabis) and/or alcohol abuse, current or in the last year.

Prior/concomitant therapy

E 15. Unstable dose of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or unstable use of topical and/or pharmacological stimulant treatment for salivary and lacrimal glands 4 weeks before Screening.

E 16. High-dose steroids (>10 mg/day prednisone equivalent), or a change in steroid dose within 4 weeks prior to Day 1/Randomization or expected changes during the course of the study.

E 17. High dose of hydroxychloroquine or chloroquine [redacted], or methotrexate [redacted] or change in hydroxychloroquine, chloroquine, or methotrexate dose within 12 weeks prior to Day 1/Randomization or expected changes during the course of the study.

E 18. Participants treated with the following medications/procedures prior to Screening within the given timeframe:

- Previous treatment with azathioprine and other thiopurines, mycophenolate mofetil, sulfasalazine, or cyclosporine A within 3 months.
- Previous treatment with cyclophosphamide, leflunomide, or belimumab within 6 months.
- Previous treatment with rituximab within 12 months.
- Previous bone marrow transplantation, total lymphoid irradiation or ablative ultra high-dose cyclophosphamide or IV Ig.
- Previous treatment with any other biologic drug within 5 times the half-life of the drug.

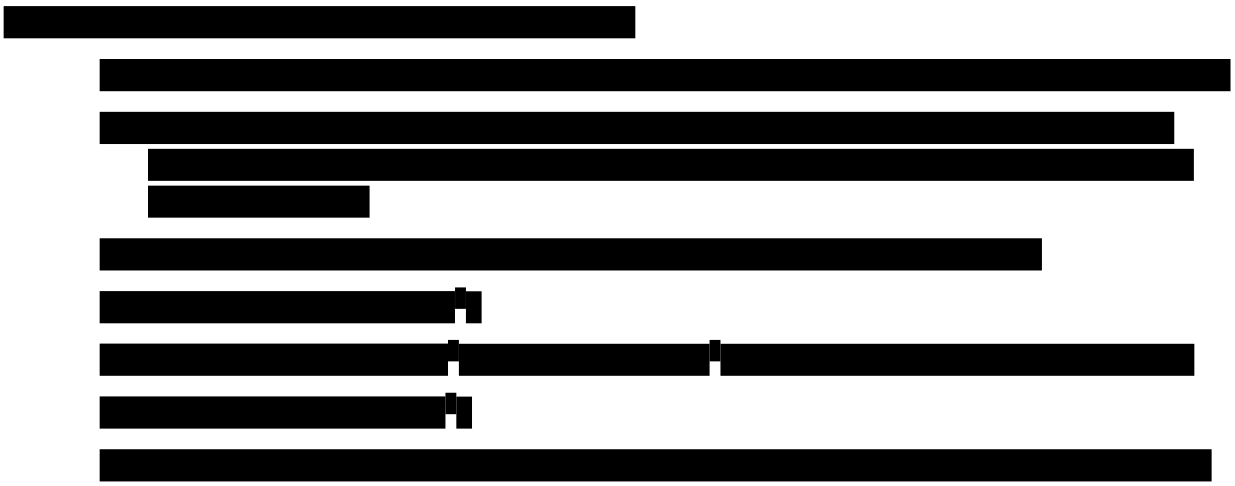
E 19. Received administration of any live (attenuated) vaccine within 3 months prior to Day 1/Randomization (eg, varicella zoster vaccine, oral polio, rabies).

Prior/concurrent clinical study experience

E 20. Treatment with any investigational drug within 1 month of Screening and/or within 5 half-lives or longer if required by local regulations (whichever is longer).

Diagnostic assessments

E 21. Clinically significant abnormal ECG or vital signs at Screening that may affect the conduct of the study in the judgment of the Investigator.



E 23. Positive human immunodeficiency virus (HIV) serology (anti-HIV1 and anti-HIV2 antibodies) or a known history of HIV infection, active or in remission.

E 24. Positive result on any of the following tests: hepatitis B surface antigen (HBsAg), anti-hepatitis B core antibodies (anti-HBc Ab), anti-hepatitis C virus antibodies (HCV-Ab).

E 25. If female, pregnant (defined as positive β-human chorionic gonadotropin [HCG] blood test) and/or breastfeeding.

Other exclusions

E 26. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 27. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 28. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation-Good Clinical Practice Ordinance E6).

E 29. Individuals residing in long-term care facilities or nursing homes.

E 30. Hypersensitivity to any of the IMPs, including any constituent thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No specific dietary restrictions are applicable throughout the study. Fasting is preferred in those visits where clinical chemistry (laboratory) will be assessed, as per the SoA (Section 1.3). Fasting is defined as no food/no drinks beside water without any supplements for at least 10 hours. This includes concomitant medication, which should be taken on site after blood drawn, to keep fasting conditions. Fasting/non-fasting status will be recorded at the time of blood collection.

5.3.2 Caffeine, alcohol, and tobacco

During the study, it is recommended that participants should try to abstain from drinking alcohol and using tobacco products as much as possible. No recommendations or restrictions apply regarding caffeine.

5.3.3 Activity

No restriction is required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAEs.

Individuals who are defined as screen failures as described above may be rescreened once, based on the inclusion or exclusion criteria leading to screen failure as described in Table 3. If other reasons prevent randomization of the participant in time (after a maximum of 30 days), which are not covered by inclusion and exclusion criteria, rescreening can be performed once, at the Investigator's discretion. If a participant was re-screened once [redacted] (Lymphocytes [redacted]/mm^3), participant might be re-screened a second time, at the Investigator's discretion.

Table 3 - [redacted]

[redacted]

There is no requirement for a waiting period between the screen failure date and the rescreen date. Rescreened participants should be assigned with a new participant number. Participants who are rescreened must sign a new informed consent and all Visit 0 procedures must be repeated.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

A complete description of the IMP and its proper handling will be provided in the pharmacy manual available to the clinical site.

6.1.1 Investigational medicinal product(s)

The IMPs are SAR441344 and matching placebo and will be supplied in vials of [redacted] mL containing SAR441344 ([redacted] mg/[redacted] mL) or matching placebo. Table 4 provides a summary of the characteristics of each IMP.

For each participant, the appropriate number of vials will be provided according to the dispensing scheme indicated in the SoA (see Section 1.3).

Home administration will not be considered in this clinical trial, particularly as this is a first in patient study. Under no circumstances will the Investigator supply the IMP to a third party, allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

Table 4 - Overview of study interventions administered

ARM name	SAR441344 Active	Placebo
Intervention name	SAR441344	Placebo
Type	Drug	Drug
Dose formulation	SAR441344 will be supplied as a [redacted] mg/[redacted] mL vial	Placebo will be supplied in vials (identical to SAR441344 in appearance)
Unit dose strength(s)	SAR441344 [redacted] mg/[redacted] mL	Placebo[redacted]mL
Dosage level(s)	One IV loading dose of SAR441344 [redacted] mg (infusion duration: 1 hour) at Day 1 followed by administration of SAR441344 [redacted] mg SC q2w	One IV loading dose of placebo[redacted] mL (infusion duration: 1 hour) at Day 1 followed by administration of placebo[redacted] mL SC q2w
Route of administration	IV loading dose at Day 1 SC at Weeks 2, 4, 6, 8, and 10	IV loading dose at Day 1 SC at Weeks 2, 4, 6, 8, and 10
Use	Experimental active	Experimental placebo
IMP and NIMP	IMP	IMP
Packaging and labeling	Study Intervention will be provided in vials in the treatment box (ie, [redacted] vials per treatment box). Each vial and box will be labeled as required per country requirement	Study Intervention will be provided in vials in the treatment box (ie,[redacted] vials per treatment box). Each vial and box will be labeled as required per country requirement
Current/Former name(s) or alias(es)	Not applicable	Not applicable

IMP: investigational medicinal product, IV: intravenous, q2w: every 2 weeks, SC: subcutaneous.

6.1.1.1 SAR441344

SAR441344 is a humanized mouse monoclonal IgG1 antagonist antibody against CD40L, with a modification to the Fc region to prevent binding to FcγRIIa and associated platelet activation.

The drug product is a sterile, clear to opalescent solution practically free of particles. It is packaged in an ISO 2R USP/Ph. Eur. Type I borosilicate glass vial, stoppered with a 13 mm USP/Ph. Eur. elastomeric stopper and sealed with an aluminum seal. Each SAR441344 product single use vial contains a nominal volume of [redacted] mL of [redacted] mg/mL SAR441344 solution.

An overfill volume of [redacted] mL is included to allow for withdrawal of [redacted] mL of solution ([redacted] mg SAR441344). The composition of SAR441344 drug product solution includes SAR441344, L-histidine HCl, L-Histidine, L-arginine HCl, sucrose, polysorbate-80, and water for injection. The pH of the formulated solution is[redacted]

6.1.1.2 Placebo

Each matching placebo is packaged as described for SAR441344 and is of the same composition as the active drug without the monoclonal antibody as described in Section 6.1.1.1.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

A complete description of the IMP preparation for IV and SC administration will be provided in the pharmacy manual available to the clinical site.

The product must be stored at 2°C to 8°C (36°F to 46°F) and protected from light prior to preparation with limited shaking (no vortex). The IMP should not be frozen. Light exposure is permitted during preparation and administration. Sites are requested to maintain a temperature log to ensure storage temperature remains within acceptable limits.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before its use.

Only participants randomized in the study may receive the IMP and only the Investigator or authorized site staff may supply or administer the IMP. The IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Handling of used vials is described in the pharmacy manual.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

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

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.2.1 Intravenous preparation and handlings

The IMP will be administered by IV infusion over a minimum of 60 minutes. The IMP will be diluted in 0.9% saline. A complete and detailed description can be found in the pharmacy manual.

