I.R.I.S.

Institut de Recherches Internationales Servier

Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	**A phase IIa efficacy and safety trial with intravenous S95011 in primary Sjögren's Syndrome patients.** **An international, multicentre, randomised, double-blind, placebo-controlled study.**
Study public title	**Efficacy and safety of S95011 in primary Sjögren's Syndrome patients.**
Test drug code	**S95011**
Indication	**Primary Sjögren's Syndrome**
Development phase	**Phase II**
Protocol code	**CL2-95011-001**
EudraCT Number	**2020-001526-59**
Universal Trial Number	**Not Applicable**
Other register number (ISRCTN, CT. gov…)	**NCT04605978**
Investigational New Drug Application Number	**147638**
Sponsor	**INSTITUT DE RECHERCHES INTERNATIONALES SERVIER (I.R.I.S.)**
Date of the document	**24 March 2022**
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Substantial Amendment(s) integrated

No.	Final version date	Countries concerned
1	12/10/2020	All
2	24/03/2022	All

CCI [redacted]

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VERSION LIST

Protocol No.	Substantial amendment No.	Final version date	Countries concerned	Nature of modifications
1.0	NA	03/07/2020	ALL	Not Applicable
1.1	NA	21/08/2020	GBR	See Appendix 8
	NA	01/09/2020	USA	Revised protocol including modifications requested by the FDA: - Implementation of a Data Safety Monitoring Board (DSMB) - Removal of the stopping rules (DSMB recommendations will be followed for the decision to prematurely discontinue or temporary halt the study for safety reasons) - Modification of the AEs list leading to premature discontinuation of the IMP
2.0	1	12/10/2020	ALL	- Implementation of a Data Safety Monitoring Board (DSMB) - Removal of the stopping rules (DSMB recommandations will be followed for the decision to prematurely discontinue or temporary halt the study for safety reasons) - Removal of appendix 8 of version V.1.1 (GBR) and replacement by Appendix 8: "Instructions to investigator for handling data rights requests" - Addition of an ECG at W010. - Extension of the screening period to 4 weeks for allowing central lab results availability and addition of a blood sample for blood cell count and CRP if ASSE visit is performed more than 14 days prior W000 for safety reason. - Addition of Section 4.4.2 about premature discontinuation of the study in an investigator site (early site closure) - Modification of the exclusion criteria concerning prior administration of rituximab or other B cell depleting agents *e.g.* VAY736

				- Modification of the last bullet and addition of 2 bullets in the exclusion criteria 31: • Cevimeline or oral pilocarpine: any increase or initiation of new doses within 2 weeks prior to randomisation (W000) • Ocular topics (excluding artificial tears, gels, lubricants, antibiotherapy): any dose modification or initiation of new doses within 90 days prior to randomisation (W000) • Required regular use of medications known to cause dry mouth/eyes as a regular and major side effect, and which have not been on a stable dose for at least 30 days prior to randomization (W000), or any anticipated change in the treatment regimen during the course of the study - Addition of a paragraph about rescue treatment - Modification of the AEs list leading to premature discontinuation of the IMP - Addition that study drug dose adjustments and/or interruptions are not allowed in the study. In case of delay in dosing administration, continuation of IMP should be discussed and agreed with the sponsor. - Modification of the reporting rules regarding the symptoms related to pSS - Other clarifications or precisions, and correction of typo errors - Precisions about the storage duration of ADA, PK, RO and exploratory blood samples - Addition of Appendix 9: Section about Trial Conduct During National or International Public Health Emergency - For US IND: Clarification for ESSDAI assessment (Section 7.2-immune panel) as well as correction of minor typos in Appendix 3 as not part of the protocols dated June 9, 2020 and September 1, 2020.

3.0	NA	26/02/2021	ALL	Integration of modifications indicated in the non-substantial amendment dated on 26 FEB. 2021: - Simplification of the "Section 6.1. IMP administered" to refer to the pharmacy manual for instructions for handling Investigational Medicinal Product (IMP), - Update of study initiation and completion dates, - Extension of the window to perform lip biopsy at W013 visit, - Clarification on authorized vaccines, - Correction regarding materials to be used for Ocular Staining Score, - Clarification on the reporting of fatals AEs occurring after the signature of ICF and before IMP intake, - Precision on archiving of electronic clinical outcome assessment (eCOA), - Correction of typo errors.
4.0	2	24/03/2022	ALL	Update of exclusion criterion No. 30 (wash out period added in case of rituximab or other B cell depleting agents, JAK inhibitors forbidden) - The planned date of the First Visit First Patient (FVFP) and of the Last Visit Last Patient (LVLP) have been updated - The exclusion criteria No. 17 has been updated regarding the exclusion period in case of participation in another clinical study - CD19 B cell count performed locally to check exclusion criterion No. 30 - Previous and concomitant treatments according to exclusion criteria No. 31 added for medications known to cause dry on mouth/eyes - Oversight of a physician on safety data collected on electronic Case Report Form (e-CRF) has been updated - Other modifications were done for clarifications or corrections

				- Integration of modifications indicated in the non-substantial amendment No. 1 dated on 26 FEB. 2021 (cf details listed above for CSP amended 3.0). *Of note, these modifications have been previously integrated in the CSP amended 3.0 according to local regulation for US and Canada*

SYNOPSIS

Name of the sponsor: I.R.I.S.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Not applicable	**Volume:**	
Name of Active Ingredient: S95011	**Page:**	

Title of study: A phase IIa efficacy and safety trial with intravenous S95011 in primary Sjögren's Syndrome patients.
An international, multicentre, randomised, double-blind, placebo-controlled study.

Study Public Title: **Efficacy and safety of S95011 in primary Sjögren's Syndrome patients**
Protocol No.: CL2-95011-001

Coordinators and Investigator
National coordinators and investigators: listed in a separate document

Study centre(s):
Approximate total number of centers = 25
Approximate total number of countries = 8

Study period: Study duration for the patient: max 32 weeks Study initiation date (planned FVFP): Q3 2021 Study completion date: (planned date of LVLP): Q4 2022	**Study development phase: II**

Objective(s):
Primary objective of the study is: to assess the effect of multiple intravenous infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment in reducing disease activity using European League Against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI).

Secondary objectives are:
To evaluate efficacy of multiple intravenous infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment on:

- Patient's symptoms using EULAR Sjögren Syndrome patient reported Index (ESSPRI),
- Fatigue using the Multidimensional Fatigue Inventory (MFI),
- Quality of life (QoL) using Short Form Health Survey (SF-36),
- Physician's global assessment (PhGA) of the disease activity using a 0 to 10 numerical rating scale (NRS),
- Patient's global assessment (PGA) of the disease activity using a 0 to 10 numerical rating scale (NRS,)
- Tear gland function using the Schirmer test,
- Tear gland function using Ocular Staining Score (OSS),
- Salivary gland function measured by sialometry under unstimulated and stimulated conditions.

To assess the safety and tolerability of multiple intravenous infusions of S95011.
To assess the pharmacokinetics (PK) of S95011 in serum.
To assess pharmacodynamics [receptor occupancy (RO)] of S95011 in blood.
To determine the incidence of anti-drug antibodies (ADA) formation.

Exploratory objectives are:

- To explore the potential effect of S95011 on lymphocytes subsets in particular T cell subsets,
- To explore the potential effect of S95011 on some proteins involved in pSS physiopathology like IL-7, cytokines, specific proteins in blood,
- To explore the potential effect of S95011 on immune panel, auto-antibody panel and β2 microglobulin,
- To explore the drug exposure and perform exploratory histology and biomarkers assessments on minor salivary glands tissue by performing lip biopsies (optional),

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- To set a biocollection to explore further the potential impact of S95011 on PBMC, extracted RNA and blood according to the advancement of the knowledge on the drug and the disease (optional sampling).

Methodology:
This is a phase IIa, international, multicentre, randomised (2:1), double-blind, placebo-controlled study.
The study will consist of:

- **Screening period without study treatment:** within 28 days prior to W000, after signing the informed consent, in order to check eligibility of patients.
- **Randomised and double-blind treatment period**: from W000 to W013 (study drug administration at W000, W002, W004, W007, W010) with 2-parallel groups (750 mg of S95011 and matching placebo), with stratification by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (*e.g.* chloroquine, hydroxychloroquine, quinacrine) (yes/no).
- **Safety follow up period without study treatment**: 15 weeks with one visit at W019 and one at W028. This follow-up period will allow sufficient time for monitoring safety until 5 half-lives of S95011. In addition, it is anticipated that more than 97% of patients have RO < 95% at W028 (meaning that almost no pharmacological effect of the product is expected).

Number of included patients:
Planned: 45 patients (30 patients with S95011 ; 15 patients with placebo)

Diagnosis and main criteria for inclusion:
The target population is male or female patients suffering from primary Sjögren's Syndrome with moderate to high activity disease level (*i.e.* systemic manifestations).
Main inclusion criteria are:
Male or female aged between 18 to 75 years (both inclusive), body mass index (BMI) of 18 (exclusive)-40 (inclusive), diagnosed for primary Sjögren's Syndrome based on 2016 American College of Rheumatology (ACR)-EULAR criteria, with an ESSDAI total score ≥ 6 during screening, with at least 6 points scored within the 7 following domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematologic and biologic. They should have at screening positive anti-SSA (Ro) antibodies or anti-nuclear antibodies (ANA) ≥ 1:320 or rheumatoid factor (RF) >20 IU/ml, and stimulated whole salivary flow rate >0 mL/minute.
Main exclusion criteria are:
Prior administration of belimumab or rituximab or other B cell depleting agents or abatacept or tumor necrosis factor inhibitors or cyclophosphamide (or any other alkylating agent) or cyclosporine (except for eye drops), or tacrolimus, or sirolimus, or mycophenolate mofetil (MMF), or azathioprine, or leflunomide in the past 3, 6, 12, or 24 months (depending on the drug agent) prior to randomisation (W000),
Corticosteroids > 10 mg/day oral prednisone (or equivalent) within 4 weeks prior to W000; any change or initiation of new dose of antimalarials (*e.g.* chloroquine, hydroxychloroquine, quinacrine) within 16 weeks prior to (W000), methotrexate > 25 mg/week; and any initiation or change of dose of methotrexate within 12 weeks prior to W000.

Test drug: S95011 – Dose: 750 mg
Dosage form: 2 mL extractable volume vials containing 100 mg of S95011 (50 mg/mL) concentrate for solution for intravenous administration.
The administration schedule is one IV infusion every 2 weeks (q2w) for the first month (W000, W002, W004) and then every 3 weeks (q3w) until W010 (W007, W010).

Comparator: placebo
2 mL extractable volume matching vials containing concentrate for solution for intravenous administration.
The administration schedule is one IV infusion every 2 weeks (q2w) for the first month (W000, W002, W004) and then every 3 weeks (q3w) until W010 (W007, W010).

Duration of treatment:
Run-in period: No treatment up to 4 weeks of screening period
Active treatment period: 13 weeks (last administration at W010)
Follow-up period: no treatment during 15 weeks

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Criteria for evaluation:

Efficacy measurements:

Primary efficacy endpoint(s):

Change from baseline in ESSDAI total score to W013.

Secondary efficacy endpoints:

- ESSDAI score by domain and total score at each visit (value & change).
- ESSPRI score by symptom and total score at each visit (value & change).
- Proportion of patients with ≥ 3 points, ≥ 5 points, ≥ 7 points of improvement from baseline in ESSDAI at each visit.
- Proportion of patients with ≥ 1 point, ≥ 2 points, ≥ 3 points of improvement from baseline in ESSPRI at each visit.
- Proportion of patients with ≥ 3 points of improvement in ESSDAI and with ≥ 1 point of improvement in ESSPRI from baseline at each visit.
- Fatigue (MFI), quality of life (SF-36), physician and patient's global assessment of the disease activity (NRS) at each visit (value and change).
- Tear gland function: Schirmer's test and in OSS at each visit (value and change).
- Salivary gland function: unstimulated and stimulated salivary flow rate at each visit (value and change).

Other secondary endpoints

Safety: the safety and tolerability assessed by incidence of adverse events (AEs), changes over time in safety parameters (vital signs, ECG, biological laboratory) and incidence of abnormal safety parameters throughout the study.

Pharmacokinetics: concentration of S95011 will be measured in serum samples

- Pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007, and W010.
- Right after the end of the IMP infusion and in the [1-3h] interval after the end of the IMP infusion at W000 and W010.
- Between W011 and W012, and at W013, W016, W019 and W028.

Other measurements:

Receptor occupancy (RO): RO will be measured in blood samples taken pre-dose (before the start of the infusion) at W000, W002, W004, W007 and W010, right after the end of the infusion of the IMP at W000 and W010, and at W013, W019, W028.

Anti-drug antibodies (ADA): ADA will be measured in serum samples taken pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007 and W010, and at W013, W019, W028.

Exploratory endpoints:

In order to improve the knowledge of the study drug,

In blood

- Lymphocytes subsets (PBMC) assessed at W000, W004, W007, W013.
- IL-7 and some cytokines will be measured at W000, W002, W004, W007, W010, W013, W019, W028.
- Other specific proteins involved in the pSS physiopathology will be measured at W000, W004, W013.
- Cytokine release panel at W000 and W002.

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- Immune panel at ASSE, W000, W004, W013.
- Auto antibody-panel at ASSE, W013.
- β2 microglobulin at W000, W004, W013.

In salivary glands:

- Lip biopsy for salivary gland collection (S95011 concentration, exploratory histology and exploratory biomarkers assessments). One optional biopsy performed at W013.

Data Safety Monitoring Board:

An independent external Data Safety Monitoring Board (DSMB) will be put in place in order to review the safety and tolerability data of the investigational drug on a regular basis. The functioning of this DSMB will be specified in a separate DSMB charter.

Contractual signatories	
I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice (GCP) and the applicable regulatory requirements. *INVESTIGATOR:*	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
HEAD OF IMMUNOINFLAMMATORY CLINICAL DEVELOPMENT:	
NAME	PPD
DATE	
SIGNATURE	
Other sponsor's signatories	
BIOSTATISTICS HEAD OR DESIGNEE:	
NAME	PPD
DATE	
SIGNATURE	

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List of abbreviations

Ab	:	Antibody
ACR	:	American College of Rheumatology
ADA	:	Anti-Drug Antibody
ADCC	:	Antibody-Dependent Cell-mediated Cytotoxicity
ADL	:	Activities of Daily Living
AE	:	Adverse Event
AEOSI	:	Adverse Event Of Special Interest
AEX	:	Anion Exchange Chromatography
ANA	:	Anti-Nuclear Antibodies
Anti-SSA (Ro)	:	Anti-Sjögren's Syndrome A Antibodies
ALT	:	ALanine aminoTransferase
aPPT	:	Activated Partial Thromboplastin Time
AST	:	ASpartate aminoTransferase
AUC	:	Area Under the Curve
AUEC	:	Area Under the Effect vs time Curve over the dosing interval
ASSE	:	Selection visit
BMI	:	Body Mass Index
bpm	:	beats per minute (heart rate unit)
Cav	:	median average Concentration over a period of time
CCF	:	Cell Culture Filtrate
CDC	:	Complement-Dependent Cytotoxicity
CD1a	:	Cluster of Differentiation 1a
CD127	:	interleukin-7 receptor-α
CD208	:	Dendritic cell-lysosomal associated membrane protein
CDR	:	Complementarity-Determining Region
CEX	:	Cation Exchange Chromatography
CHO	:	Chinese Hamster Ovary
CK	:	Creatine Kinase
cm	:	Centimetre
CISO	:	Chief Information Security Officer
CMP	:	Clinical Monitoring Plan
Cmax	:	Maximum Concentration
CNS	:	Central Nervous System
CPMP	:	Committee for Proprietary Medicinal Products
CRF	:	Case Report Form
e-CRF	:	Electronic Case Report Form

CRO	:	Contract Research Organisation
CRP	:	C-Reactive Protein
CSR	:	Clinical Study Report
CTCAE	:	Common Terminology Criteria for Adverse Events
CV	:	Curriculum Vitae
D	:	Day
DAP	:	Data Analysis Plan
DBP	:	Diastolic blood pressure
dL	:	decilitre
DL_{CO}	:	Diffusing-capacity of the Lung for Carbon monOxyde
DP	:	Drug Product
DPO	:	Data Protection Officer
DRF	:	Dose Range Finding
DS	:	Drug Substance
DSMB	:	Data Safety Monitoring Board
DSP	:	Downstream Process
DTH	:	Delayed Type Hypersensitivity
ECG	:	Electrocardiogram
e-COA	:	electronic Clinical Outcome Assessment
ECLIA/MSD	:	Electrochemiluminescence assay/Meso Scale Discovery
EEA	:	European Economic Area
e-PRO	:	electronic Patient Reported Outcome
e.g.	:	Exempli gratia (for example)
eGFR	:	estimated Glomerular Filtration Rate
ELISA	:	Enzyme-Linked ImmunoSorbent Assay
EMG	:	Electromyography
ERIN	:	Event Requiring Immediate Notification
ESSDAI	:	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	:	EULAR Sjögren's Syndrome Patient Reported Index
ESR	:	Erythrocyte Sedimentation Rate
EULAR	:	European League against Rheumatism
FIH	:	First-In-Human
FU	:	Follow-up (period)
FVC	:	Forced Vital Capacity
g/dL	:	Grams per Decilitre
GCP	:	Good Clinical Practice
GLP	:	Good Laboratory Practice
GGT	:	Gamma Glutamyl Transferase

GSK	:	GlaxoSmithKline
GVHD	:	Graft Versus Host Disease
HBs	:	Surface antigen of Hepatitis B virus
HbA1c	:	glycated Haemoglobin
HBV	:	Hepatitis B Virus
HC	:	Heavy Chains
HCP	:	Host Cell Protein
HCV	:	Hepatitis C Virus
HIS	:	Human Immune System
HIV	:	Human Immunodeficiency Virus
HRCT	:	High Resolution Computer Tomography
HV	:	Healthy Volunteers
ICF	:	Information Consent Form
ICH	:	International Conference on Harmonisation
ID	:	Identity
IDR	:	Intradermal Reaction
i.e.	:	id est (that is)
IE	:	Intercurrent Event
IFNγ	:	Interferon gamma
i.p.	:	intraperitoneal
IEC	:	Independent Ethics Committee
Ig G	:	Immunoglobulin G
IGRA	:	Interferon Gamma Release Assay
IL-7	:	Interleukin 7
IL-7Rα	:	Alpha chain of the Interleukin 7 (IL-7) Receptor (= CD127)
ILC	:	Innate Lymphoid Cell
IMP	:	Investigational Medicinal Product (S95011/Placebo)
I.R.I.S.	:	Institut de Recherches Internationales Servier
IRB	:	Institutional Review Board
IUD	:	IntraUterine (contraceptive) Device
IU/ml	:	International Unit/millilitre
IV	:	Intravenous
IWRS	:	Interactive Web Response System
JAK	:	Janus Kinase
kg	:	kilogram
L	:	Litre
LC	:	Light chains
LDH	:	Lactate DeHydrogenase

LFS	:	Labial Focus Score
LLOD	:	Lower Limit Of Detection
LLOQ	:	Lower Limit Of Quantification
LVLP	:	Last Visit Last Patient
MAA	:	Marketing Authorization Application
mAb	:	Monoclonal Antibody
MAD	:	Multiple Ascending Dose
MAH	:	Marketing Authorization Holders
MAR	:	Missing At Random
MedDRA	:	Medical Dictionary for Regulatory Activities
MNAR	:	Missing Not At Random
mPBPK	:	minimal PBPK
MFI	:	Multidimensional Fatigue Inventory
mg	:	milligram
min	:	minute
mL	:	Millilitre
mm	:	Millimetre
MMF	:	Mycophenolate mofetil
mmHG	:	Millimetre of mercury
NaCl	:	Sodium Chloride
NHP	:	Non-Human Primate
NK	:	Natural Killer cells
NOAEL	:	No Observed Adverse Effect Level
NOD SCID	:	Non Obese Diabetic/Severe Combined Immune Deficiency
NRS	:	Numerical Rating Scale
NSAID	:	Non-steroidal anti-inflammatory drugs
NSG mice	:	NOD SCID Gamma mice
OSE-127-biot	:	biotine conjugated form of OSE-127
OSS	:	Ocular Staining Score
PBMCs	:	Peripheral Blood Mononuclear Cells
PBPK	:	Physiologically Based Pharmacokinetic
PD	:	Pharmacodynamics
PEE	:	Punctate epithelial erosions
PF	:	Pfizer
PK	:	Pharmacokinetics
PGA	:	Patient’s global assessment
PhGA	:	Physician’s global assessment
PNS	:	Peripheral Nervous System

PoC	:	Proof of Concept
PSS	:	Primary Sjögren's Syndrome
pSTAT5	:	Phosphorylated Signal transducer and activator of transcription 5
PT	:	Prothrombin Time
QoL	:	Quality Of Life
QTc	:	QT interval corrected for heart rate
RBC	:	Red Blood Cells
RF	:	Rheumatoid Factor
RNA	:	RiboNucleic Acid
RO	:	Receptor Occupancy
RS	:	Randomised Set
SAD	:	Single Ascending Dose
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SBP	:	Systolic Blood Pressure
SC	:	Subcutaneous
SF-36	:	Short Form Health Survey
SLE	:	Systemic Lupus Erythematosus
SRBC	:	Sheep-Red Blood Cells
SSA	:	Sjögren's syndrome A
STAR	:	Sjögren's syndrome Tool for Assessing Response
STAT5	:	Signal Transducers and Activator of Transcription 5
TARC	:	thymus- and activation-regulated chemokine
TB	:	Tuberculosis
TEAE	:	Treatment Emergent Adverse Event
Teff	:	Effector T cells
Th2	:	T-helper type 2
TK	:	Toxicokinetic
TMDD	:	Target Mediated Drug Disposition
TNBS	:	2,4,6-trinitrobenzenesulfonic acid
TNFα	:	Tumor Necrosing Factor
Tregs	:	Regulatory T cells
TSLP	:	Thymic Stromal LymphoPoietin
TU	:	Therapeutic Units
TUTF	:	Therapeutic Unit Tracking Form
UC	:	Ulcerative Colitis
ULN	:	Upper Limit of reference range
ULOD	:	Upper Limit Of Detection

US	:	United States
W	:	Week
WBC	:	White Blood Cells
WD	:	Withdrawal
WHO-Drug	:	World Health Organization, Drug Dictionary
WMA	:	World Medical Association
WOCBP	:	Woman of Child Bearing Potential

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-sponsor parties, sponsor parties and CRO responsible for local management of the study are described in a separate document entitled Administrative part of clinical study protocol.

The list of investigators for each country is given in separate documents attached to the protocol and entitled "List of investigators for [name of the country]".

2. BACKGROUND INFORMATION

Primary Sjögren's syndrome:

Primary Sjögren's Syndrome (pSS) is one of the commonest chronic systemic autoimmune diseases, with a female-to-male predominance of 9:1 and peak incidence in women aged between 55 and 65 years. The estimated prevalence of pSS worldwide is 60.82 *per* 100 000 inhabitants according to a meta-analysis of epidemiological studies in primary Sjögren's Syndrome (Qin *et al*, 2015).

pSS is characterized by lymphocytic infiltrates of salivary and lacrymal glands leading to xerostomia and xerophthalmia associated with fatigue and pain. These symptoms are present in more than 80% of the patients with this disease, with a major effect on quality of life and loss of work productivity, primarily because of disabling fatigue. At present, pSS is diagnosed using the 2016 American College of Rheumatology (ACR)–European League against Rheumatism (EULAR) classification criteria which require the presence of anti-SSA (Ro) antibodies in serum and/or focal lymphocytic sialadenitis in labial salivary gland biopsy (Shiboski *et al*, 2017).

Systemic manifestations occur in approximately 30 to 40% of the patients with pSS. They can affect different organs or systems such as joint, lung, nervous system, kidney or non-exocrine glands such as the thyroid (Rosas *et al*, 2019). The risk of B-cell lymphoma is 15 to 20 times higher among pSS relative to the general population (Mariette *et al*, 2018), with 2.7% to 9.8% patients eventually developing lymphomas (Rosas *et al*, 2019). Thus, the clinical phenotype of pSS varies significantly between patients and over time.

pSS is considered to be a multifactorial disease, in which environmental factors trigger inflammation in genetically prone individuals. The exact pathophysiological mechanisms of the disease are not yet fully elucidated. A complex interplay of immune cell types such as T-cells, B-cells, dendritic cells, monocytes/macrophages and NK cells and their effector molecules, is thought to cause the disease, leading eventually to B-cell hyperactivity, autoantibody production and formation of germinal center-like structures in the salivary glands (Van der Heijden *et al*, 2018).

To date, no systemic treatment has been proven effective in altering the course of pSS and the medical need of pSS remains unmet. The treatment of pSS mostly relies on symptomatic agents (Nocturne *et al*, 2015). Severe organ manifestations are treated in accordance with guidelines for systemic lupus erythematosus and other connective tissue disorders. Agents that are commonly used include steroids, hydroxychloroquine, immunosuppressants (including methotrexate, mycophenolate sodium, azathioprine and cyclosporine) (Mariette *et al*, 2018) but the evidence-based medicine demonstrating the efficacy of these drugs is scarce (Nocturne *et al*, 2015; Saraux *et al*, 2016; Del Papa *et al*, 2018). One recent study suggested the clinical efficacy for leflunomide and hydroxychloroquine combination therapy. However, this study has to be confirmed by larger randomised clinical trials (Radstake *et al*, 2018).

Given the key role of chronic B cell activation, studies are conducted with B cell-targeted therapies. Up to now, the first studies conducted with rituximab failed to reach their primary endpoints of efficacy, but some secondary outcome measures were improved (Nocturne *et al*, 2015). Methodological progresses in conducting the studies and validation of new primary endpoints (ESSDAI, ESSPRI) could help to demonstrate treatment efficacy. In the light of a better understanding of pSS pathophysiology, new approaches are currently investigated including T cell costimulation and inhibition of ectopic germinal centre formation (Bombardieri *et al*, 2018).

IL-7 and IL-7R

S95011 (also called OSE-127) is a humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) conjointly developed by OSE Immunotherapeutics and Servier. S95011 targets CD127, the α chain of the Interleukin 7 (IL-7) receptor (IL-7R), and blocks access of IL-7 to the IL-7R. IL-7 is a limiting and non-redundant cytokine that is mainly produced by epithelial and stromal cells in non-hematological tissues (intestinal epithelium, lungs, skin) and in thymus. It regulates T cell homeostasis, proliferation and survival (Mackall *et al*, 2011; Lundstrom *et al*, 2013) for both memory and naïve T cell subsets. Upon activation, IL-7R delivers proliferative and anti-apoptotic signals. Almost all conventional mature T lymphocytes express high levels of IL-7R, with the notable exception of naturally-occurring regulatory T cells (Tregs). This specific expression pattern provides an opportunity for a selective targeting of pathogenic effectors while preserving regulatory immune mechanisms (Seddiki *et al*, 2006; Liu *et al*, 2006).