6.2.2 Subcutaneous preparation and handlings

The IMP should be prepared in an appropriate syringe (details are provided in the pharmacy manual). Each SC dose will require [redacted] injections with [redacted] mL IMP per injection. All IMP SC injections should be administered in the abdomen. It is recommended that SC injection sites are alternated between the 4 quadrants of the abdomen with the injection sites at least 2 cm from the umbilicus.

A complete and detailed description can be found in the pharmacy manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A randomized treatment kit number list will be generated centrally by Sanofi for the IMPs. The IMPs (SAR441344 or matching placebo) will be packaged in accordance with the list. The Sanofi Clinical Supply Chain team will provide the randomized treatment kit number list to the centralized treatment allocation system (interactive response technology [IRT]). This centralized treatment allocation system will generate the participant randomization list according to which it will allocate the IMP to the participants. The Investigator or designee will obtain the treatment kit number at randomization (Day 1, Baseline) and subsequent scheduled dosing visits via an IRT that will be available 24 hours/day. Although the kit number will vary for the individual participant, the treatment group assignment and randomization will not change throughout the study.

Randomization will take place on Baseline/Day 1. Randomization will be stratified by ESSPRI <5 or ESSPRI ≥5 at Baseline. For the process of randomization at Baseline/Day 1, the ESSPRI collected at Baseline/Day 1 and the ESSDAI collected at Screening (based on the 7 domains listed in inclusion criterion I 04 [Section 5.1]) will be entered in the IRT before randomization takes place.

A participant who has been allocated to a randomized study intervention will be considered a randomized participant, regardless whether the treatment kit was used or not (ie, participant registered by the IRT). A participant cannot be randomized more than once in the study.

SAR441344 and placebo will be provided in identically matched [redacted] mL vials. To protect the blind, each treatment kit of [redacted] mL (SAR441344/placebo) vials will be prepared so that the treatments (SAR441344 and its matching placebo) are identical and indistinguishable and will be labeled with a treatment kit number.

Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if the unblinding of a participant's intervention assignment is warranted (eg, in case of an AE, the code must only be broken in circumstances when the knowledge of the IMP is required for treating the participant). Participant safety must always be the first consideration when making such a decision. If the Investigator decides that the unblinding is warranted, he/she may, at his/her discretion, contact Sponsor to discuss the situation prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment of the participant. Code breaking can be performed at any time by using the proper module of the IRT. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date, time of the day, and reason that the blind was broken must be recorded in the source documentation and electronic case report form (e-CRF), as applicable. If the code is broken by the Investigator, the participant must be withdrawn from the study treatment.

Methods of blinding

- This is a double-blind study.
- There is a slight color difference between SAR441344 and matching placebo, but the difference is not visually apparent, so SAR441344 and placebo cannot be distinguished by the site staff and participant.
- The Bioanalyst and the Pharmacokineticist responsible for the sample analysis and PK evaluation will be unblinded. However, they will agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule. The preliminary PK and biomarker data, if needed and available during the course of the study, will refer to mean data with descriptive statistics and individual data, without revealing any individual randomization numbers or participant numbers.
- In case of an interim analysis, a Statistician, Programmer, and the Clinical Study Director will be unblinded for the analyses and work independently to the study team to ensure maintenance of the blind. They will keep the randomization schedule in a locked area, which is not accessible to the Sponsor's clinical team and will not disclose the randomization or the individual unblinded data before the official opening of the randomization (see Section 9.5).

- The DMC will have access to unblinded data if deemed necessary by the DMC. No unblinding information will be shared by the DMC with the study team. Details about the distribution of unblinding data to the DMC while protecting the blind are described in the DMC charter and Appendix 1 (Section 10.1.5).
- For the ESSDAI (outcome measurement, not for inclusion), an evaluation of the single domains will be performed by the Investigator and recorded in the e-CRF. The total score will not be displayed by the e-CRF to the Investigator, site staff, or the study team.
- Laboratory assessments listed as PD markers and biomarkers in the SoA (see Section 1.3) will be blinded from Baseline/Day 1 throughout the study, except for those which are needed for screening and primary endpoint rating, ie, [redacted] (see Table 9). In case of a safety concern, unblinding can be performed by the Investigator and/or Sponsor for the PD marker.

6.4 STUDY INTERVENTION COMPLIANCE

As participants are dosed at the site, they will receive the IMP directly from the Investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the e-CRF. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the IMP. Details on administration of the IMP and recording of the IMP administration can be found in the pharmacy manual.

6.5 CONCOMITANT THERAPY

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of randomization or receives during the study must be recorded along with:

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

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

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

6.5.1 Prohibited concomitant medication

- High-dose steroids [redacted], or a change in steroid dose within 4 weeks prior to Day 1/Randomization, or changes during the course of the study.
- High dose of hydroxychloroquine or chloroquine[redacted], or a change in hydroxychloroquine or chloroquine dose within 12 weeks prior to Day 1/Randomization, or expected changes during the course of the study.
- High dose of methotrexate [redacted], or change in methotrexate dose within 12 weeks prior to Day 1/Randomization, or expected changes during the course of the study.
- Pharmacological stimulant treatment for lacrimal and salivary gland function with [redacted] and during the course of the study.
- Ocular dryness treatment with [redacted] and during the course of the study.
- Previous treatment with azathioprine or other thiopurines, mycophenolate mofetil, sulfasalazine, or cyclosporine A [redacted] and during the course of the study.
- Previous treatment with cyclophosphamide, leflunomide, or belimumab [redacted] and during the course of the study.
- Previous treatment with rituximab within [redacted] and during the course of the study.
- Previous treatment with bone marrow transplantation, total lymphoid irradiation or ablative ultrahigh-dose cyclophosphamide or IV Ig, and during the course of the study.
- Previous treatment with any other biologic drug [redacted] and during the course of the study.
- Received administration of any [redacted] and during the course of the study.
- Products [redacted]

6.5.2 Key authorized concomitant medications

- Oral corticosteroids [redacted] No change in dose is permitted during the study unless for the management of an AE. The dose and any change will be recorded on the participant e-CRF. Oral corticosteroids cannot be started during the course of the study.
- Low dose hydroxychloroquine or chloroquine treatment [redacted] No change in dose is permitted during the study unless for the management of an AE. Dose and any change will be recorded on the participant e-CRF. Hydroxychloroquine or chloroquine cannot be started during the course of the study.

- Methotrexate up to [redacted]. No change in dose is permitted during the study unless for the management of an AE. Dose and any change will be recorded on the participant e-CRF. Methotrexate cannot be started during the study. Concomitant therapy with folic acid is permitted.
- Nonsteroidal anti-inflammatory drugs are allowed, if a stable compound with a stable dose (on-demand medication is permitted if the dose is stable) is used [redacted] No change in dose is permitted during the study unless for the management of an AE. Dose and any change will be recorded on the participant e-CRF. Nonsteroidal anti-inflammatory drugs cannot be started during the course of the study. Medication has to be paused at least 12 hours before glandular function tests.
- Topical medication (eg, artificial tears) for treatment of dryness of mouth and eyes is allowed, if a stable compound [redacted] and if the medication is not listed in Section 6.5.1. No change in dose is permitted during the study. Dose and any change will be recorded on the participant e-CRF. Topical medication cannot be started during the course of the study. Medication has to be paused at least 12 hours before glandular function tests.

  [redacted]. No change in dose is permitted during the study. The dose and any dose changes will be recorded on the participant e-CRF. Pharmacological stimulants cannot be started during the course of the study. This medication has to be paused at least 12 hours before glandular function tests.

[redacted]

[redacted]

- Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the Medical Monitor.

6.6 DOSE MODIFICATION

No dose modifications are planned for this study. For the justification of dose, see Section 4.3. Details on temporary and definitive IMP discontinuation on an individual level is described in Section 7.

6.7 INTERVENTION AFTER THE END OF THE STUDY

No intervention is planned following the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

In certain instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the IMP. See Section 7.1.1.1 for how to proceed in case of definite discontinuation and the SoA (Section 1.3) for data to be collected at the time of discontinuation of IMP and follow-up and for any further evaluations that need to be completed.

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

In case of the following events, a definitive discontinuation of the IMP is mandatory. This list is not intended to be exhaustive:

- At the request of the participant: ie, withdrawal of consent for the study.
- Pregnancy of a female participant.
- Thromboembolic events including, but not limited to, deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke.
- Occurrence of any malignancy.
- Severe hypersensitivity or anaphylactic reaction.
- Severe injection site reaction.
- Any AE, per Investigator judgment, that may jeopardize the safety of the participant.
- Any code breaking performed by the Investigator.
- At the specific request of the Sponsor.

Discontinuation of the IMP for laboratory abnormalities should be considered by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) or if the Investigator believes that it is in the best interest of the participant.

In the case of biologically proven COVID-19 infection, the Investigator may permanently

discontinue the IMP for the participant, who will be asked to continue attending the protocol scheduled visits until EOS. If according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant, the Investigator can consider a temporary discontinuation per Section 7.1.2.

The participant cannot restart IMP until the participant's COVID-19 PCR is negative. All COVID-19 infections will be reviewed by the DMC as AESI.

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

7.1.1.1 Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion (EoS visit), 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 definitive discontinuation of the IMP, participants will be assessed using the procedure normally planned for the End of Treatment (EoT) visit, including a PK and ADA sample. Afterwards, the complete follow-up period should be performed, if possible.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary IMP discontinuation may be considered by the Investigator because of suspected AE(s). For all temporary IMP discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF. Planned visits should take place as scheduled, if possible, during this period of discontinuation. Temporary IMP discontinuation can appear only once per subject/treatment period.

Temporary IMP discontinuation may also apply in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer feasible. In the case of an exceptional temporary treatment discontinuation, the discontinuation should be approved by the Sponsor. The Sponsor should also be notified to determine if treatment should be resumed. If deemed safe, the treatment can be resumed at the next scheduled visit. During the discontinuation period, remote checks (eg, telephone calls) will take the place of on-site visits per the SoA.