IL-7 may be a driving factor for the persistence of autoimmune disease (Dooms, 2013) and targeting IL-7R . may be beneficial for inflammatory conditions (Dooms, 2013; Katzman, *et al*, 2011). In pSS, the cytokine IL-7 is prominently expressed in the labial salivary glands (Bikker *et al*, 2010). IL-7 seems to contribute to local T cell dependent B cell activation in patients. In particular, based on *in vitro* data, it is suggested that IL-7 associated with an increased number of IL-7Rα T cells could lead to an increased and continuing pro-inflammatory response (as IFNγ and IL-17A cytokines) in salivary glands of patients with pSS (Bikker *et al*, 2010), thus leading to tissue destruction. In concordance with these findings, elevated numbers of IL-7-producing cells in patients with pSS correlate with increased glandular inflammation, as indicated by an increased labial focus score (LFS) and a decreased percentage of IgA+ plasma cells in labial salivary glands (Bikker *et al*, 2010). In addition, in the labial salivary gland of patients, increased numbers of CD4+ and CD8+ IL-7Rα cells are found in comparison to non Sjögren-sicca patients and increased IL-7Rα expression on T cells in the labial salivary glands of pSS patients was associated with the severity of glandular inflammation (*i.e.* sialadenitis) (Bikker *et al*, 2012). Moreover, IL-7Rα cells numbers also strongly correlate with IL-7 expression, numbers of CD3 T cells, CD20 B cells, and CD1a and CD208 myeloid dendritic cells (Bikker *et al,* 2012). At serum level, soluble IL-7Rα concentrations are significantly higher in pSS patients compared to healthy controls (Hillen *et al,* 2016). In addition, Innate Lymphoid Cells (ILCs), known to produce pro-inflammatory cytokines, are also CD127+ and hence represent a valid cell target to inactivate in order to decrease tissue response to inflammation (Wenink *et al,* 2017). Collectively, S95011 is expected to inhibit IL-7 dependent T-cell as well as ILC responses in pSS patients.

Preclinical data

Based on data of Hz-127 mAb, the first humanized IgG4 antibody, S95011 drug presented good binding and affinity toward recombinant human CD127 *in vitro*. It presented a full antagonistic activity by dose-dependently inhibiting the IL-7-induced STAT5 phosphorylation and the IL-7-dependent T cells proliferation. The drug presented no cytotoxic activity (ADCC) and no complement-dependent cytotoxicity based on IgG4 properties (Davies & Sutton, 2015) and a weak effect on TSLP activity on dendritic cells (weak inhibition of TARC secretion, as IL-7Rα is also used as part of the Thymic Stromal Lymphopoietin receptor). In order to complete this data set, a thorough side by side analysis was performed to compare Hz-127 and S95011 (or OSE-127) regarding in vitro potency (ELISA), affinity, productivity and trend to aggregation. This analysis revealed similar potency and affinity for both mAbs but S95011 demonstrated higher productivity and was less prone to aggregation as compared to Hz-127, validating the sequence optimization process and confirming S95011 as the final lead candidate for further preclinical and clinical development. Potency of S95011 on inhibition of the IL-7-induced STAT5 phosphorylation was further confirmed in human volunteers and was demonstrated to be similar in Peripheral Blood Mononuclear Cells (PBMCs) of Sjögren patients. A strong correlation between IL-7 receptor occupancy (RO) and signaling inhibition (pSTAT5) was also observed in PBMCs of human volunteers and Sjögren patients. These data in connection with the fact that receptor occupancy profiles of S95011 in cynomolgus monkey were found similar with RO observed in human volunteers have supported the PK/PD modeling approach.

For *in vivo* pharmacological studies, as conventional mice models are unlikely to recapitulate the complex biology of human diseases where the IL-7/IL-7R plays a central role, Servier's partner (OSE Immunotherapeutics) conducted *in vivo* pharmacology studies in non-conventional humanized mice of colitis models since S95011 is also developed in ulcerative colitis disease. For Sjögren pathology, rodent models were not considered as relevant to human physiopathology for assessing the activity of a humanized IgG4 mAb, thus S95011 was not tested in such models.

The efficacy of local and systemic IL-7Rα blockade by Hz-127 mAb was assessed *in vivo* at 5mg/kg intraperitoneal (i.p.) over 3 weeks in the TNBS-chemically-induced acute colitis model in humanized Nonobese diabetic/severe combined immune deficiency (NOD SCID) gamma (NSG) mice and in a graft versus host disease (GVHD) model using humanized NSG mice, "surrogate" models of chronic colon inflammation. In both models, Hz-127 mAb significantly reduced colon inflammation by decreasing colitis and restoring intestinal integrity or by decreasing histological score in colon and human CD3+ T-cell infiltrate, respectively. In the GVHD model the overall survival was increased as well as the colon length in comparison to control.

Further, using *in vivo* immune responses models in non human primates (NHPs) or in humanized mice, Chi-127 an early chimeric antibody demonstrated strong impact on T cell responses by preventing Delayed Type Hypersensitivity (DTH) cutaneous responses in baboons and dampening antibody responses after immunization with Sheep-Red Blood Cells (SRBC) (used as T-helper type 2 (Th2) model of pathogenic antigen stimulation) in baboons after single 10mg/kg IV. administration. This data obtained in NHPs indicates a better control of Teff and a better control of pathologic antigen-specific memory T cell responses. In this study, no immune depletion was observed either in the blood or lymph nodes.

In sum, the involvement of T lymphocytes in the pathophysiology of pSS, the elevated levels of IL-7 and IL-7R in the blood and tissues of pSS patients, together with the properties of the S95011 antibody provide a strong rationale for investigating its potential therapeutic use in Sjögren patients.

Toxicological data

A toxicological program for S95011 was carried out in accordance with ICH guidelines. *In vitro* studies were performed, including a tissue cross reactivity analysis on human healthy tissues and a cytokine release assay on healthy human PBMCs and on whole blood culture, without issues of concern. The potential toxicity of S95011 *in vivo* was evaluated in the cynomolgus monkey, selected as relevant species for S95011. A non GLP-compliant escalating dose study and a GLP-compliant [12 + 8]-week repeat-dose study (IV or SC treatment + recovery periods) were conducted in cynomolgus monkey. The latter study included safety pharmacology primary endpoints regarding central nervous system and cardiorespiratory functions. S95011 was given either by the IV route (15-minute infusion) once or twice a week for 12 weeks at 20, 50 and 100 mg/kg/day or by the subcutaneous (SC) route once a week for 6 weeks at 50 mg/kg/day. Reversibility was evaluated in selected animals kept for an 8-week treatment-free period.

During the dosing phase, significant changes in the RO and toxicokinetic (TK) profiles were observed as a result of anti-drug antibody (ADA) occurrence. Therefore, only results from animals without ADA and with significant sustained RO were considered as relevant in terms of pharmacokinetics, for the evaluation of S95011 of targets for toxicity.

Overall, in the GLP-compliant toxicity study, there were no drug-related mortalities, and there were no significant findings in any in-life parameters.

At histomorphologic examination, a slight perivascular inflammatory cell infiltrate with evidences of gliosis in the brain and pituitary was observed in the nervous system of one high-dose male, with an unusual wide extension. A relationship to the test item cannot be completely ruled out. Thus, the NOAEL was cautiously set at the mid-dose, 50 mg/kg/administration, IV.

Clinical data

The phase I first-in-human (FIH) OSE-127-C101 study, sponsored by OSE Immunotherapeutics, was conducted in Belgium and included 63 healthy adult male and female volunteers. Among them, 45 participants were exposed to S95011 up to 10 mg/kg (single and multiple doses (one administration every 2 weeks (q2w) for 4 weeks)).

Clinical safety

No serious adverse events were reported. None of the subjects prematurely discontinued their participation in the study for safety issue. No remarkable differences or dose-dependent trend in AE incidence could be observed between the different S95011 doses and placebo or between IV and SC administration of S95011.

Overall, 36 (57.1%) subjects of the study, all treatment groups combined, experienced at least one Treatment Emergent Adverse Events (TEAE) and treatment-related TEAEs were reported in 19 (30.1%) subjects. The most frequently reported TEAEs were headache (in 20 [31.7%] subjects overall), nasopharyngitis (in 6 [9.5%] subjects overall) and diarrhoea (in 5 [7.9%] subjects overall). The most frequently reported treatment-related TEAE was headache (in 13 [20.6%] subjects, all treatment groups combined). There were no clinically significant abnormalities in vital signs, physical examination, laboratory data and ECG. No cytokine release (IFNγ, IL12p70, IL4, IL5, IL6, IL8, TNFα) has been observed following S95011 administration in healthy volunteers. Overall, the drug is considered to be safe in healthy volunteers.

Pharmacokinetics

No significant dose effect was observed on dose-normalized C_{max} in the single administration part (Part 1) (dose range: 1 mg/kg to 10 mg/kg). A more than dose-proportional increase in AUC_{last} was observed between doses 1 vs 4 mg/kg and 1 vs 10 mg/kg. Half life increased from 111 to 280 h over the dose range of 1 mg/kg to 10 mg/kg.

Relative bioavailability measured as C_{max}, AUC_{last}, and AUC_{tau} was about 10-13% after s.c. administration compared to IV. infusion as OSE-127.

After multiple IV. infusions of S95011 (Part 2) (one administration every 2 weeks (q2w) for 4 weeks), approximate dose proportionality for C_{max} and AUC_{last} was observed from 6 to 10 mg/kg. The accumulation ratio was about 1.5 for AUC_{tau} and about 1.25 for C_{max}.

Pharmacodynamics

CD127 receptors were saturated at the first sampling time after the end of infusion with RO ≥95%. CD127 RO AUEC increased with increasing single IV. doses from 0.02 mg/kg to 10 mg/kg and the median time of CD127 RO >95% (t_{abl}) and >20% (t_{Emin}) was longer for higher doses. The same trend was observed after multiple IV. doses. CD127 RO AUEC increased with increasing S95011 AUC_{last} and AUC_{tau}.

Overall, no clear impact on lymphocyte subsets and cytokines nor clinically relevant elevation of cytokines was observed.

Immunogenicity

No anti-S95011 antibodies (Abs) were formed after single IV. infusion of S95011 0.002 mg/kg and 0.02 mg/kg. Abs were formed as of Day 15 (0.2 mg/kg; 1 subject), Day 29 (1 mg/kg; 2 subjects and 4 mg/kg; 1 subject), or FU1-Day 71 (10 mg/kg; 2 subjects). The last sampling timepoint the Abs were present was Day 43 (0.2 mg/kg; 1 subject), FU1-Day 71 (1 mg/kg; 4 subjects), FU2-Day 85 (4 mg/kg; 6 subjects), or FU4-Day 113 (10 mg/kg; 5 subjects).

After s.c. administration (1 mg/kg), Abs were formed on Day 29 (2 subjects) and present until FU1-Day 71 (4 subjects).

In Part 2, Abs were formed on Day 57 (6 mg/kg; 1 subject) or FU2-Day 85 (10 mg/kg; 1 subject) and were present until FU5-Day 127 (6 mg/kg; 6 subjects) or FU6-Day 141 (10 mg/kg; 5 subjects).

To date, no safety concern arose either from the non-clinical safety studies or from the clinical study.

Study design

This is a proof-of-concept, phase IIa study.

This study is designed to evaluate preliminary therapeutic efficacy of multiple intravenous infusions of 750 mg of S95011, the safety, tolerability, pharmacokinetics and pharmacodynamics in patients with primary Sjögren's syndrome.

This phase IIa study is a prospective, international, multicentre, randomised (2:1), double-blind, placebo-controlled study. It is expected to include 45 patients (30 receiving S95011, 15 Placebo).

A randomized, placebo-controlled, double-blind approach is used to eliminate potential bias in reporting clinical efficacy and safety data in this first exploratory study in pSS patients. Patients will be randomized to S95011 or placebo in a 2:1 ratio in order to minimize exposure to placebo and to gather more data on S95011. Stratified randomization is done in order to limit imbalances between active and placebo arms in baseline intake of oral corticosteroids and baseline intake of antimalarials. The placebo to S95011 will be used as comparator to provide objective clinical efficacy as well as safety data generated from patients exposed to the experimental therapy. Since there is no established, clinically effective disease modifying treatment for patients with pSS, potential treatment with placebo (on top of standard of care therapy, if necessary) is justified.

Study Population

Patients with primary Sjögren's Syndrome have to be diagnosed according to the 2016 American College of Rheumatology (ACR)–European League against Rheumatism (EULAR) classification criteria which require the presence of serum anti-SSA antibodies and/or focal lymphocytic sialadenitis on biopsy of labial salivary glands (Shiboski *et al*, 2017) (Appendix 2).

To be eligible, the patients should have an ESSDAI total score ≥ 6. For this study with a primary endpoint assessed at 13 weeks, the minimal baseline total score of 6 points on the ESSDAI is needed within the 7 following domains which are expected to change within 3 months of treatment: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematologic and biologic. This population represents patients with moderate to high activity disease level (*i.e.* systemic manifestations). Furthermore, these patients should have an active immunological profile with positive anti-Sjögren's syndrome A (SSA) antibodies or anti-nuclear (ANA) antibodies or rheumatoid factor (RF). (Bournia *et al*, 2012). This is a population considered for treatment with biologic therapies.

In order to ensure population homogeneity, patients with secondary Sjögren's Syndrome are excluded from the study.