- If the above emergency scenario occurs during the follow-up period, one or more follow-up visits can be performed remotely (eg, via telephone call), but at least one follow-up visit should be performed on site (EoS visit), even if the visit window needs to be extended (to a maximum of 8 weeks). Remote follow-up should be done according to local regulations and approved by the Sponsor.

- If the above emergency scenario leads to site closure or complete regional or national lock-down, the study may be suspended for the affected sites (Section 10.1.9).

In case of suspicion of COVID-19 (eg, fever, cough, shortness of breath in a context of possible infected contact), temporary discontinuation of IMP will be considered. The following should be considered to evaluate individual benefit-risk for resuming or stopping of IMP: the probability of COVID 19 disease, possibility of rapid diagnosis, severity of symptoms, and risk factors.

In the case of biologically proven COVID-19 infection, if according to the Investigator a permanent IMP discontinuation is not necessary or in the best interest of the participant and the participant does not have severe or critical COVID-19 as defined by WHO guidelines (25), the participant can temporarily discontinue IMP until the participant's COVID-19 PCR is negative.

A discontinuation of IMP greater than 30 days +2 days (according to the visit window) will be considered definitive and relevant e-CRF sections should be populated.

7.1.2.1 Rechallenge

Reinitiation of treatment with the IMP will be considered with close and appropriate clinical and/or laboratory monitoring after the Investigator has determined, according to his/her best medical judgment, that the causality of the event was unlikely related to the IMP(s) and if the selection criteria for the study are still met (see Section 5.1 and Section 5.2).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his/her own request or may withdraw at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. In these situations, if possible, the EoT visit (including a PK and ADA sample collection) should be performed if discontinuation is during the treatment period, or the EoS should be performed if discontinuation is during the follow-up period, as shown in the SoA (see Section 1.3).

If participants no longer wish to receive the IMP, they will be encouraged to remain in the study. The EoT visit should be performed and the Investigator should discuss with the participants to attend the follow-up period visits.

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

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

In addition, a participant may withdraw his/her consent to stop participating in the study. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested (eg, archival

samples for future use), and the Investigator must document this in the site study records. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be randomized more than once in the study. Their participant and randomization numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, several telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

The Statistical Analysis Plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, FSH) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA and/or in inclusion or exclusion criteria (see Section 1.3 and Section 5).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL (the exact assessment specific volumes are described in the laboratory manual). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, this could be done locally if approved by the Sponsor.
- Participants will be contacted before each visit (latest on the day before the visit) by the Investigator or designee, to evaluate for signs and symptoms of a potential SARS-CoV-2 infection. In case of suspicion of such infection, the participant will be asked to not come to the study site and will be referred to a testing facility or her/his primary care physician according to local regulations. If the suspicion of a SARS-CoV-2 infection is excluded and there is no other reason to pause treatment due to the Investigator judgment, the treatment can continue. If the suspicion of a SARS-CoV-2 infection is confirmed, treatment should be stopped (Section 7.1.1).

8.1 EFFICACY ASSESSMENTS

8.1.1 European League Against Rheumatism Sjögren's Syndrome Disease Activity Index

The ESSDAI is a validated and established outcome measurement for therapeutic efficacy in SjS, evaluating disease activity mainly on extra-glandular manifestations. This score consists of 12 organ-specific domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, PNS, CNS, hematological, and biological), which are scored based on organ-specific items in 3 to 4 different severity grades. This score is summed up over all 12 domains in a weighted way to summarize into a total score (7, 36). The maximum theoretical range is 0 to 123. Within this study all domains will be measured, and the primary objective is based on the total score. Inclusion (ESSDAI ≥5) will be based on the following 7 domains:

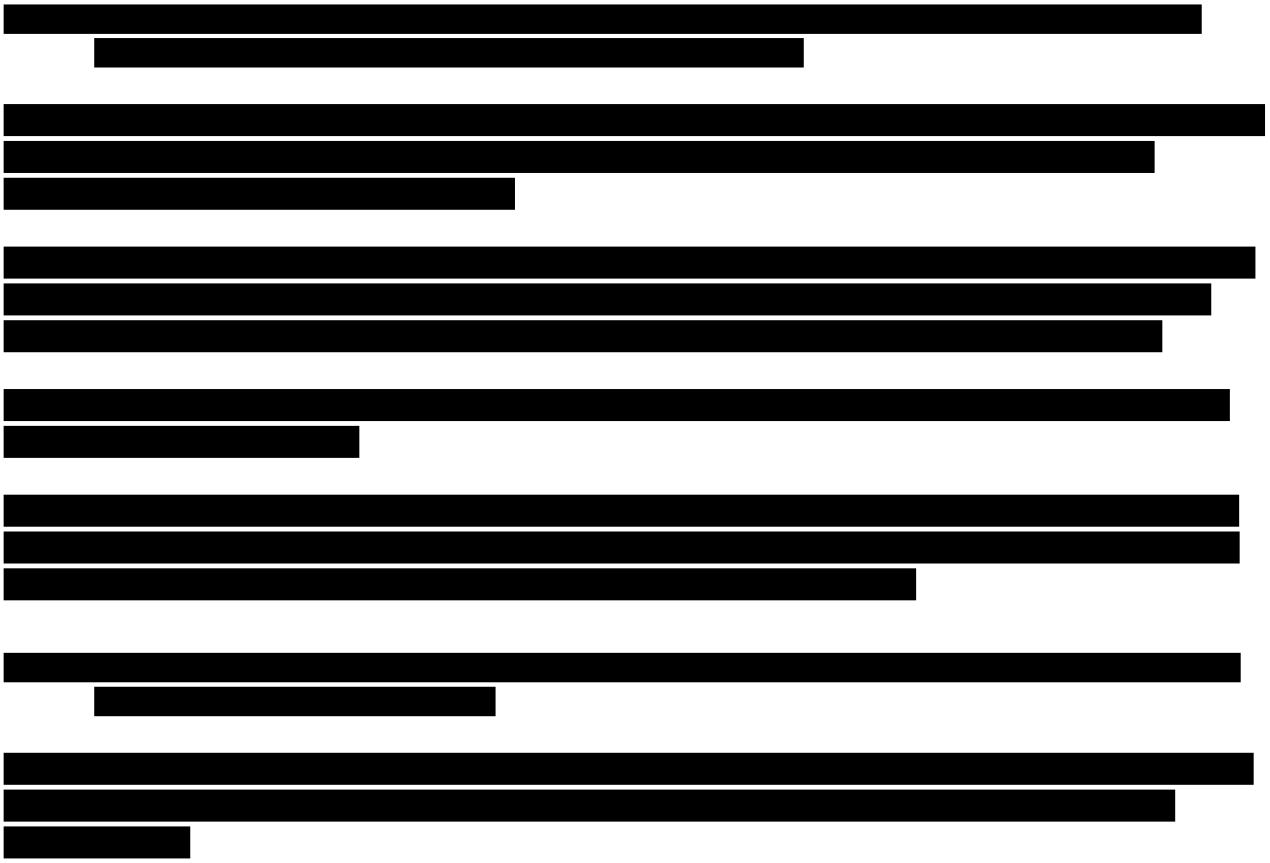
glandular, articular, muscular, hematological, biological, constitutional, and lymphadenopathy. During the study, ESSDAI should be rated by the same Investigator or designee for one participant, if possible (8).

8.1.2 European League Against Rheumatism Sjögren's Syndrome Patient Reported Index

The ESSPRI is a validated and established outcome measurement, reported by patients, which rates the key disease manifestations fatigue, dryness, and pain based on a numeric scale ranging from 0 to 10, where 0 is defined as no symptoms and 10 as maximum imaginable complaints. The total score is the mean score of the 3 scales (7, 37).

8.1.3 Multidimensional Fatigue Inventory

The MFI is a validated, 20-item self-report instrument to evaluate fatigue by investigating the following components: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Using a scale from 1 ("yes, this is true") to 5 ("no, this is not true"), patients indicate how the listed statements apply to their current fatigue situation. Each of the 5 scales is to be considered independently. Scores can range from the minimum of 4 to the maximum of 20. A total score ranged from 20 to 100 will also be derived. A higher score is related with a higher degree of fatigue (38).



[redacted]

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

[redacted]

Height and weight

- Height (in cm) will be measured only at Screening.
- Weight (in kg) should be taken with the participant wearing light clothing, no shoes. The same scale should be used throughout the study.
- Body mass index will be calculated automatically at each visit weight is measured as per the SoA (Section 1.3).

8.2.2 Vital signs

- Vital signs will be measured in a sitting position after 5 minutes of rest and will include tympanic temperature, systolic and diastolic blood pressure, and pulse.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- A single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).
- Electrocardiogram parameters will be based upon the automatic reading of the device. These ECG parameters and morphology need to be reviewed by the Investigator. If the device does not provide automatic reading, then the ECG parameters will need to be determined and interpreted by the Investigator.
- At the post-randomization visits, ECGs will be performed prior to IMP administration. All ECGs will be performed with the participant in a reclined position. Electrocardiogram parameters include: heart rate, QRS duration, PR, QT, and QTc interval.

8.2.4 Clinical safety laboratory assessments

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

- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the e-CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 weeks after the last dose of IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (see Section 1.3).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the e-CRF.

8.2.5 Local tolerability

The evaluation of SC injection site reactions following IMP injection will be performed by the Investigator or designees. [redacted]

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative (see Appendix 1 [Section 10.1]).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue the study.

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the ICF until the EoS visit at the time points specified in the SoA (see Section 1.3).