Study primary outcome

ESSDAI is a physician-administered clinical index which has been validated to objectively assess systemic manifestations in pSS patients (Nocturne *et al*, 2015; Seror *et al*, 2015) (Appendix 3). ESSDAI content validity has been established through a rigorous consensus process and additional consultation with an expert steering committee. Evidence presented in the literature suggested that ESSDAI is a reliable and valid measure that is able to detect change over time (Bombardieri, 2018). ESSDAI has been found sensitive to change in open label studies, (Mariette *et al*, 2015) as well as in some randomised controlled trials (Moerman, 2014). Recently, results were obtained on the ESSDAI total score as a primary efficacy endpoint in pSS patients with moderate to high activity in a randomised, double blind, placebo-controlled, multi-centric, phase IIa proof of concept (PoC) study with CFZ533 (iscalimab) monoclonal antibody against CD40 (Fisher *et al*, 2020). Therefore, it is currently considered that the ESSDAI total score is an appropriate outcome criterion to evaluate systemic manifestations in pSS patients and can be used as a primary efficacy measure in populations similar to the one included in this study. The primary endpoint will be evaluated after 13 weeks of treatment as this biological treatment is expected to have an early onset of action, as demonstrated in animals (See Investigator's Brochure). Indeed, by fully inhibiting the IL-7R from the first month of administration, it is expected to induce a prompt impact on glandular inflammation by modifying the local T cell dependent B cell activation in patients. Furthermore, in Sjögren's Syndrome, in a recent phase IIa study with CFZ533 (iscalimab) monoclonal antibody against CD40, beneficial effects based on an improvement of ESSDAI total score were observed at W12, showing the sensitivity to change of this tool in this time frame (Fisher *et al*, 2020).

Choice of doses

The choice of the dose level was based on safety/tolerability, pharmacokinetics and receptor occupancy (RO) data obtained from phase I study as well as toxicological and pharmacological studies.

A minimal PBPK model was developed with data of the healthy volunteers (HV) enrolled in the FIH study. A covariate analysis was performed to test any potential effect of demographic characteristics on the dose-exposure-response relationship. From this analysis, only body weight was identified as a factor influencing the distribution volume of the product.

The model built in healthy volunteers was then adapted to predict dose-exposure-response (*i.e.* receptor occupancy) in Primary Sjogren syndrome (pSS) patients by including data from the literature describing expression of the soluble form of IL-7R in serum as well as salivary glands expression of IL-7R in Sjögren patients (Bikker *et al*, 2012; Hillen *et al*, 2016).
One of the observations in the HV model is that the body weight was not identified as a factor influencing the clearance of the product. Therefore, it was investigated whether the dose could be administered as a flat dose for this study. The extrapolated pSS model was used to perform simulations and test the effect of two different dosing strategies in exposure and RO. The aim of these simulations was to choose the most appropriate dosing strategy allowing to maintain a RO over 95% (which corresponds to a full inhibition of the target) between two administrations of the drug in PBMC (considered as plasmatic) and in targeted tissues.

One thousand patients were simulated for each dosing strategy:

- 10 mg/kg of S95011 every 2 weeks (q2w) for the first month and then every 3 weeks (q3w) until W10,
- 750 mg of S95011 every 2 weeks (q2w) for the first month and then every 3 weeks (q3w) until W10.

The q2w-q3w regimen was chosen to increase the patients' acceptability to the IV infusions regimen when compared to the more frequent administration regimen (q2w) performed in the FIH trial.
The results showed that the administration of a flat dose would lead to smaller inter-subject variability with regards to PK exposure than when dose is normalized by the body weight. Moreover, the flat dose of 750 mg would allow maintaining a higher proportion of patients (94,3%) with RO > 95%, resulting in a higher chance of efficacy in the pSS patients than the weight-normalized dose of 10 mg/kg (91,4% of patients with RO > 95%).

The median average concentration over a period of time (Cav) simulated for the patients treated with 750 mg q2w-q3w are lower than the maximal observed Cav in healthy volunteers dosed at 10 mg/kg q2w during all the treatment. This means that more than half of the pSS patients receiving 750 mg q2w-q3w would achieve exposures lower than the maximal exposure observed in FIH. However, the difference increases up to +24.5 % when considering the 95th percentile of Cav simulated before the primary endpoint in pSS patients (meaning that 95% of these patients would not achieve exposures higher than 29.4% of the maximal exposure observed in FIH).

Nonetheless, the simulated exposure (Cav) in humans is lower than the one observed in monkeys. More accurately, the safety margin calculated from average concentration observed at the NOAEL (50mg/kg) of the main toxicology GLP 12-week study in cynomolgus monkey and the simulated data in human at the flat dose of 750mg, gives a value that is large enough (21.7) to be confident that this choice of dose will be safe for the patients who will be included in the Phase 2a.

Benefit-Risk assessment

Currently, limited data exist regarding the use of agents that block the IL-7/IL-7R pathway.

Benefit

It is established that T lymphocytes are involved in the pathophysiology of pSS. IL-7 has a role in regulating T cell homeostasis, proliferation and survival. Based on the current data on IL-7 and IL-7R in the blood and tissues of pSS patients, together with the properties of the S95011 antibody, there is a strong rationale for investigating S95011 potential therapeutic use in Sjögren patients.

However, S95011 has never been used in patients with pSS, so at this stage, no statement can be made of its efficacy in treating this disease.

Risks

Apart S95011, two other anti IL-7Rα antagonist mAbs (GSK 26118960 [GlaxoSmithKline] and PF 06342674 [Pfizer]), were developped against the same target as S95011 (*i.e.*, IL-7Rα). They have been tested in several Phase 1 trials in healthy volunteers as well as in Multiple Sclerosis and type I diabetes patients. The development of these 2 anti IL-7Rα antagonist mAbs was stopped for strategic reasons.

Five studies have been conducted with GSK 26118960 and PF 06342674 in around 150 people including at least 98 healthy volunteers with administered single or multiple weekly doses from 0.25 mg/kg to 6 mg/kg IV or SC. Two of these studies (Ellis *et al*, 2018; Herold *et al*, 2019) have been published and partial results from the other studies can be found on https://clinicaltrials.gov. (NCT01808482; NCT02293161; NCT01740609; NCT02045732; NCT02038764). No significant adverse event nor adverse drug reaction has been described within the available information.

Up to now, no safety issue in the phase 1 study in healthy volunteers was reported with S95011. However, due to its nature, IV administration and mechanism of action, the following reactions will be closely monitored:

- Acute hypersensitivity

Humans administered with foreign proteins are at risk of developing allergic reactions, including anaphylaxis. Patients can present with the following symptoms: itching, flushing, headache, nausea/vomiting, hypotension, urticaria, bronchospasm, or angioedema.

- Infections

Subjects treated with S95011 may be at an increased risk of infection. Administration of S95011 could be expected to result in immunomodulation with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin when full receptor occupancy has been achieved.

- Cytokine release syndrome

No cytokine release has been observed in FIH study (IFNγ, IL12p70, IL4, IL5, IL6, IL8, TNFα). However, given the risk of cytokine release syndrome observed in certain therapeutic monoclonal antibodies, this event cannot be ruled out in patients treated with S95011.

- Vaccination

Vaccination of patients during treatment with S95011 and prior to clearance of S95011 is likely to result in non-protective vaccinal antibody titers due to the pharmacologic activity of the antibody.

- Immunogenicity

Extrapolation of immunogenicity risks from healthy subjects to pSS patients is unknown.

- Lymphopenia

No clinically significant lymphopenia has been observed neither in the phase 1 study nor in preclinical studies. However, due to S95011 mechanism of action, a possible lymphopenia cannot be ruled out.

The possible risks and their mitigations are presented in the table below.

Risks	Mitigations
Acute hypersensitivity	- Patients with history of severe allergic or anaphylactic reactions to monoclonal antibodies will be ineligible for the study. - At W000, W002 (2 first administrations of S95011) close monitoring for 2 hours after completion of IV infusion (or longer, at the discretion of the Investigator) for vital signs, and signs or symptoms of adverse events including development of an injection reaction. - At all other visits with investigational medicinal product (IMP) administration, post- dose assessments will include assessing infusion site, physical examination and vital signs before dismissing the patient from the clinical site. - Discontinuation of IMP in patients developing allergic reaction or infusion related reaction of grade 3 or higher intensity (according to CTCAE/v5.0 grading) considered as related to the IMP administration. - Any allergic reaction grade 3 or higher according to CTCAE/v5.0 grading including infusion related reaction must be immediately notified to sponsor as adverse event of special interest.

Infections	- Negative Tuberculosis test (Quantiferon or T-Spot test) during screening for all included patients - Will not be included in the study: • patients with signs or symptoms of a viral, bacterial, parasitic or fungal infection within 2 weeks (14 days) prior to randomisation (W000) according to the assessment of the investigator; • patients having had any infection requiring IV antimicrobial (antibiotic, antiviral, antiparasitic or antifungal) treatment within 8 weeks prior to randomisation (W000), • patients with positive test for anti-human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBs) (or negative HBs antigen with positive anti HBc antibody and negative anti HBs antibody) or anti-hepatitis C virus (HCV) antibodies with a positive test for HCV viral RNA, - There will be a close, regular and careful monitoring for signs and symptoms which might indicate a severe infection. - IMP discontinuation in patients developing infection of grade 3 or higher intensity (according to CTCAE/v5.0 grading) considered as related to the IMP administration. - Any infection grade 3 or higher according to CTCAE/v5.0 grading must be immediatetly notified to the sponsor as adverse event of special interest.
Cytokine release syndrome	- In case of any suspected cytokine release syndrome, a blood sample for cytokines assay will be performed and analyzed locally. • Discontinuation of IMP in patients developing study treatment related cytokine release syndrome of grade 2 or higher (CTCAE/v5.0 grading), • Any cytokine release syndrome must be immediately notified to sponsor as adverse event of special interest.
Vaccination protection decrease	• All vaccinations deemed necessary by the investigator for the patient should be up to date before inclusion • Administration of live or attenuated vaccination prohibited in the current study and within 30 days prior to randomization
Immunogenicity (Anti-drug antibodies (ADA) formation)	ADA formation will be assessed by blood samples collected during the trial at W000; W002; W004; W007; W010; W013; and FU visits.
Lymphopenia	- Patients with lymphopenia < 500x106/L will not be included in the study - Lymphocytes count will be assessed in blood samples collected during the trial at W000; W002; W004; W007; W010; W013; and FU visits - IMP discontinuation in patients developing lymphopenia of grade 3 or higher intensity (according to CTCAE/v5.0 grading) considered as related to the IMP administration.

	- Lymphopenia < 500x10^6/L (grade 3 or higher according to CTCAE/v5.0 grading) must be immediately notified to the sponsor as adverse event of special interest.

It is of note that after the treatment period, patients will enter a 15-week follow-up period (until W028) to allow sufficient time for monitoring safety until 5 half-lives of S95011. In addition, it is anticipated that more than 97% of patients have RO < 95% at W028 (meaning that almost no pharmacological effect of the product is expected).

In summary, S95011 has never been used in patients with pSS, so at this stage, no statement can be made of its efficacy in treating this disease. No safety issue was reported in the phase 1 study in healthy volunteers. However, some risks exist due to the nature and mechanism of action of S95011and adapted measures will be taken to prevent these risks.

In addition, patients safety will be closely monitored including an independent external DSMB that will meet regularly (and urgently if needed) in order to assess safety and tolerability data.

The study will be conducted in compliance with the protocol, GCP, the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements.

Patients with pSS have been consulted along the process of protocol, patient information sheet and informed consent writing and their comments have been reviewed and integrated.

3. STUDY OBJECTIVES AND ENDPOINTS

This study is designed to evaluate preliminary therapeutic efficacy of multiple intravenous infusions of 750 mg of S95011, the safety, tolerability, pharmacokinetics and pharmacodynamics in patients with primary Sjögren's syndrome. The results of this first study in patients with primary Sjogren's syndrome will be informative for further development in treatment of pSS.

3.1. Primary objective

The primary objective of the study is to assess the effect of multiple intravenous infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment in reducing disease activity using EULAR Sjögren Syndrome Disease Activity Index (ESSDAI).

3.2. Secondary objectives

The secondary objectives are:

To evaluate efficacy of multiple intravenous (IV) infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment on:

- Patient's symptoms using EULAR Sjögren Syndrome patient reported Index (ESSPRI)
- Fatigue using the Multidimensional Fatigue Inventory (MFI)
- Quality of life (QoL) using Short Form Health Survey (SF-36)
- Physician's global assessment (PhGA) of the disease activity using a 0 to 10 numerical rating scale (NRS)
- Patient's global assessment (PGA) of the disease activity using a 0 to 10 numerical rating scale (NRS)
- Tear gland function using the Schirmer test
- Tear gland function using Ocular Staining Score (OSS)

- Salivary gland function measured by sialometry under unstimulated and stimulated conditions

To assess the safety and tolerability of multiple intravenous infusions of S95011,

To assess the pharmacokinetics (PK) of S95011 in serum,

To assess pharmacodynamics [receptor occupancy (RO)] of S95011 in blood,

To determine the incidence of anti-drug antibodies (ADA) formation.

3.3. Exploratory objectives

Exploratory objectives are:

To explore the potential effect of S95011 on lymphocytes subsets in particular T cell subsets,

To explore the potential effect of S95011 on some proteins involved in pSS physiopathology like IL-7, cytokines and specific proteins in blood,

To explore the potential effect of S95011 on immune panel, β2 microglobulin, and on the auto-antibody panel: anti-SSA (Ro) antibodies, anti-nuclear antibodies (ANA) and rheumatoid factor (RF),

To explore drug exposure and perform exploratory histology and exploratory biomarkers assessments on minor salivary glands tissue by performing lip biopsies (optional),

To set a biocollection to explore further the potential impact of S95011 on PBMC, extracted RNA and blood according to the advancement of the knowledge on the drug and the disease (optional sampling).