All AEs will be collected from the signing of the ICF at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs (defined in Section 8.3.6) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end date, all SAEs and AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

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

- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of IMP and until the EoS visit.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse event of special interest

Adverse event of special interest

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

All reported AESIs will be reviewed by an independent DMC.

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

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical study or in a female partner of a male participant entered in the clinical study. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP:
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator and any qualified designees and defined as:
    - Intravenous doses: increase of at least 30% of the dose to be administered or the dose is administered in less than 30 minutes.
    - Subcutaneous doses: At least twice the intended dose within the planned intervals (2 weeks ±2 days).

  Of note, asymptomatic overdose has to be reported as a standard AE.
- If increase in ALT >3 × ULN, see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6).
  - However, if the increase in ALT is ≥2 × the baseline value (with baseline ALT ≥ULN) but ≤3 × ULN, then ALT should be retested within 72 hours of initial sample to determine if the retest value meets the AESI criterion of ALT >3 × ULN. If so, proceed as above and follow the guidelines of Appendix 6 (Section 10.6). If not, monitoring of the laboratory findings will be up to the medical judgment of the Investigator.

Other project specific AESI(s)

- Confirmed diagnosis of an arterial and/or venous thrombotic or embolic event. All signs and symptoms, clinical or biological, suggestive of a thromboembolic event should be investigated immediately. Only confirmed thromboembolic events should be reported as an AESI.
- Confirmed diagnosis of lymphoma, due to the risk of lymphoma in SjS patients. All signs and symptoms, clinical or biological, suggestive of a lymphoma should be investigated. Only confirmed lymphoma should be reported as an AESI.
- Anaphylaxis.
- Severe infusion related reactions.

- Severe IMP injection or infusion site reaction.
- Severe infections including opportunistic infections.
- Tuberculosis or initiation of medications for suspected tuberculosis.
- Diagnosed and biologically proven SARS-CoV-2 infection.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities, at least for 28 days.
3. Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

SAR441344 concentrations at selected time points will be reported using descriptive statistics. Additional PK parameters such as C_{max}, t_{max}, $t_{1/2z}$, and $AUC_{0\text{-}tau}$ will be estimated using a population PK approach. These parameters will be presented in a separate standalone report.

- Blood samples will be collected for measurement of plasma concentrations of SAR441344 as specified in the SoA (see Section 1.3). Detailed procedures of sample preparation, storage, and shipment will be described in the specific laboratory manual.
- A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of SAR441344. Each plasma sample will be divided into 2 aliquots (1 each for PK and a backup). Samples collected for analysis of SAR441344 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples unless consent for this was signed by the participant. Participant confidentiality will be maintained.
- At visits during which plasma samples for the determination of multiple aspects of the IMP will be taken, one sample of sufficient volume can be used.

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

8.6 PHARMACODYNAMICS

Several biomarkers related to the mechanism of action of SAR441344 and pathophysiology of SjS will be used to assess PD effects of SAR441344. The following PD parameters (which are well known markers to investigate PD effects in clinical studies for pSjS) will be assessed: [redacted]

All other biomarkers will be described in Section 8.8.

- A positive treatment effect of SAR441344 should result [redacted] as indicated by:
  - Decrease in [redacted] pointing to a polyclonal B-cell activation within pSjS, if treatment results in a decrease, a PD effect could be demonstrated. [redacted] levels are part of the ESSDAI score.
  - Decrease in [redacted] as an autoantibody is a B-cell activation marker and known to be increased in pSjS, a PD effect could be shown by a reduction of [redacted] level.
  - Decrease in [redacted]: both factors are associated with increased disease activity in pSjS and a PD effect could be demonstrated by a reduction in [redacted]
- The evidence of [redacted] is characterized by poor prognosis and more severe organ manifestation in pSjS. A PD effect could be shown by an elevation of [redacted]

8.7 GENETICS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] (Section 1.3), [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] as indicated in Section 8.7.

[redacted]

- Serum samples will be tested for [redacted] Details on the rationale can be found in Section 8.6.
- Serum samples will be tested for anti-Ro/SSA antibodies (only at Screening) to ensure presence of disease activity at inclusion.

[redacted]

- Leftover samples will be stored and used for future analysis as described below, if consented.

- [redacted]
  - Tested in plasma samples,
  - Exploratory PD marker to evaluate [redacted] activity in response to SAR441344,
  - [redacted] protein levels in plasma are expected to show a decrease with SAR441344 treatment, indicative of reduced[redacted]
- [redacted]
  - Tested in plasma samples,
  - Exploratory PD marker to evaluate [redacted] in response to SAR441344.
- [redacted]
  - Tested in whole blood,

- Exploratory PD marker to evaluate effects on [redacted] in response to SAR441344,
- [redacted] levels in plasma are expected to show a decrease in this marker with SAR441344 treatment, indicative for an effect on the [redacted]

[redacted] (see SoA [Section 1.3]) [redacted]

[redacted] (see Section 8.7.2),

[redacted]

A summary of sample volumes and timing of collection for the above biomarker assessment is presented in the laboratory manual.

8.9 IMMUNOGENICITY ASSESSMENTS

Antidrug antibodies to SAR441344 will be evaluated in serum samples collected from all participants according to the SoA (see Section 1.3). Additionally, serum samples should also be collected at the final visits from participants who discontinued the IMP or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to SAR441344 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to SAR441344 and/or further characterize the immunogenicity of SAR441344.

The detection and characterization of antibodies to SAR441344 will be performed using a validated assay method by or under the supervision of the Sponsor. Plasma samples will be collected for detection of antibodies to SAR441344 for evaluation of SAR441344 serum concentration to enable interpretation of the antibody data. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to SAR441344.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing will be performed.

9.2 SAMPLE SIZE DETERMINATION

The sample size was derived with respect to the primary endpoint (mean change from Baseline to Week 12 in the ESSDAI score) for applying the Quantitative Decision Making approach as described by Quan et al (45). Assuming a variability of [redacted] and an effect size of [redacted], as derived based on (39), a sample size of 80 evaluable participants results in an overall probability [redacted].

Approximately 88 participants are expected to be randomly assigned to the IMP, expecting a total of 80 evaluable participants with approximately 40 evaluable participants per group.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention (by IRT) regardless of whether the intervention was received or not. Participants treated with the study intervention without being randomized or before the randomization will not be considered as randomized.
Efficacy	All randomly assigned participants who did actually receive at least 1 complete dose of IMP with at least 1 post-IMP administration measurement, with available Baseline assessment of the ESSDAI. Participants will be analyzed according to the intervention they actually received.
Safety	All randomized participants exposed to the IMP (regardless of the amount of treatment administered) are included in the safety population. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	All randomized and treated participants (safety population) with adequate PK results. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they received.
Pharmacodynamic	All randomized and treated participants (safety population) with at least one post-baseline PD data. Participants will be analyzed according to the intervention they received.
PK/PD population	All participants being included in both the PK and the PD populations will be included in the PK/PD population. However, participants being included in the PD population and having received only placebo will be part of the PK/PD population.
ADA	All randomized participants treated with SAR441344 with at least one post-baseline ADA result (positive, negative or inconclusive).

ADA: Anti-drug antibodies, ICF: informed consent form, IMP: investigational medicinal product, PD: pharmacodynamic, PK: pharmacokinetic.

Note: "Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

9.4 STATISTICAL ANALYSES

A SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

The treatment difference in primary endpoint will be assessed based on the Quantitative Decision Making methodology. Specific decision criteria to be used will be documented separately before database lock.

Descriptive analyses will include summarization of quantitative variables (using n, mean, standard deviation, inter-quartile range, median, minimum, and maximum) and qualitative data (by reporting absolute and relative frequencies).

9.4.2 Primary endpoint(s)

For the primary analysis, a linear mixed model with repeated measurements will be fitted to estimate the difference in mean change in ESSDAI from Baseline to Week 12. The model includes fixed effects for participant-specific baseline ESSDAI, visit, treatment group, and visit-by-treatment group interaction. Repeated measurements for each visit are taken within subject (Table 6). Point estimate and 90% confidence interval for the difference of means between the 2 groups (SAR443144 versus placebo) will be derived from the linear model framework.

Table 6 - Primary endpoint analysis

Primary Endpoint	Statistical Analysis Methods
Change in ESSDAI from Baseline to Week 12.	The difference to placebo of mean change from Baseline to Week 12 in ESSDAI score will be derived using a linear mixed model with repeated measurements over time within participant, including fixed effects for participant-specific baseline ESSDAI, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence interval.

ESSDAI: European League Against Rheumatism Sjögren's Syndrome Disease Activity Index.

9.4.2.1 Additional analyses of the primary endpoint

For sensitivity analysis of the primary endpoint, a linear mixed model with repeated measurements will be fitted to estimate the mean change in ESSDAI over time, including fixed factors for participant-specific baseline ESSDAI, visit, stratum, treatment group, visit-by-stratum interaction, visit-by-treatment group interaction, stratum-by-treatment group interaction, and visit-by-stratum-by-treatment group interaction. Repeated measurements for each visit are taken within subject.

The model-based estimate of the difference between treatments of the change in ESSDAI from Baseline to Week 12 will be provided, jointly with a 90% confidence interval.

Observed mean and mean change from Baseline in single domains of ESSDAI will be summarized descriptively by visit.

Descriptive statistics of the observed change from Baseline to Week 12 in ESSDAI will be provided overall and by ESSPRI at Baseline (ESSPRI <5 or ESSPRI ≥5).

9.4.3 Key secondary endpoint(s)

The main analysis provided for the primary endpoint of change from Baseline to Week 12 will be repeated for the key secondary endpoints (ESSPRI, MFI general fatigue subscale and other subscales; Table 7).