3.4. Endpoints

See Sections 7, 8 and 9 for more details

Primary efficacy endpoint:

Change from baseline in ESSDAI total score to W013

Secondary efficacy endpoints:

- ESSDAI score by domain and total score at each visit (value & change)
- ESSPRI score by symptom and total score at each visit (value & change)
- Proportion of patients with ≥ 3 points, ≥ 5 points, ≥ 7 points of improvement from baseline in ESSDAI at each visit
- Proportion of patients with ≥ 1 point, ≥ 2 points, ≥ 3 points of improvement from baseline in ESSPRI at each visit
- Proportion of patients with ≥ 3 points of improvement in ESSDAI and with ≥ 1 point of improvement in ESSPRI from baseline at each visit
- Fatigue (MFI), quality of life (SF-36), physician and patient's global assessment of the disease activity (NRS) at each visit (value and change)
- Tear gland function: Schirmer's test and in OSS at each visit (value and change)
- Salivary gland function: unstimulated and stimulated salivary flow rate at each visit (value and change)

Other secondary endpoints:

- **Safety:**

The safety and tolerability assessed by incidence of adverse events (AEs), change over time in safety parameters (vital signs, ECG, biological laboratory) and incidence of abnormal safety parameters throughout the study.

- **Pharmacokinetics**

Pharmacokinetics of S95011 in serum

- **Pharmacodynamics**

Receptor Occupancy (RO) of S95011 in blood

- **Incidence of ADA**

Exploratory endpoints:

- **In blood:**
  - Lymphocytes subsets (PBMC)
  - Some proteins involved in pSS physiopathology (IL-7, cytokines, specific proteins …)
  - Cytokine release panel
  - Immune panel, auto antibody-panel, β2 microglobulin.
- **In salivary glands:**
  - Lip biopsy for salivary gland collection (S95011 concentration, exploratory histology and exploratory biomarkers assessments) (optional biopsy at W013).

4. STUDY DESIGN

This is a phase IIa, international, multicentre, randomised (2:1), double-blind, placebo-controlled study.

The study will consist of:

- **Screening period without study treatment:** within 28 days prior to W000, after signing the informed consent, in order to check eligibility of patients.
- **Randomised and double-blind treatment** period: from W000 to W013 (study drug administration at W000, W002, W004, W007, W010) with 2-parallel groups (750 mg of S95011 and matching placebo), with stratification by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (*e.g.* chloroquine, hydroxychloroquine, quinacrine) (yes/no).
- **Safety follow up period without study treatment**: 15 weeks with one visit at W019 and one at W028. This follow-up period will allow sufficient time for monitoring safety until 5 half-lives of S95011. In addition, it is anticipated that more than 97% of patients have RO < 95% at W028 (meaning that almost no pharmacological effect of the product is expected).

The expected duration of patient participation will be 32 weeks maximum.

4.1. Investigational plan

4.1.1. Study plan

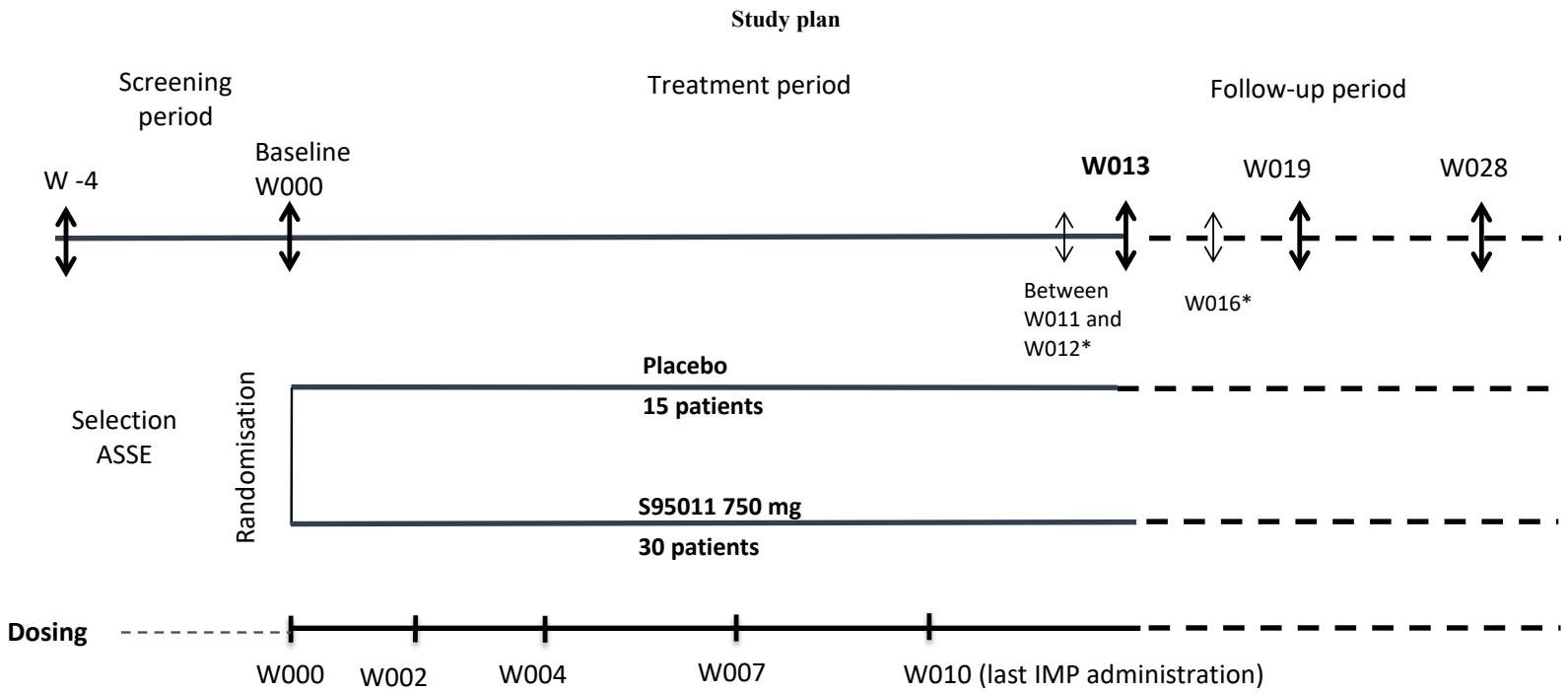
The study plan is shown in Figure (4.1.1) 1.

In case of non-inclusion of a patient, it is the investigator's responsibility to ensure, in accordance with the local standards of care and medical practices that:

- The reason of non-inclusion is explained to the patient,
- Any event associated with any procedure/condition required by the study protocol (*e.g.* an event occurring following the discontinuation of a forbidden treatment) is collected,
- An adequate alternative medical care is proposed to the patient.

A non-inclusion visit is not mandatorily carried out, providing these requirements are met and documented in the medical file of the patient and in the electronic Case Report Form (e-CRF). Rescreening of non included patients (*e.g.* in case of acute infection, temporary abnormal lab results …) is allowed without limited time period, providing that a new informed consent is signed.

Figure (4.1.1) 1 - Study plan



*One blood sample will be performed for PK assessment between W011 and W012 and at W16 (± 5 days), at site or not according to local facilities.

The study start is defined as the date of the first visit of the first patient.
End of Trial is defined as the date of the last follow-up of the last patient (including a phone contact), or the date of the last contact attempt if the last patient is declared lost to follow-up.

4.1.2. Investigation schedule

Table (4.1.2) 1 describes the measurement of efficacy and safety assessed during the study.

Table (4.1.2) 1 - Investigation schedule

	Screening *	Baseline	Treatment period						FU period	
Week	**Within W-4 prior to W000**	**W000**	**W002 ±2d**	**W004 ±2d**	**W007 ±2d**	**W010 ±2d**	**Between W011 and W012[#]**	**W013 (WD) ±2d**	**W16[##] ±5d**	**FU visits** W019, W028 ±7d**
Informed consent	X									
Inclusion/exclusion criteria		X								
Relevant medical/surgical history	X									
Infectious disease panel (HIV, hepatitis B and C) (local)	X									
Hemoglobin HbA1c (local)	X									
Tuberculosis test: Quantiferon or T-Spot (IGRA) (local)	X									
Chest X Ray (within 90 days prior to signing the ICF. or during the screening period)	X									
Previous treatment/concomitant treatment	X	X	X	X	X	X		X		X
IMP (S95011/placebo) – allocation IWRS		X[1]	X[1]	X[1]	X[1]	X[1]				
Efficacy										
ESSDAI	X[2]	X[2]		X[2]				X[2]		
ESSPRI		X		X				X		
SF-36, MFI, NRS (physician & patient)		X						X		
Schirmer test***		X						X		
OSS***		X		X				X		
Sialometry (unstimulated and stimulated salivary flow) ***	X			X				X		
Safety										
Adverse events		X	X	X	X	X		X		X
Physical examination	X	X	X	X	X	X		X		X
Body height (ASSE only) and body weight	X	X		X		X		X		X
Vital signs (pulse, blood pressure, body temperature)	X	X	X	X	X	X		X		X

	Screening*	Baseline	Treatment period						FU period	
Week	**Within W-4 prior to W000**	**W000**	**W002 ±2d**	**W004 ±2d**	**W007 ±2d**	**W010 ±2d**	**Between W011 and W012[#]**	**W013 (WD) ±2d**	**W16[##] ±5d**	**FU visits** W019, W028 ±7d**
Biochemistry/Haematology (central)	X[3]	X[4]	X[4]	X[4]	X[4]	X[4]		X[4]		X[4]
Erythrocyte sedimentation rate (ESR) (local)	X	X	X	X	X	X		X		X
Urinalysis (local)	X	X	X	X	X	X		X		X
Coagulation tests (central)	X	X	X	X	X	X		X		X
Pregnancy test (Serum)[5](local)	X									
Pregnancy test (Urines)[5](local)		X	X	X	X	X		X		X
12-lead ECG (local)		X		X		X		X		X
Pharmacokinetics/ Roccupancy/ Immunogenicity (blood)										
Blood samples PK (central)		X[6]	X	X	X	X[6]	X	X	X	X
Blood samples(RO) (central)		X[7]	X	X	X	X[7]		X		X
Blood samples (ADA) (central)		X	X	X	X	X		X		**X**
Exploratory measurements										
Blood										
Lymphocytes subsets (PBMC's) (central)		X		X	X			X		
IL-7 and some cytokines (central)		X	X	X	X	X		X		X
Cytokines release panel (central)		X[8]	X[8]							
Other proteins (central)		X		X				X		
Immune panel (central)	X	X		X				X		
Auto-antibody panel (central)	X							X		
β2 microglobulin (central)		X		X				X		
Salivary glands										
Lip biopsy (optional)								(X)[9]		
Other										
Biocollection (blood: serum and plasma) (optional) (central)		(X)		(X)				(X)		
Biocollection (PBMC) (optional) (central)		(X)				(X)				
Biocollection (extracted RNA) (optional) (central)		(X)		(X)				(X)		

- For each patient, there will be a screening period between W -4 and W000. Patients who meet the eligibility criteria at screening will be admitted to inclusion visit (W000).
- The time windows that are given for the visits (±2d etc..) are given compared to W000
- Lip biopsy should not be performed before the sialometry
- Physical examination, vital signs and 12-lead ECG will be performed pre-dose

* The results of the examinations should be available at W000, to assess the inclusion criteria.
**Two follow-up visits will be scheduled for safety and PK/PD assessments: the first visit will be performed at W019, and the second visit at W028. Between visits, the patient will be able to contact the site in case of any problem. In case of premature IMP discontinuation, the FU visits will be performed 9 and 18 weeks after the last IMP administration, for safety assessments.
*** Schirmer, OSS and Sialometry can be performed within 2 days before the scheduled visit's date at W000 and W004. At W013 these tests can be performed in the time window allowed by the protocol (+/- 2 days).
# One blood sample will be performed between W011 and W012 for PK assessment. The blood sample will be performed at site or not according to local facilities
One blood sample will be performed at W16 ± 5 days for PK assessment. The blood sample will be performed at site or not according to local facilities
1 At W000 and W002, patients will be monitored closely for 2 hours after completion of IV. infusion (or longer, at the discretion of the Investigator) for vital signs, physical examination, and signs or symptoms of adverse events including development of an injection reaction. At all other visits with IMP administration, post dose assessments will similarly include assessing infusion site, physical examination and vital signs before dismissing the patient from the clinical site
2 At each ESSDAI assessment, cryoglobulins measurement will be performed locally and the result will be used for ESSDAI scoring. Cryoglobulin result obtained from a previous sampling performed within 1 month before screening visit could be used for ESSDAI scoring at screening. In case of presence of cryoglobulinaemia, cryoglobulin will be identified (type I, II or III). In addition, for assessments not listed in the protocol as mandatory tests but which may be needed to estimate ESSDAI, including Chest X-ray, pulmonary high resolution computer tomography (HRCT), lung function test (Diffusing-capacity of the lung for carbon monoxyde (DLCO), forced vital capacity (FVC)), estimated glomerular filtration rate (eGFR), electromyography (EMG), muscle (or any other) biopsy, it is at the investigator's discretion to have these assessed based on the signs and symptoms of the patient so to provide correct ESSDAI readout (see section 7.2).
3 If ASSE blood samples for haematology and biochemistry are performed more than 14 days before W000, blood samples for blood cell count and CRP must be repeated (central or local) within a maximum of two weeks before W000. These tests repeated should be obtained within the allowed screening period, and must be considered for the patient inclusion.
4 Blood samples for biochemistry/haematology will be performed after 10 hours fasting.
5.Only in women of childbearing potential

For all blood samples planned at visit with IMP administration, only one pre-dose sample has to be performed (before Investigational medicinal product (IMP) administration.
Except for :
6. **PK samples:** One pre-dose sample (before IMP) + 2 post dose samples (one right after the end of the infusion and one in the [1-3h] interval after the end of the IMP infusion at W000 and W010
7. **Receptor occupancy (RO) samples:** One pre-dose sample (before IMP) and one sample right after the end of the infusion of the IMP (just after PK sample) at W000 and W010
8. **Cytokine release panel:** One pre-dose sample (before IMP) and one post-dose sample right after the end of IMP infusion at W000 and W002
9. Lip biopsy can be performed the day before and up to 2 days after the scheduled visit's date. In any case sialometry has to be performed before biopsy. The consent for participating in the lip biopsy can be proposed an other time to the patients during the course of the study until W013

For further practical details, methods of measurement are provided in Sections 7, 8 and 9.