Table 7 - Key secondary endpoints analyses

Secondary Endpoint	Statistical Analysis Methods
Change in ESSPRI from Baseline to Week 12.	The difference to placebo of mean change from Baseline to Week 12 in ESSPRI will be derived using a linear mixed model with repeated measurements over time within participant, including fixed effects for participant-specific baseline ESSPRI, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence interval.
Change in MFI general fatigue subscale and other subscales from Baseline to Week 12.	The difference to placebo of mean change from Baseline to Week 12 in MFI general fatigue subscale and other subscales (physical fatigue, mental fatigue, reduced motivation, and reduced activity) will be derived using a linear mixed model with repeated measurements over time within participant, including fixed effects for participant-specific baseline, visit, treatment group, and visit-by-treatment group interaction, jointly with 90% confidence intervals.

ESSPRI: European League Against Rheumatism Sjögren's Syndrome Patient Reported Index, MFI: Multidimensional Fatigue Inventory.

9.4.3.1 Additional analyses of the key secondary endpoints

A linear mixed effects model similar to the model applied to the primary endpoint will be fit to the key secondary endpoints (ESSPRI, MFI general fatigue subscale).

Descriptive statistics of the observed mean and mean change from Baseline by visit in single domains and overall score will be provided for the key secondary endpoints (ESSPRI, MFI general fatigue subscale and other subscales).

[redacted]

Details on the analysis of tertiary endpoints will be provided in the SAP.

9.4.5 Analysis of safety data

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, figures) and, if needed, on statistical analysis (appropriate estimations, confidence intervals). No statistical significance tests will be performed on safety data.

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 reviews and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG parameters.

All the safety analyses will be performed using the safety population.

For all safety data variables, the following observation periods are defined and used for classification of AEs, determination of on-treatment PCSA values, and the last on-treatment value for laboratory and vital sign parameters:

- The pre-treatment period is defined as the time between informed consent signature and the first IMP administration.
- The TEAE period is defined as the time from the first IMP administration up to the EoS visit (EoS included). It may be split further into the following periods:
  - On-treatment period, defined as the time from the first IMP administration up to EoT visit +7 days (last day included),
  - Residual treatment period, defined as the time from EoT visit + 8 days up to the EoS visit (EoS included).
- The post-treatment period is defined as the time starting after the TEAE period.

9.4.5.1 Adverse events

9.4.5.1.1 Definitions

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version in use by the Sponsor at the time of database lock). Clinical judgment should be used to determine the severity of AEs as described in Section 10.3.3.

Adverse events will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs: AEs that occurred, worsened, or became serious during the pre-treatment period.
- Treatment-emergent AEs: AEs that occurred, worsened, or became serious during the TEAE period.
- Post-treatment: AEs that occurred, worsened, or became serious during the post-treatment period.

Treatment-emergent AEs will be assigned to the treatment received as per safety population.

If the onset date (or time) of an AE (occurrence, worsening, or becoming serious) is incomplete or missing, the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or post-treatment event.

All AEs reported in the study will be listed, sorted by participant, onset date, and time.

Table 8 - Safety analyses

Safety measures	Statistical analysis methods
Adverse events • AEs • TEAEs • SAEs • AEs leading to IMP or study discontinuation • AEs leading to death • AESIs • PCSAs	Treatment-emergent adverse event incidence tables will be presented by system organ class, high-level group term, high-level term, and preferred term for each treatment group and overall, showing the number (n) and percentage (%) of participants experiencing a TEAE. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages will be the safety population within each treatment group. In addition, TEAEs will be described according to maximum intensity and relation to the IMP. Adverse events that occur outside the treatment emergent period will be listed separately. Proportion of patients with at least 1 TEAE, treatment emergent SAE, TEAE leading to death, and TEAE leading to definitive treatment discontinuation will be tabulated by treatment group and overall. The incidence of PCSAs occurring during the TEAE period will be summarized by treatment group overall and by baseline status.

AE: adverse event, AESI: adverse event of special interest, IMP: investigational medicinal product, PCSA: potentially clinically significant abnormality, SAE: serious adverse event, TEAE: treatment-emergent adverse event.

9.4.5.2 Local tolerability

The number (%) of participants with injection site reactions will be summarized overall and by maximum severity by treatment group. Observed mean and mean change from Baseline in VDS will be summarized descriptively by visit. The incidence of AEs related to local tolerability findings will be summarized over time.

9.4.5.3 Immunogenicity

Antidrug antibodies to SAR441344 will be summarized by visit.

9.4.5.4 Extent of study treatment exposure and compliance

A summary table presenting the exposure of treatment (ie, the number of days or weeks of administration) will be provided by treatment group for the safety population.

9.4.5.5 Laboratory data

Descriptive statistics of laboratory variables (laboratory values and changes from baseline), will be provided for each scheduled visit where laboratory data will be collected as per the SoA (Section 1.3; Baseline and post-Baseline time points). Descriptive statistics of changes from Baseline to last on-treatment value and from Baseline to worst on-treatment value will be presented for selected parameters by treatment group.

9.4.5.6 Vital signs

Descriptive statistics of all vital signs variables (values and changes from Baseline) will be calculated for each scheduled visit (baseline and post-baseline time points). Descriptive statistics of changes from Baseline to last on-treatment value and from Baseline to worst on-treatment value will be presented for selected parameters by treatment group.

9.4.5.7 Electrocardiogram

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

9.4.6 Analysis of pharmacokinetic data

9.4.6.1 Pharmacokinetic parameters

The analysis of PK parameters will be described and reported separately.

9.4.6.2 Pharmacokinetic/Pharmacodynamic analysis

The analysis of PK/PD relationship will be described and reported separately.

9.4.7 Other analyses

9.4.7.1 Biomarkers

Biomarker analyses will be described and reported separately.

9.5 INTERIM ANALYSES

An interim analysis for decision making may be implemented once approximately 50% of the planned participants have completed the study up to EoT (Week 12). The outcome may lead to early termination, continuation without any changes, or continuation with changes.

A protocol amendment/amended protocol will be submitted for approval before any substantial changes to the study conduct are implemented.

For this interim analysis, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding.

A separate SAP for this interim analysis, if performed, will describe the corresponding analyses to be performed at interim and in greater detail.

Once all participants have completed their EoT (Week 12) visit, selected sponsor personnel including study statistician and study programmer may be unblinded to generate initial reports (early analysis) based on the final SAP for internal decision making. Details of the personnel to be unblinded will be documented separately.

Beside those described interim analyses, additional analyses for internal decision making might be conducted. For those analyses, if decided to do so, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding.

9.6 DATA MONITORING COMMITTEE (DMC)

For details on the DMC, refer to Appendix 1 (Section 10.1.5).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

  - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
  - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

For the ICF and the optional future use of sample ICF, the following applies:

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study, in language and terms they are able to understand.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed and dated ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The optional future use of the sample ICF will address the use of remaining mandatory samples and the use of the archival samples for optional exploratory research (see Section 1.3, Section 8.7, and Section 8.8). The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR.

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African-American population for the FDA) and due to several differences noted in SjS patients of different ethnicities eg, in genome-wide analysis of genetic polymorphisms showing different results in different ethnicities (2).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

10.1.5 Committees structure

Data Monitoring Committee

The DMC will be charged with monitoring the safety of participants in this study. It will also be responsible for providing recommendations for protecting the safety and ensuring the welfare of these participants to the Sponsor during the study. The DMC is justified by the early stage of development of SAR441344 in patients with pSjS. This committee is comprised of externally-based individuals with expertise in the diseases under study or clinical research and biostatistics.

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 study continuation with or without alterations or of potential study termination.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or e-CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study reference manual.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

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

- Note: in case of investigational site closure or complete regional or national lock-down due to a local epidemic or international pandemic, the study may be suspended regionally or nationally at the affected sites. Every effort will be kept to continue the follow-up of already recruited patients as close to the SoA as possible.

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

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

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

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 9 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results must be entered into the e-CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations Pregnancy testing: For Screening, a HCG test (blood) will be obtained from all female participants, which must be deemed negative (see Section 5) During the study, β-HCG testing will be performed for women of childbearing potential (WOCBP), if the urine test is positive, a blood test will be sent to the central laboratory.

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	• Platelet count • Red blood cell (RBC) count • Hemoglobin • Hematocrit • RBC indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), % reticulocytes • White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Coagulation	• International normalized ratio (INR), activated partial thromboplastin time (aPTT)
Clinical chemistry[a]	• Blood urea nitrogen (BUN), creatinine (including glomerular filtration rate calculation, according to the Cockcroft-Gault formula) • Serum glucose[b] • Serum electrolytes: potassium, sodium, calcium • Liver function tests: aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, total and direct bilirubin • Creatine phosphokinase • Total protein
Routine urinalysis	• pH, specific gravity, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase (performed by dipstick locally at the site), quantitative measurement for glucose, protein, erythrocytes, and leucocytes count will be required in the event that the urine sample test is positive for any of the above parameters by urine dipstick and rated clinically significant by the Investigator (sample will be sent to central laboratory) • Microscopic examination (if blood or protein is abnormal) • β-human chorionic gonadotropin (HCG) for women of childbearing potential (performed locally at the site)[c]
Test only performed at Screening	• Follicle-stimulating hormone (as needed in postmenopausal women)

Laboratory assessments	Parameters
	• Highly sensitive serum β-HCG pregnancy test • Serology: human immunodeficiency virus antibody 1/2, hepatitis B surface antigen (HBsAg), hepatitis B core antibody, (HBc Ab), and hepatitis C antibody (HCV-Ab) • QuantiFERON® tuberculosis-Gold test • Anti-Ro/SSA
PD/Genetics/Biomarker	• Performed in the central laboratory: [redacted], rheumatoid factor[e], [redacted][d], [redacted] • Performed by the Sponsor[d]: deoxyribonucleic acid, ribonucleic acid samples, [redacted]
	• All study-required laboratory assessments will be performed by a central laboratory if not listed otherwise in this table

NOTES:
a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6 (Section 10.6).
b Fasting glucose is preferred. Fasting/non-fasting status will be recorded at the time of blood collection for glucose assessment.
c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or Institutional Review Board/Independent Ethics Committee.
d The Investigator and study site will be blinded for these parameters. Unblinding is appropriate in case of a safety issue.
e Rheumatoid factor will be unblinded at Screening, but blinded from Visit 1 on throughout the study.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Therefore, the Investigator and the study site will be blinded for[redacted], [redacted] ([redacted] is unblinded at Screening), [redacted] as well as all analysis performed by the Sponsor as indicated in Table 9. Unblinding is appropriate in case of a safety issue and deemed necessary in the discretion of the Investigator.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease) eg,
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from Baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the e-CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AESI/AE/SAE e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: an event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathology examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed e-CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

- Contacts for SAE reporting can be found in the Investigator site file.

SAE reporting to the Sponsor via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator site file.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential

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

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy,

   For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>ULN as defined by central laboratory readout) is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study randomization.

CONTRACEPTION GUIDANCE:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Vasectomized partner
  (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence
  (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive the investigational medicinal product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

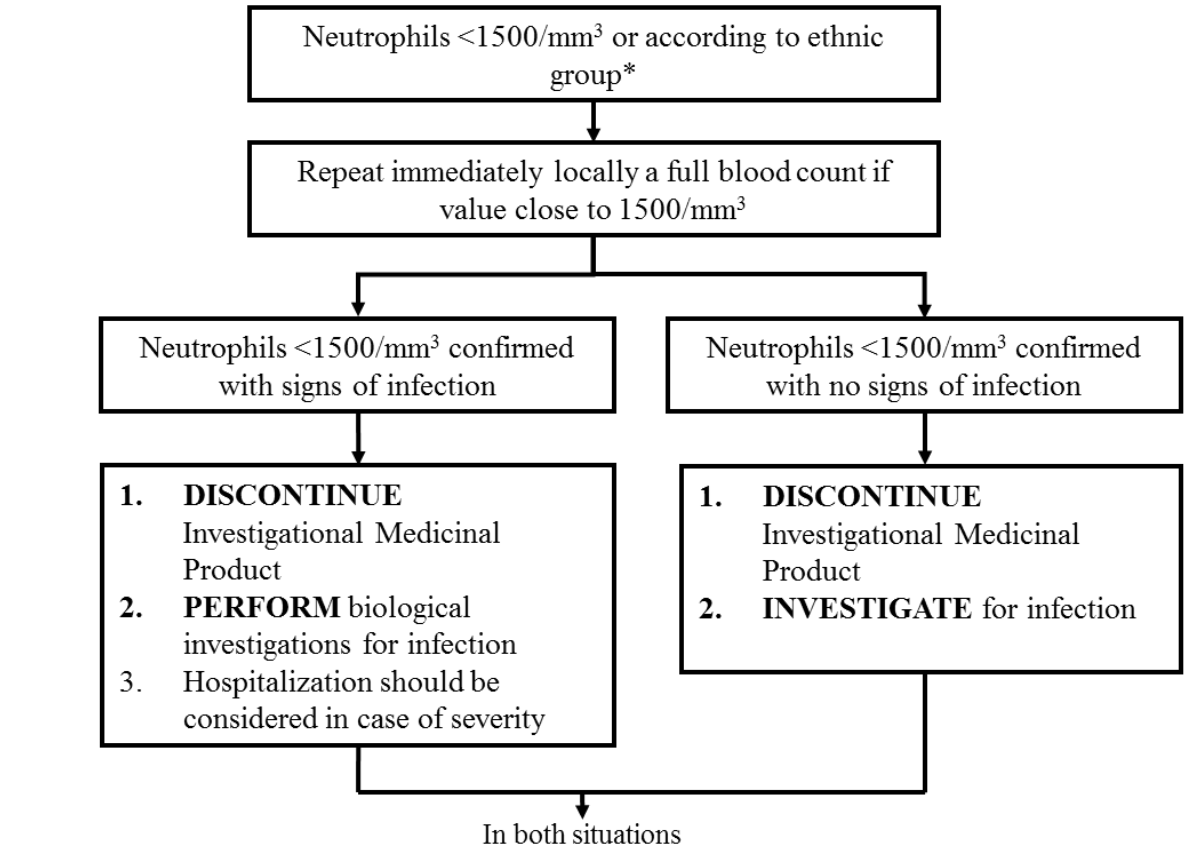
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

[redacted]

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

NEUTROPENIA

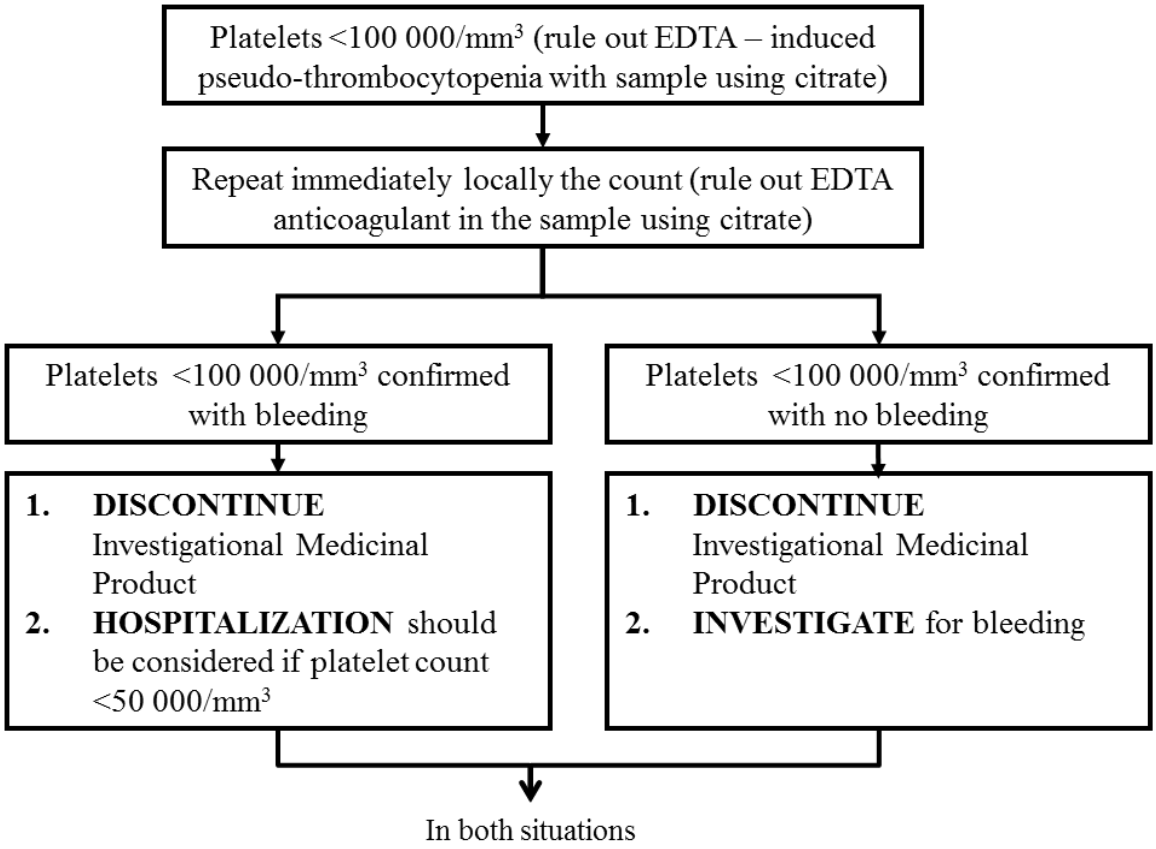


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
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

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

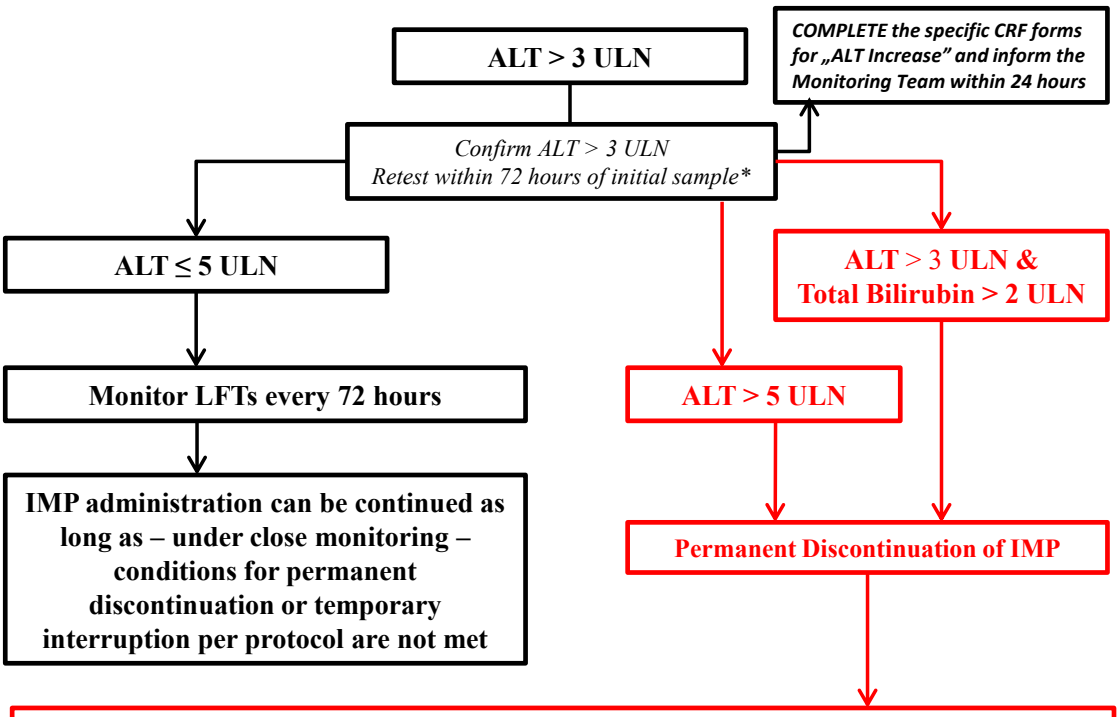
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