The maximum total volume of blood collected per patient during the study will be 520 mL.

4.2. Measures to minimise bias

This is a double-blind, placebo-controlled study.

The appearance and form of S95011 vials and placebo vials as well as the solutions to be administered will be similar, in order to protect the blinding with regard to the patients and the investigators.

Patients will be randomised to S95011 or placebo in an overall 2:1 ratio in order to minimise exposure to placebo and to gather more data on S95011. The randomisation will be non-adaptive, stratified by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarials (*e.g.:* chloroquine, hydroxychloroquine, quinacrine) (yes/no).

Treatment randomisations and allocations will be centralized by Interactive Web Response System (IWRS). The structure responsible for designing and constructing the randomisation lists in blind will be the biostatistics department of I.R.I.S.

The questionnaires and patient's NRS will be administered to the patient with an electronic patient outcome (e-COA) in the local language. The same electronic device will be provided to each study patient. Data will be entered by the patient. The aim of this technology is to enhance quality of patient reported outcomes by reducing missing data and improving completion of the questionnaires.

Stability of the corticosteroids and disease background treatment(s) will be required during a pre- specified period before screening and during the study.

ESSDAI score will be completed by a trained investigator. The training will be performed before the inclusion of any patient in the site.

Over the course of the study, the ESSDAI will be completed by the same trained investigator for a given patient(insofar as possible).

A central laboratory will be used for the laboratory assessments (Serum haematology and biochemistry, coagulation tests, immune and auto antibodies panels, lymphocytes subsets…) in order to centralize and harmonize the data.

The determination of the drug concentration, of IL-7 and of receptor occupancy will be analysed by a central bioanalytical laboratory. The randomisation list will be sent to the bioanalytical lab in order to select the samples to be analysed.

4.3. Study products and blinding systems

4.3.1. Products administered (IMP)

S95011 will be manufactured by OSE (Nantes, France) and placebo by Les Laboratoires Servier Industrie (Gidy, France).
Les Laboratoires Servier Industrie (Gidy, France) will pack, release and supply the therapeutic units (TUs) of S95011/Placebo.

During the screening period (from ASSE to W000), no treatment will be dispensed.

During the treatment period (from W000 to W013):
- S95011 or placebo will be dispensed for a double-blind period, from W000 to W010.

During the follow up period, no treatment will be dispensed.

Table (4.3.1) 1 provides a description of the IMP (S95011/Placebo)

Table (4.3.1) 1 - Description of the IMPs

	IMP	
	S95011	**Placebo**
Pharmaceutical form	Concentrate for solution for infusion	Concentrate for solution for infusion
Unit dosage	50mg/mL	NA
Appearance	A colorless to slightly yellow, clear to slightly opalescent aqueous solution	A colorless to slightly yellow, clear to slightly opalescent aqueous solution
Composition	Histidine acetate, sorbitol, glycine, polysorbate 20, anti-CD127 mAb and water for injection	Histidine acetate, sorbitol, glycine, polysorbate 20 and water for injection

Table (4.3.1) 2 provides a description of the packaging of the IMP(s).

Table (4.3.1) 2 - Description of packaging

Number of units of the pharmaceutical form per primary packaging	A vial of 2 mL of S95011 concentrate for solution at 50mg/mL or placebo
Number of primary packaging per secondary packaging	1 vial per box
Number of secondary packaging per patient	9 boxes per visit

The labelling of packages complies with the regulatory requirements of each country involved in the study.

4.3.2. IMP management

The Interactive Web Response System (IWRS) will trigger the first shipments of the IMPs and the resupplies.

IMP receipt, dispensing according to the experimental design of the study (for the description of dispensing methods, refer to Section 6.2), accountability and collection are the responsibility of the investigator and/or pharmacist of the medical institution.

Destruction of the IMP is the responsibility of the sponsor and/or the investigator and/or the pharmacist of the medical institution.

Remaining treatments (used and unused IMPs) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMP management. Used IMPs will be collected by the centre at the time of preparation / administration along with the other wastes to be destroyed according to local routines.

A certificated destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. The practical procedures for destruction of unused IMP will be defined by the sponsor and adapted to the centre.

An IMP collection and destruction form will be completed before the shipment of IMP to destruction. Destruction of IMP may be possible (after drug accountability and sponsor authorization) when the product has been used, has expired or after at least the last visit of the last treated patient.

The IMP should be stored in a secure area with restricted access.

Specific storage conditions are mentioned on IMP labelling. The investigator/pharmacist is responsible for the IMP temperature monitoring on a daily basis using FONT-CIRT-FORM-311 “Therapeutic Unit temperature log sheet - centre” (recording Min-Max temperature every working day) or an equivalent document.

In case of temperature deviation, the investigator/pharmacist should immediately:

- block the IWRS for the concerned IMPs and place them in quarantine,
- alert the monitor or the local project manager if the monitor is absent, forward him all needed information and implement the instructions received.

Furthermore, the investigator/pharmacist must put in place an adequate corrective/preventive action once the first temperature deviation occurs in order to avoid recurrence.

IMP management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the medical institution and/or a designated person from their study team must complete in real time all the documents provided by the sponsor concerning IMP management (therapeutic unit tracking form or an equivalent document). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfil.

The investigator and/or the pharmacist of the medical institution should only use the IMP provided for the patients involved in the study.

All defects or deterioration of IMPs or their packaging are to be reported to the study monitor, and to the IWRS. The investigator will notify the monitor of all complaints set out by a patient/pharmacist (change of appearance…).

In the event of anticipated return of IMPs to the sponsor (batch recall), the sponsor will prepare an information letter intended for the investigator and/or pharmacist of the medical institution. This letter will be sent by the person locally responsible for the study to each study centre.

4.3.3. Management of blinding systems

The blind for any study patient should only be broken by the investigator or authorised person if it is absolutely necessary to ascertain the type of treatment given. The reason for unblinding must be recorded in the IWRS.

The circumstances under which the blind may be broken are:

- when knowledge of the treatment allocation will influence patient management. For example, after overdose of the study treatment, or
- when the outcome of a life-threatening medical emergency depends on knowing which treatment the patient has received.

In the cases where the study treatment blind needs to be broken by the investigators for an imperative justified medical reason, a centralised decoding system integrated to IWRS is adopted for the study. No sealed envelopes will be used.

The centralised decoding procedure will be performed by the investigators or an authorised person by contacting the IWRS. The system will be available 24 hours a day, 7 days a week. The procedure to be followed is detailed in the IWRS manual.

If IWRS is not available, the helpdesk of the IWRS will be contacted by phone. Additionally, decoding will be possible by calling the Emergency Phone Number of I.R.I.S. (+33 1 55 72 60 00) 7/7d and 24/24h) which will either transmit the request to the Immuno-inflammatory disease centre for therapeutic innovation or will reach the external out-of-office hours contact who have access to a decoding list (available only to authorized and identified persons during the study).

The DSMB may also ask for decoding in specific cases as far as the safety of patients is concerned.

4.4. Discontinuation of the study

4.4.1. Premature discontinuation of the study or temporary halt

After having informed the national coordinators/investigators, this study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause (including unsatisfactory patient enrolment, new scientific knowledge or other conditions which would place the patient at undue risk if continuing in the study) by the sponsor (or by the sponsor further a recommendation from Data Safety Monitoring Board (DSMB)) or by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or the Competent Authorities.

Specific safety criteria for which the study can be discontinued or temporary halted by the Sponsor following DSMB recommendations as well of the list of data/events for which urgent DSMB meetings will be triggered, will be defined in the DSMB charter.

In case of premature study discontinuation or temporary halt, two copies of the written confirmation will be dated and signed by the coordinators/investigators. The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued, the on-going patients should be seen as soon as possible and the same assessments as described in Section 5.6.2 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor and the DSMB following approval from the IRB/ IEC and Competent Authorities, according to local regulations.

The **patient withdrawal** criteria are described in Section 5.6.

4.4.2. Premature discontinuation of the study in an investigator site (early site closure)

The sponsor reserves the right to close a study site at any time for any sufficient reasonable cause at the sole discretion of the sponsor.

The investigator may also 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 the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Competent Authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

The IRB/IEC(s) and Competent Authorities will be informed according to local regulations.

4.4.3. Discontinuation of the study in the event of objective reached

Not applicable

4.5. Source data

Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study.

Source data will be required for all data recorded in the e-CRF.

The following documents are considered as source documents:

- Notes in the medical file (including nurse files and ESSDAI scoring documentation)
- Therapeutic Unit Tracking Form (TUTF)
- Report/images (*e.g.* central and local laboratory reports), ECG, X-Ray, Biopsy report, *etc*.
- OSS report
- Schirmer test results
- Unstimulated and Stimulated Salivary Flow rates
- ESSDAI and PhGA NRS scores collected in e-COA*
- Questionnaires: ESSPRI, MFI, SF36, PGA NRS recorded by e-PRO*
- Requisition forms (*e.g.* PK)
- IMP preparation and administration documents or reports

**e-PRO/e-COA service provider's database will be considered as source data. The investigator will have access to the e-source data via a web portal.*

5. INCLUSION AND WITHDRAWAL OF PATIENTS

5.1. Inclusion criteria

All patients included should present the following characteristics:

1. Male or female aged between 18 to 75 years (both inclusive),
2. Patients must have a body mass index (BMI) of 18 (exclusive)-40 (inclusive),
3. Diagnosis of primary Sjögren's Syndrome based on 2016 ACR-EULAR criteria (Appendix 2),
4. ESSDAI total score ≥ 6 during screening, with at least 6 points scored within the 7 following domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematologic and biologic,
5. Positive anti-SSA (Ro) antibodies or anti-nuclear antibodies (ANA) ≥ 1:320 or rheumatoid factor (RF) > 20 IU/ml during screening period, measured in a central laboratory,
6. Stimulated whole salivary flow rate > 0 mL/minute,
7. Negative Tuberculosis test (Quantiferon or T-Spot test) during screening,
8. A chest x-ray obtained during the screening period or anytime within 90 days prior to signing the ICF with no evidence of current active infection (*e.g.* TB), malignancy, or clinically significant abnormalities (unless due to pSS),
9. All vaccinations deemed necessary by the investigator for the patient, up to date,
10. Female patient is postmenopausal, surgically sterile (having had a hysterectomy or bilateral oophorectomy) and/or is using a highly effective method of contraception (described in Section 5.3) until the last follow-up visit. In case of use of oral contraception women should have been stable on the same contraceptive drug for at least 3 months prior to the first IMP administration,
11. Non-vasectomized male patients having a female partner of childbearing potential must agree to the use of a highly effective method of contraception from first IMP administration until the last follow-up visit,
12. Willing to adhere to the prohibitions and restrictions specified in this protocol,
13. Signed written informed consent (obtained as described in Section 13.3 of the protocol).

5.2. Exclusion criteria

14. Unlikely to cooperate in the study,
15. Pregnant and lactating women,
16. Women of childbearing potential (WOCBP) tested positive in a serum pregnancy test at screening or urinary pregnancy test at inclusion,
17. Participation in another interventional study at the same time or for a period of less than 5 half-lives after the last IMP administration prior to screening; participation in non-interventional registries or epidemiological studies is allowed,
18. Patient already enrolled in the study and having received at least one IMP administration (rescreening of patients having not received IMP is allowed),
19. History of severe allergic or anaphylactic reactions to monoclonal antibodies,
20. History of an allergy or hypersensitivity to the IMP (including its excipients)
21. Secondary Sjögren's Syndrome,

22. Signs or symptoms of a viral, bacterial, parasitic or fungal infection within 2 weeks (14 days) prior to randomisation (W000) according to the assessment of the investigator; any infection requiring IV antimicrobial (antibiotic, antiviral, antiparasitic or antifungal) treatment within 8 weeks prior to randomisation (W000),
23. Positive test for anti-human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBs) (or negative HBs antigen with positive anti HBc antibody and negative anti HBs antibody) or anti-hepatitis C virus (HCV) antibodies with a positive test for HCV viral RNA,
24. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × ULN or total bilirubin > 2 × ULN (unless due to Gilbert's disease) at screening, or evidence of chronic liver disease,
25. Severe or unstable disease of any type (independent of Sjogren's syndrome) that could interfere with safety and efficacy assessments (*e.g.,* uncontrolled cardiovascular, pulmonary, renal, hepatic, gastro-intestinal, endocrine disorders) according to investigator's judgment
26. Vaccination with a live/attenuated vaccine within 30 days prior to randomisation (W000). Recombinant or killed virus or messenger RNA or replication-incompetent vector vaccines, including SARS-CoV-2 vaccines, are permitted. Live seasonal flu and H1N1 vaccines are permitted ≥ 2 weeks prior to inclusion,
27. Poorly controlled diabetes (hemoglobin A1c > 8%),
28. History of malignancy within 10 years, except for basal or squamous cell carcinoma of the skin or cervical carcinoma in situ (cervical intraepithelial neoplasia Grade 3) treated with documented success of curative therapy,
29. Any of the following blood abnormality at screening:
    - Total white blood cell count < 1,500 × 10^6/L;
    - Neutrophil count < 800 × 10^6/L;
    - Lymphocyte count < 500× 10^6/L
    - Platelet count < 50,000 × 10^6/L;
    - Hemoglobin < 8 g/dL.
30. Prior administration of any of the following:
    - Belimumab in the past 6 months prior to randomisation (W000)
    - Rituximab or other B cell depleting agents *e.g.* VAY736 in the past 24 months prior to randomisation (W000). However, rituximab or other B cell depleting agents are allowed in the]12-24] months period if the CD19 B cell count is within normal range at randomisation (W000)
    - Abatacept in the past 3 months prior to randomisation (W000)
    - Tumor necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, and biosimilars) in the past 3 months prior to randomisation (W000)
    - Tocilizumab in the past 3 months prior to randomisation (W000)
    - Cyclophosphamide (or any other alkylating agent) in the past 6 months prior to randomisation (W000)
    - Cyclosporine (except for eye drops), tacrolimus, sirolimus, mycophenolate mofetil (MMF), azathioprine, or leflunomide in the past 3 months prior to randomisation (W000)
    - Janus kinase (JAK) inhibitors in the past 1 week prior to randomisation (W000)