THROMBOCYTOPENIA



Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

INCREASE IN ALT

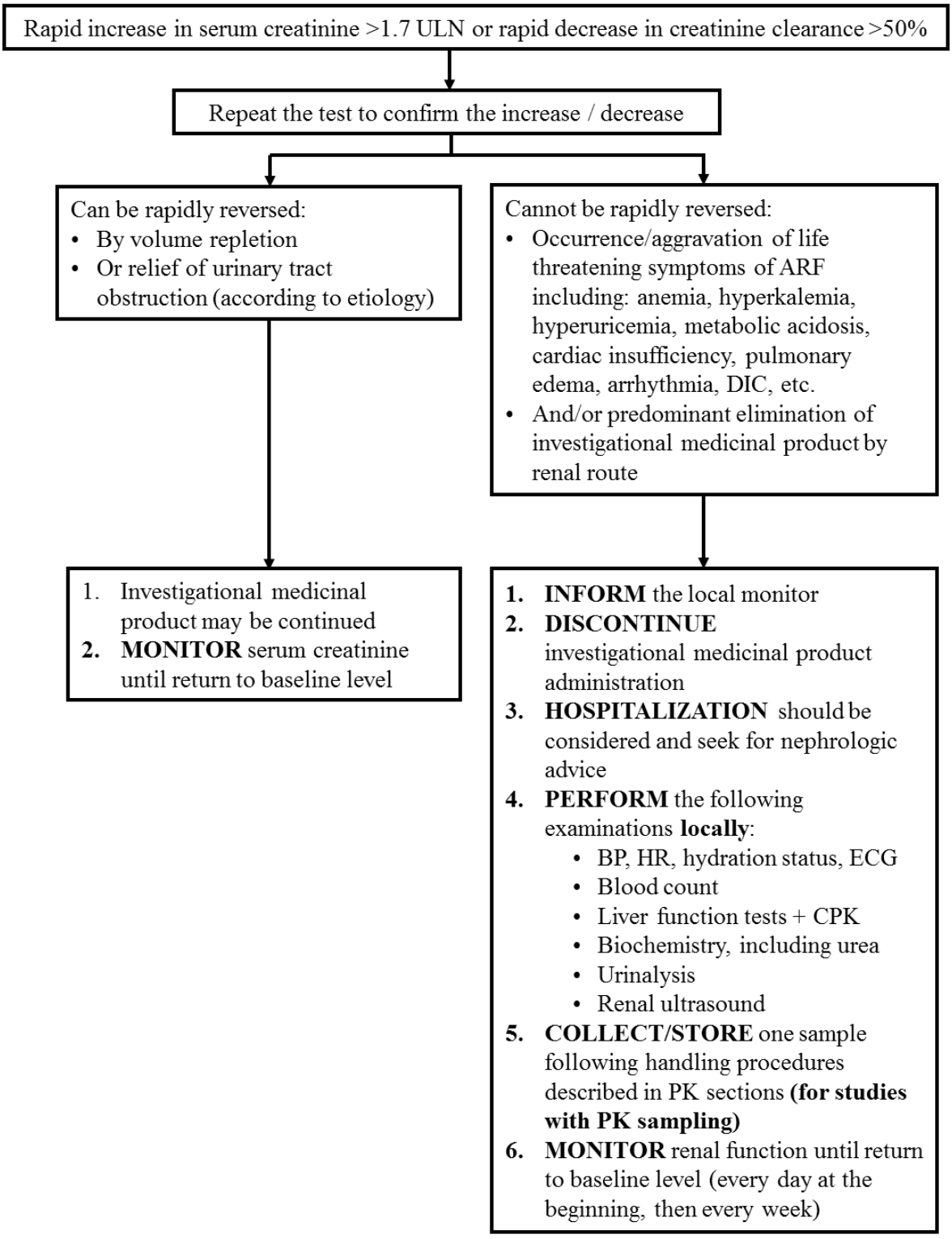


In ANY CASE, FOLLOW the instructions listed in the box below:

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

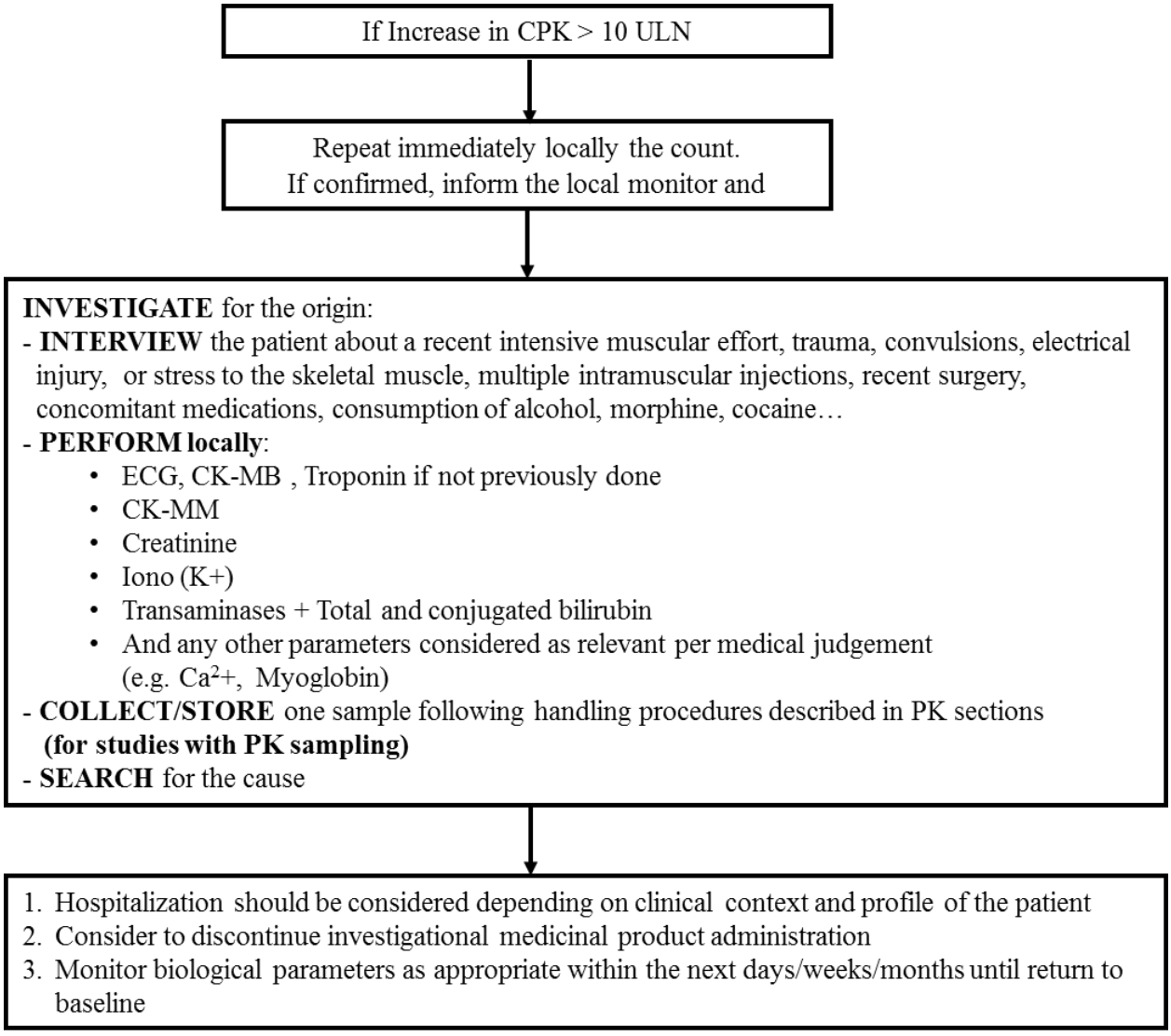
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Appendix 3 (Section 10.3) for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

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



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

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



Increase in creatine phosphokinase (CPK) is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: ABBREVIATIONS

ADA: antidrug antibody
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
anti-HBc Ab: anti-hepatitis B core antibodies
AST: aspartate aminotransferase
AUC: area under the curve
$AUC_{0\text{-}tau}$: area under the curve over the dosing interval
[redacted]
CD40: cluster of differentiation 40
CD40L: cluster of differentiation 40 ligand
CFR: Code of Federal Regulations
CIOMS: Council for International Organizations of Medical Sciences
C_{max}: maximum concentration
CNS: central nervous system
CONSORT: Consolidated Standards of Reporting Trials
COVID-19: coronavirus infectious disease due to SARS-CoV-2
CPK: creatine phophokinase
CRF: case report form
CSR: clinical study report
[redacted]
DMC: Data Monitoring Committee
[redacted]
ECG: electrocardiogram
e-CRF: electronic case report form
EoS: End of Study
EoT: End of Treatment
EQ-5D-5L: EuroQoL questionnaire with 5 dimensions and 5 levels per dimension
ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index
EULAR: European League Against Rheumatism
FIH: first in human
FSH: follicle-stimulating hormone
GCP: Good Clinical Practice
GDPR: General Data Protection Regulation
GLP: Good Laboratory Practice
HBsAg: hepatitis B surface antigen
HCG: human chorionic gonadotropin