31. Meeting any of the following conditions:
    - Corticosteroids: > 10 mg/day oral prednisone (or equivalent) within 4 weeks prior to randomisation (W000); Any change or initiation of new dose of oral prednisone (or equivalent) within 4 weeks prior to randomisation (W000); Intramuscular, IV, or intra-articular corticosteroids within 4 weeks prior to randomisation (W000); Any change or initiation of new dose of topical corticosteroids within 2 weeks prior to randomisation (W000)
    - Antimalarials: any change or initiation of new dose of antimalarials (*e.g.* chloroquine, hydroxychloroquine, quinacrine) within 16 weeks prior to randomisation (W000)
    - Methotrexate: > 25 mg/week of methotrexate within 12 weeks prior to randomisation (W000); any initiation or change of dose of methotrexate within 12 weeks prior to randomisation (W000); any change in route of administration within 4 weeks prior to randomisation (W000)
    - Non-steroidal anti-inflammatory drugs (NSAIDs): Any change or initiation of new dose of regularly scheduled NSAIDs within 2 weeks prior to randomisation (W000)
    - Cevimeline or oral pilocarpine: any increase or initiation of new doses within 2 weeks prior to randomisation (W000)
    - Ocular topics (excluding artificial tears, gels, lubricants, antibiotherapy): any dose modification or initiation of new doses within 90 days prior to randomisation (W000)
    - Required regular use of medications known to cause dry mouth/eyes as a regular and major side effect, and which have not been on a stable dose for at least 30 days prior to randomization (W000), or any anticipated change in the treatment regimen during the course of the study

32. A condition that, in the opinion of the investigator, could compromise the well-being of the patient or course of the study, or prevent the patient from meeting or performing any study requirements.

5.3. Definition of women of childbearing potential and contraception methods

The investigator must inform the patient about the risks not to use an effective method of birth control during the course of the study.

Women of childbearing Potential

A woman is considered of childbearing potential (WOCBP) *i.e.* fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception methods:

Definition of highly effective contraception methods for the study:

Highly effective methods of birth control refer to those which result in a low failure rate (*i.e.* less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), bilateral tubal occlusion, male sterilization (vasectomy).

5.4. Retest management during screening period

A patient who has a laboratory result(s) that does not satisfy the entrance criteria may have the test (s) repeated once providing that the investigator judges it relevant according to the patient previous results, or medical history and if s/he considers laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the patient will not be required to sign another informed consent, and the original patient ID number assigned by the investigator will be used.

In any case, the last result available for each parameter must be considered for the patient inclusion.

In the particular case where the ASSE visit is performed more than 14 days before W000, blood samples for blood cell count and CRP must be repeated (central or local) within a maximum of two weeks before W000. These tests repeated should be obtained within the allowed screening period, and must be considered for the patient inclusion.

Furthermore, laboratory tests can be repeated during the study (retest) in case of samples lost, broken, or if the the investigator judges it relevant according to the patient previous results.

5.5. Additional information recorded at the selection/inclusion visit

The following information will be recorded in the e-CRF: race and ethnicity, life habits (smoking habits, alcohol and caffeinated drinks consumption), date of diagnosis of pSS.

5.6. Patient withdrawal

5.6.1. Withdrawal criteria

Study drug dose adjustments and/or interruptions are not allowed in this study. However, in case of delay in dosing administration for any reason (*e.g.* AE,…), continuation of IMP should be discussed and agreed with the sponsor.

Patients may voluntarily discontinue the study for any reason at any time.

The Investigator should discontinue IMP for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

The reasons for premature discontinuation of IMP are:

- **Adverse events** according to the judgement of the investigator or according to the following predefined criteria:
  - Any adverse event ≥ Grade 3 (according to CTCAE/v5.0 grading) considered as related to the IMP administration,
  - Study treatment related cytokine release syndrome of grade 2 or higher (CTCAE v5.0 grading),
  - Major worsening of primary Sjögren's syndrome as judged by the Investigator.
- Pregnancy of the patient,
- Major deviation to protocol if it jeopardises patient's safety, *e.g.* any medical event requiring administration of an unauthorised concomitant treatment (see Section 6.3).
- Non-medical reason (to be carefully described) *e.g.* consent withdrawal, patient's removal.

Patients who discontinue study treatment should not be considered withdrawn from the study unless they withdraw their consent. They will perform a withdrawal visit (with all investigations described at W013 visit) and two FU visits, 9 and 18 weeks after the last IMP administration (see investigations in the investigational schedule table).

Information to be collected during the last visit of these patients is given in Section 5.6.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all patients who received the IMP.

5.6.2. Procedure

The investigator must record in the medical file and in the e-CRF, the reason and the date for the premature discontinuation of treatment / for the withdrawal from the study, the main assessment criteria, and the medical follow-up data.

If there are several reasons, the investigator must indicate the main reason.

A withdrawal visit (with investigations planned at W013) and FU visits respectively 9 and 18 weeks after last IMP administration should always be suggested to the patient.

In the case of premature withdrawal from the study due to an adverse event (event requiring immediate notification or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (see Section 8.9). This information is recorded in that part of the electronic case report form which concerns adverse events. If the investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the patient.

If the study is stopped / IMP is discontinued as a result of an event requiring immediate notification, the procedure described in Section 8.9.2.5 is to be implemented.

The dispositions to be taken after the IMP discontinuation are described in Section 6.5.

If a patient withdraws from further participation in the study (consent withdrawal), then no further study visits or data collection should take place.

5.6.3. Lost to follow-up

When the investigator has no news of the patient, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones…etc.), to establish the reason for the discontinuation of IMP and to suggest the patient comes to an end-of-study visit. If all these attempts to contact the patient fail, the investigator can then declare the patient "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PATIENTS

6.1. IMPs administered

S95011/matching placebo will be provided to the site in 2 mL extractable volume vials containing 100 mg of S95011/matching placebo (50 mg/mL) concentrate for solution. IMP will be stored in the original packaging in a limited access area at the temperature specified on the drug label and protected from light.
Instructions for handling the IMP to prepare and administer the infusion solutions are provided in the pharmacy manual, addressed to the investigator's site.

Preparation of the IMP solution will be performed by appropriate dilution of the IMP concentrate for solution in NaCl 0,9%, in the site pharmacy or site dedicated area under aseptic conditions under a laminar air flow cabinet or equivalent equipment by a qualified staff, according to instructions provided in the Pharmacy Manual.

After preparation, the infusion bag of S95011/placebo diluted in NaCl will be stored in controlled temperature room (≤ 25°C), up to 4 hours in infusion bag (including infusion).

IMP in the infusion bag will be administered by IV infusion in at least 60 min. If infusion related adverse reactions occur, the infusion flow rate will be decreased. If related adverse reactions continue, S95011/placebo will be stopped. In case of any signs of an acute reaction, clinical treatment will be provided as determined by the investigator on a case-by-case basis and depending on the severity, using symptomatic treatment, anti-histamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenalin.

In addition, at the 2 first visits with IMP administrations (W000 and W002), patients will be monitored closely for 2 hours after completion of infusion (or longer, at the discretion of the Investigator) for vital signs, physical examination and signs or symptoms of adverse events including development of an injection reaction. At all other visits with IMP administration (W004, W007 and W010), post-dose assessments will similarly include assessing infusion site, physical examination and vital signs before dismissing the patient from the clinical site.

All the details for preparation and administration will be provided in the pharmacy manual.

6.2. IMPs dispensing

The treatment group will be allocated *via* IWRS using a central randomisation (2:1) to S95011 or placebo with stratification by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (*e.g.* chloroquine, hydroxychloroquine, quinacrine) (yes/no).

At inclusion visit (W000), patient will be randomised to S95011 or placebo by IWRS. A connection to the IWRS should be performed at each concerned visit (from W000 to W010) to know the allocated kit numbers to be used for the infusion bag preparation (see details in IWRS manual).

Therapeutic units will be identified by a 6-digit number for identification, tracking and stock management purposes. For each administration, 9 vials of IMP will be delivered.

The detachable portion of the label on the IMP box must be stuck by the investigator's staff on the prescription form when the IMPs are dispensed by a pharmacist.

For each patient, the IMP will only be dispensed during the study. At W010 visit, the last administration of the IMP will be performed.

At last study visit, the investigator will propose a treatment adapted to the nature of the clinical state of the patient.

6.3. Previous and concomitant treatments

For treatments prohibited and authorised before the study, refer to Section 5.

Previous treatments are all treatments received and stopped within 12 months before screening visit (including vaccinations*).

C**oncomitant treatments** are treatments ongoing at screening visit as well as new treatments initiated during the study.

**for this study, all vaccinations deemed necessary by the investigator for the patient should be up to date before inclusion. Therefore, the corresponding last vaccinations and last boosters will be considered and reported as previous treatment (even if administered more than 12 months prior to the screening visit).*

Previous and concomitant treatment (prescriptions or over-the-counter medications) must be reported in the e-CRF. Reported information will include a description of the type of the drug, treatment period, dosing regimen, route of administration and its indication.

Any change in dosage must also be reported in the Concomitant Treatments e-CRF section. Data on concomitant medication will be collected up to the last follow-up visit, even after withdrawal of a patient.

Those patients who are receiving permitted medications for pSS [oral corticosteroids at a dose of max 10 mg per day (prednisone or equivalent), anti-malarials, methotrexate at a stable dose (up to 25 mg per week), NSAIDs, artificial tears and artificial saliva/salivary stimulants (*e.g.* cevimeline, pilocarpine), cyclosporine eye drops and lifitegrast], and/or regular use of medications known to cause dry mouth/eyes as major side effects, **must be maintained on a stable regimen** (and for methotrexate, route of administration) throughout the treatment period compared to baseline. These treatments are considered "usual" background therapy in the absence of recognized standard of care. The IMP is evaluated as add-on to background treatment and not as a monotherapy.

The safety profile of such combinations is considered acceptable taking into account the mechanism of action of S95011 and the knowledge acquired with other biologics.

The salivary stimulants (*e.g.* cevimeline, pilocarpine), cyclosporine eye drops and lifitegrast should not be used during the **12 hours prior to**, and during the assessment of clinical disease outcome measurements (Schirmer test and sialometry). Artificial tears and artificial saliva should not be used during the **4 hours prior to**, or during the assessment of clinical disease outcome measurements (Schirmer test and sialometry).

Prohibited Concomitant Medications

Patients are not permitted to receive any of the following immunosuppressants or biological therapy (monoclonal antibodies, fusion proteins) while receiving IMP. These treatments act as S95011 on the immune system and the safety profile of such combinations are not yet known. Duration of wash out periods depends on half lifes of products and immune system recovery.

- Corticoids greater than 10mg/day prednisone or equivalent
- Methotrexate > 25 mg/week
- Belimumab
- Rituximab
- Abatacept
- Tumor necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab and biosimilars)
- Tocilizumab
- Cyclophosphamide (or any other alkylating agent),
- cyclosporine (except for eye drops), tacrolimus, sirolimus, mycophenolate mofetil, azathioprine, or leflunomide
- JAK inhibitors

Furthermore, any live or attenuated vaccine are forbidden. Administration of recombinant or killed virus or messenger RNA or replication-incompetent vector vaccines, including SARS-CoV-2 vaccines, are acceptable. Vaccination of patients during treatment with S95011 and prior to clearance of S95011 is likely to result in non-protective antibody titers due to the pharmacologic activity of S95011. Consequently, all vaccinations deemed necessary by the investigator for the patient should be up to date before inclusion.

If the patient needs to receive one of these prohibited medications, she/he will have to discontinue the investigational product and will perform a withdrawal visit (with all investigations described at W013 visit) and two FU visits, 9 and 18 weeks after the last IMP administration (see investigations in the investigational schedule table).

A list of the above prohibited and unauthorized treatments **by drug class** can be consulted in the e-CRF.

Rescue treatment

There is no established, approved immunosuppressive treatment for pSS. However, patients may receive usual background therapy as outlined in section 6.3 and as long as it is maintained on a stable regimen all along the study.

Rescue medicine is to be provided by the investigator or the personal physician. Use of rescue medication must be recorded on the Concomitant medications in the e-CRF after start of study drug.

6.4. IMP compliance

The number of injectable vials dispensed and used are to be counted by the investigator or the pharmacist. The real volume and concentration of the solution administered and the exact start and end times of each infusion will be recorded in the electronic case report form and therapeutic unit tracking form, or an equivalent document.

6.5. Discontinuation of the IMP

After the discontinuation of the IMP, the patients' medical care is left at the physician's discretion.

Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

Efficacy measurements performed during the study are indicated in Table (4.1.2) 1.

7.2. Methods and measurement times

- **ESSDAI (EULAR Sjögren Syndrome Disease Activity Index):** ESSDAI is a physician-administered clinical index used to evaluate systemic disease activity. The instrument contains 12 organ-specific domains contributing to disease activity (*i.e.*, organ systems: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system (PNS), central nervous system (CNS), haematological, glandular, constitutional, lymphadenopathic, biological). For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The maximum theoretical score is 123 (Appendix 3).