HCV-Ab:	hepatitis C antibody
HIPAA:	Health Insurance Portability and Accountability ACt
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
Ig:	immunoglobulin
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
IV:	intravenous(ly)
KLH:	keyhole limpet hemocyanin
mAb:	monoclonal antibody
MedDRA:	Medical Dictionary for Regulatory Activities
MFI:	Multidimensional Fatigue Inventory
[redacted]	
NOAEL:	no observed adverse effect level
NSAID:	nonsteroidal anti-inflammatory drug
PBMC:	peripheral blood mononuclear cell(s)
PCSA:	Potentially clinically significant abnormality
PD:	pharmacodynamic(s)
[redacted]	
PK:	pharmacokinetic(s)
PNS:	peripheral nervous system
pSjS:	primary Sjögren's syndrome
q2w:	once every 2 weeks
RF:	rheumatoid factor
rhsCD40L:	recombinant human soluble cluster of differentiation 40
[redacted]	
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SARS-CoV-2:	severe acute respiratory syndrome coronavirus-2
SC:	subcutaneous(ly)
SjS:	Sjögren's syndrome
SoA:	Schedule of Activities
SUSAR:	suspected unexpected serious adverse reaction
$t_{1/2z}$:	terminal half-life
TDAR:	T-cell dependent antibody response
TEAE:	treatment-emergent adverse event
Th:	T helper
t_{max}:	time to maximum concentration

ULN: upper limit of normal
VAS: visual analogue scale
VDS: verbal descriptor scale
WOCBP: women of childbearing potential

10.9 APPENDIX 9: PROTOCOL AMENDMENT HISTORY

Amended protocol 01 (27 August 2020)

This amended protocol (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of the amendment is to have minor adjustments in the exclusion criteria E01, E11, E14, and E30 to address comments raised by the EU participating National Competent Authorities during review of the clinical trial application, via the Voluntary Harmonisation Procedure. It was clarified that participants with any autoimmune disease (except primary Sjögren's syndrome and Hashimoto thyroiditis) are excluded from the study (E01), that participants with an addiction history within the last year are excluded from the study (E14). In addition, it was specified, that participants with a history of hypersensitivity against humanized monoclonal antibodies are excluded from the study (E11), as well as participants with known hypersensitivity to any constituent of the IMP (E30). Finally, clarification of minor discrepancies are also being addressed in this amendment, as well as minor editorial and document formatting revisions.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Multidimensional Fatigue Inventory (MFI) at Screening deleted.	Correction of the timepoint. Assessment was not planned at screening (typing error) and would add additional burden to participants, as assessment is not necessary at this timepoint.
5.2 Exclusion criteria	E 01. Any autoimmune disease (except **p**SjS and Hashimoto thyroiditis) with or without secondary SjS.	Clarification that participants with any autoimmune disease (except primary Sjögren`s syndrome [pSjS] and Hashimoto thyroiditis) are excluded from this study.
5.2 Exclusion criteria	E11. History of a systemic hypersensitivity reaction or significant allergies, other than localized injection site reaction, to any ~~biologic molecule~~ **humanized monoclonal antibody**.	Clarification that participants with a history of a systemic hypersensitivity reaction or significant allergies against humanized mAb are excluded from the study to increase subject safety.
5.2 Exclusion criteria	E14. ~~Current~~ Substance abuse (including cannabis) and/or alcohol abuse, **current or in the last year**.	Adapted that participants with a 1-year addiction history are excluded as well.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	E 30. ~~Sensitivity~~ **Hypersensitivity** to any of the IMPs, **including** ~~or components~~ **any constituent** thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study	Adaption for clarification.
7.1.2 Temporary discontinuation.	For all temporary IMP discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF. Planned visits should take place as scheduled, if possible, during this period of discontinuation. **Temporary IMP discontinuation can appear only once per subject/treatment period. [….].** A discontinuation of IMP greater than 30 days **+ 2 days (according to the visit window)** will be considered definitive and relevant eCRF sections should be populated.	Specification is added for clarification and according to the visit window.
9.2 Sample size determination	Assuming a variability of[redacted] and an effect size of[redacted], **as derived based on (38),** a sample size of 80 evaluable participants results in an overall probability [redacted].	Reference is added for clarification.
10.4 Appendix 4	However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>ULN as defined by central laboratory readout ~~40 IU/L or mIU/mL~~) is required.	Discrepancy with Inclusion criteria I09 was corrected.

pSjS: primary Sjögren`s syndrome, IMP: investigational medicinal product, e-CRF: electronic case report form, FSH: follicle-stimulating hormone, mAb: monoclonal antibody, ULN: upper limit of normal.

Amended protocol 02 (28 July 2021)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of the amendment is to have an adjustment in the inclusion criterion I03 and to allow re-screening for I06 to better reflect the participant population to aid recruitment without compromising on safety requirements. In addition, Section 9.5 (Interim analysis) was extended with an early analysis after all participants have completed their End of Treatment/ Week 12 visit, to allow for internal decision making. Further Section 6.2 was adapted to allow destruction of vials according to local regulations and a reference to the pharmacy manual was added. Finally, clarification of discrepancies are also being addressed in this amendment, as well as minor editorial and document formatting revisions.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
2.2.2.2 Clinical data [redacted]	[redacted] is a completed ~~a~~ Phase 1, double-blind, randomized, parallel design, placebo-controlled single ascending dose study […].	Correction of a typing error.
2.2.2.2 Clinical data [redacted]	[redacted] is a ~~concluded~~ **completed** Phase 1, double-blind, randomized, placebo-controlled multiple ascending dose study [….].	Adapted: [redacted] is completed.
2.3.3. Overall benefit: risk conclusion	No safety or tolerability concerns have been identified in the ~~ongoing~~ Phase 1 first in human studies.	Adapted: Phase first-in human studies are completed.
5.1 Inclusion criteria	I 03. Disease duration since first diagnosis of pSjS ≤ ~~7~~ **15** years based on medical history.	Adjustment to more accurately reflect the pSjS population.
5.4 Screen Failures Table 3	I06 is added to Inclusion criteria leading to screen failure, which are permitted for rescreening. With the following footnote:" **Re-Screening of I06 is permitted if in the investigator`s discretion due to disease activity a change of these parameters could be expected**."	Adjustment to more accurately reflect the pSjS population.
6.2 Preparation/ handling/ storage/ accountability	T~~he used vials will be kept by the Pharmacist in a secure location up to the full documented reconciliations performed with the Sponsor at the end of the study. The Pharmacist should wait for the written approval form from the Sponsor before proceeding with their destruction. Any annotation on the vials should be considered as source documents until the time of vial destruction~~. **Handling of used vials is described in the pharmacy manual.**	Adaption to allow destruction of vials according local regulations. Reference to the pharmacy manual added.
6.3 Measures to minimize bias: Randomization and blinding	If the Investigator decides that the unblinding is warranted, **he/she may, at his/her discretion, contact Sponsor to discuss the situation** ~~the Investigator should make every effort to contact the Sponsor~~ prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment of the participant.	Adapted due to adapted Sponsor wording.
7.1.2 Temporary discontinuation	A discontinuation of IMP greater than 30 days + 2 days (according to the visit window) will **be** considered definitive and relevant e-CRF sections should be populated.	Correction of a typing error.
8.5 Pharmacokinetics	Blood samples ~~of approximately 2 mL~~ will be collected for measurement of plasma concentrations of SAR441344 as specified in the SoA.	For clarification. Details will be in the laboratory manual. A maximum amount of blood collection will not exceed 500 mL over the duration of the study (see Section 8).

Section # and Name	Description of Change	Brief Rationale
8.7.1 Deoxyribonucleic acid	A ~~3 mL~~ whole blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study at Baseline	For clarification. Details will be in the laboratory manual. A maximum amount of blood collection will not exceed 500 mL over the duration of the study (see Section 8).
8.7.2 Ribonucleic acid	At the study visits specified in the SoA (Section 1.3), a ~~2.5 mL~~ RNA blood samples will be collected and stored from consenting participants.	For clarification. Details will be in the laboratory manual. A maximum amount of blood collection will not exceed 500 mL over the duration of the study (see Section 8).
8.9 Immunogenicity assessments	Antidrug antibodies to SAR441344 will be evaluated in serum samples ~~(3.5 mL per sample)~~ collected from all participants according to the SoA.	For clarification. Details will be in the laboratory manual. A maximum amount of blood collection will not exceed 500 mL over the duration of the study (see Section 8).
9.3 Populations for analyses	Table◦5 - Populations for analyses: ~~Enrolled: All participants who sign the ICF.~~ **Screened: All participants who sign the ICF.** Randomized: ~~All enrolled participants who are randomly assigned to the IMP~~. **All participants from screened population who have been allocated to a randomized intervention (by IRT) regardless of whether the intervention was received or not. Participants treated with the study intervention without being randomized or before the randomization will not be considered as randomized.** **ADA: All randomized participants treated with SAR441344 with at least one post-baseline ADA result (positive, negative or inconclusive).**	Adaptation to follow current standards in population definition and adding a missing population (ADA) needed for analysis.
9.5. Interim Analyses	~~In all scenarios mentioned above~~ **For this interim analysis**, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding. ~~The~~ **A separate SAP for this interim analysis, if performed**, will describe the **corresponding** analyses to be performed at interim in greater detail, ~~if it is to be performed~~.	For clarification.
9.5 Interim Analyses	**Once all participants have completed their EoT (Week 12) visit, selected sponsor personnel including study statistician and study programmer may be unblinded to generate initial reports (early analysis) based on the final SAP for internal decision making. Details of the personnel to be unblinded will be documented separately.**	Adaption to allow for internal decision making while keeping the blind once all subjects have completed their EoT visit.

ADA: Anti-drug antibodies, EoT: End of treatment, pSjS: primary Sjögren`s syndrome, SAP: statistical analysis plan, SoA: Schedule of Assessments.

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