  During screening, ESSDAI total score should be ≥ 6, with at least 6 points within the 7 following domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematologic and biologic.

  Then, ESSDAI will be applied to the study patients at ASSE, W000, W004 and W013.

  The approximative total duration of the measurement is 30 minutes.

  This scale must be administered by a trained clinician. The training will be performed before the inclusion of any patient in the site.

  Over the course of the study, the ESSDAI should be completed by the same trained investigator for a given patient (insofar as possible). If there is a change in site personnel over the course of the study, new investigators must be trained and certified prior to performing the ESSDAI.

At each ESSDAI assessment, cryoglobulins measurement will be performed locally and the result will be used for ESSDAI scoring. In case of presence of cryoglobulinaemia, cryoglobulin will be identified (Type I, II or III) and reported in e-CRF. Cryoglobulin result obtained from a previous sampling performed within 1 month before screening visit could be used for ESSDAI scoring at screening.

In addition, immune panel (C3 and C4 complement fractions, CH50 (or CH100), quantitative immunoglobulins, and immunofixation electrophoresis) will be assessed at each visit with ESSDAI assessment for exploratory endpoint, by a central laboratory. The results will be provided to the investigator and used for ESSDAI scoring (see Section 9.5.1).

For assessments not listed in the protocol as mandatory tests but which may be needed to estimate ESSDAI, including Chest X-ray, pulmonary high resolution computer tomography (HRCT), lung function test (Diffusing-capacity of the lung for carbon monoxyde (DLCO), forced vital capacity (FVC)), estimated glomerular filtration rate (eGFR), electromyography (EMG), muscle (or any other) biopsy, it is at the investigator's discretion to have these assessed based on the signs and symptoms of the patient so to provide correct ESSDAI readout.

ESSDAI questionnaire will be filled in by the investigator on an electronic device (e-PRO e-COA). All the documentations used for the ESSDAI scoring and justification of scoring will be stored in the patient's medical file and considered as source documents.

- **ESSPRI (EULAR Sjögren's Syndrome Patient-Reported Index):** ESSPRI is a patient-administered questionnaire to assess patient symptoms within the last 2 weeks and combines 0–10 numerical rating scales for dryness, fatigue and pain (joint and muscular pain in legs and arms). The maximum theoretical score is 10 (mean score of the 3 subscores) (Appendix 4).

  ESSPRI will be applied to the study patients at W000, W004 and W013.

  The approximative total duration to complete the questionnaire is 5 minutes.

- **MFI** (Multidimensional Fatigue Inventory): the MFI is a self-report measure designed to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. The MFI is a 20-item scale ranging from 1 to 5 to indicate how aptly certain statements regarding fatigue represent the individual experiences. Higher total scores correspond with more acute level of fatigue (Appendix 5A).

  MFI will be applied to the study patients at W000, and W013.

  The approximative total duration to complete the questionnaire is 5-10 minutes.

- **SF-36** (Short Form Health Survey): SF-36 is a self-report questionnaire for the quality of life. It is a survey with 36 questions evaluating individual patients' health status which also monitors and compares patients' disease burden. It consists of eight scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section (Appendix 5B).

  SF36 will be performed at W000 and W013.

  The approximative total duration to complete the questionnaire is 20 minutes.

- **Physician (PhGA) and Patient Global assessment (PGA)** of the pSS activity assessed on numerical rating scales (NRS) (Appendix 6):
  - The PhGA NRS represents the investigator's overall assessment of pSS disease activity on a 0 to 10 scale, with 0 indicating 'inactive disease' and 10 indicating 'very highly active disease'.

    Every attempt should be made to have the same investigator complete the PhGA NRS for each patient throughout their study participation.
  - The PGA NRS represents the patient's overall assessment of pSS disease activity on a 0 to 10 scale: "Considering now your symptoms related to your Sjögren's syndrome (your dryness, your fatigue, your pain and your mental fatigue), as well as their consequences on your professional or personal life, how severe was your Sjögren's syndrome during the last 2 weeks?"

PhGA and PGA NRS will be applied using e-PRO and e-COA, respectively, at W000 and W013.

The questionnaires (ESSPRI, SF-36, MFI, and PGA) will be explained to the patient by the investigator (or a delegate person) and will be filled in by patients during the visits on an electronic device (e-PRO). Data entered by the patient will be sent to a central database via a secured transfer.

Under certain exceptional circumstances (for example, unexpected technical issue), the patient might complete the self-reported questionnaires (ESSPRI, MFI, SF36, PGA) remotely using a secured internet link provided by the site.

- **Schirmer test**:

  Cyclosporine eye drops and lifitegrast should not be used during the **12 hours prior to**, and during the assessment of the test. Artificial tears should not be used during the **4 hours prior to**, or during the assessment of the test.

  Both eyes are tested at the same time. Calibrated strips of a non-toxic filter paper are used. One free end is placed within the lower eyelid. Patient has to keep eyes gently closed for 5 minutes and then, the paper strips are removed from each lower eyelid and the amount of wetting of the paper strips is measured (< 5 mm = dry eye, 5-10 mm = grey zone, > 10 mm = normal).

  If performed on the same day, the Schirmer test should be performed before Ocular Staining Score.

  The approximative total duration of the Schirmer test is 15 minutes.

  The Schirmer test will be performed at W000 and W013.

  The result of the Schirmer test will be recorded by paper and data will be entered by the investigator or a delegate person on e-CRF.

- **Ocular Staining Score (OSS):** The SICCA OSS uses lissamine green dye to grade the conjunctiva and fluorescein dye to grade the cornea. Total ocular staining scores of 0 to 12 *per* eye assess the range of severity of keratoconjunctivitis sicca.

  The test will be performed by an ophthalmologist or by a qualified person with experience in using the OSS in Sjögren patients:

Corneal fluorescein staining pattern (step 1 of the OSS scoring system)

Each cornea is examined at the slit lamp using the cobalt blue filter. Grading of the fluorescein pattern is initiated between 4 and 8 minutes after instillation of fluorescein. Alternatively, strips can be used.

Punctate epithelial erosions (PEEs) that stain with fluorescein are counted and scored. An additional point is added if: (1) PEE occurred in the central 4-mm diameter portion of the cornea; (2) one or more filaments is seen anywhere on the cornea; or (3) one or more patches of confluent staining, including linear stains, are found anywhere on the cornea. The total fluorescein score for the cornea (the PEE grade plus any extra points for modifiers) is noted in the central square of the SICCA ocular staining score form. The maximum possible score for each cornea is 6 (see Appendix 7).

Conjunctival lissamine green staining pattern (step 2 of the OSS scoring system)

After the external examination, 1 drop of 1% lissamine green dye is applied to the inferior conjunctival fornix of both eyes. Alternatively, lissamine green strips can be used and placed in the inferior conjunctival fornix of both eyes.

The same method of administering lissamine green should be used for an individual patient at each assessment time point. The conjunctivae are examined with the slit lamp at x10 magnification, using a neutral density filter over the light source to avoid blanching of the conjunctiva. It is important to examine and grade the eyes immediately after instilling lissamine green dye because the intensity and extent of the ocular staining diminishes rapidly after the first 2 minutes. It is also important for the patient to blink several times to keep dye from pooling in the conjunctival folds which can mimic conjunctival staining. If adequate dye is not instilled initially, a second drop can be given and the examination performed immediately thereafter. The number of dots is counted for grading of the scored dots; nasal and temporal bulbar conjunctivae graded separately).

Because of the difficulty of counting individual dots in a moving eye at the slit lamp, any area of confluent staining of 4 mm^2 or more is considered to be more than 100 dots. Nasal and temporal areas of the conjunctiva are graded separately with a maximum score of 3 for each area or a total maximum score of 6 for each eye (nasal plus temporal) (See Appendix 7).

Calculation of total OSS

The total OSS for each eye is the summation of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva. The maximum possible score for each eye is 12 (See Appendix 7).

The approximative total duration of the OSS test is 20-30 minutes.

OSS assessment will be performed at W000, W004 and W013.

The result of the OSS will be recorded by paper (Appendix 7) and data will be entered by the investigator or a delegate person on e-CRF.

- **Sialometry under unstimulated and stimulated conditions**:

  Unstimulated whole saliva collection always should precede stimulated whole saliva collection.

  Patients receiving standard of care for xerostomia must discontinue use of pilocarpine or cevimeline for at least 12 hours and artificial saliva for at least 4 hours prior to the collection of saliva. Patients should be prohibited from eating or drinking for at least 90 minutes prior to the collection of saliva.

  During the unstimulated salivary flow assessment, patients should refrain from speaking or swallowing, with the exception of a single swallow, immediately prior to the initiation of the procedure. The entire duration of the procedure is expected to be approximately 5 minutes, during which patients will be asked to allow saliva to accumulate in the oral cavity for a period of 60 seconds prior to emptying into a pre-weighed container; this is to be repeated a total of 5 times during the test.

  Stimulated salivary flow rate and collection should always be performed after unstimulated salivary flow and collection. Patients may be offered a single rinse with water between the procedures. For stimulated saliva measurements, the same procedures are followed as for the unstimulated collections, except that stimulus with 2% citric acid directly to both sides of the posterior lateral tongue will be applied for 5 seconds every 30 seconds for 2 minutes prior to the first stimulated collection.

  The weight of the collection vial is to be determined and recorded before and after the collection, with the difference representing the saliva volume.

  As for unstimulated sialometry, stimulated salivary secretions are collected over 5 minutes.

  The same method of saliva collection and salivary flow rate determination should be used for an individual patient at each assessment time point and for each purpose, respectively.

  The approximative total duration of the sialometry assessment is 20-30 minutes

  Sialometry assessments will be performed at ASSE (Stimulated whole salivary flow rate > 0 mL/minute), W004 and W013

  The results of the sialometry tests will be recorded on paper as source document and also in the e-CRF. Flow rate of saliva = Volume (mL)/minute will be calculated automatically in the e-CRF.

  If deemed more convenient, Schirmer, OSS and Sialometry can be performed the day before the scheduled visit's date.

8. ASSESSMENT OF SAFETY

All adverse events and other situations relevant to the safety of the patients must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of safety parameters

Safety measurements performed during the study are indicated in Table (4.1.2) 1.

- **Adverse events,**
- **Physical examination,**
- **Body weight (kg),**
- **Vital signs:**
  - Systolic blood pressure (SBP) (mmHg)
  - Diastolic blood pressure (DBP) (mmHg)
  - Pulse Rate (bpm)
  - Body temperature
- **12-lead ECG,**
- **Laboratory examinations (serum biochemistry and haematology, pregnancy tests, coagulation tests, cryoglobulins, urinalysis):**
  - **Serum biochemistry (central):** Albumin, total protein, C reactive protein (CRP), alkaline phosphatase, total bilirubin, gamma glutamyltransferase (GGT), aspartate amino transferase (AST), alanine amino transferase (ALT), lipase, amylase, bicarbonate, calcium, chloride, potassium, sodium, lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol, triglycerides, glucose, creatinine, urea and uric acid. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

    In addition, **HbA1c** assay will be performed **locally** at screening for eligibility criteria and **ESR** will be also performed locally at each visit for the assessment of the inflammatory status.
  - **Serum Haematology (central):** Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (*e.g.* neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count.
    CD19 B cell count performed **locally** at screening to check eligibility criterion n°30 (rituximab or other B cell depleting agent).
  - **Urinalysis (local):** A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood. If dipstick urinalysis is abnormal, microscopic examination for WBC, RBC, crystals, and casts will be performed.
  - **Coagulation test (central):** Prothrombin time (PT), activated partial thromboplastin time (aPTT) will be measured.
  - **Cryoglobulins (local):** at each ESSDAI assessment (ASSE, W000, W004, W013), cryoglobulins measurement will be performed (see Section 7.2). Cryoglobulin result obtained from a previous sampling performed within 1 month before screening visit could be used for ESSDAI scoring at screening.
  - **Pregnancy tests in WOCBP (local):** Serum pregnancy tests will be performed at screening. At all other times urine pregnancy tests may be used.

8.2. Methods and measurement times

- **Physical examination:** will be performed at ASSE, W000, W002, W004, W007, W010, W013, W019, W028.
- **Vital signs (pulse, blood pressure, body temperature):** will be assessed after 5 min rest, in supine position Blood pressure will be measured preferably on the same arm. All devices routinely used in the centre to measure blood pressure are accepted.

  Vital. signs will be performed at ASSE, W000, W002, W004, W007, W010, W013, W019, W028.

  On the days of administration, the physical examination and vital signs will be performed:
  - pre-dose
  - and post dose (before discharge): at W000 and W002, patients will be monitored closely for 2 hours after completion of IV infusion (or longer, at the discretion of the Investigator) for vital signs, and signs or symptoms of adverse events including development of an injection reaction. At all other visits with IMP administration (W004, W007, W010), post dose assessments will similarly include assessing infusion site, physical examination and vital signs before dismissing the patient from the clinical site.
- **Body weight (kg):** will be measured with an empty bladder, the patient being in indoor clothing, without shoes at ASSE, W000, W004, W010, W013, W019, W028.
- **12-lead ECG:** A standard 12 lead ECG will be recorded in lying position after 5-10 minutes rest. The investigator or designated physician will review and sign all ECGs. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

  Clinically significant ECG abnormalities, as judged by the investigator, will be recorded on the relevant medical history CRF page prior to first dosing and on the Adverse Events page thereafter.

12-Lead ECG will be performed at W000, W004, W010, W013, W019, W028.

On the days of administration, the 12-lead ECG will be performed pre-dose.

- **Laboratory examinations**

Laboratory tests analysis will be subcontracted to a central laboratory except for assessments such as infectious disease panel, HBA1c, tuberculosis test and for ESR, cryoglobulins, urinalysis and pregnancy tests. The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual.

In the particular case where the ASSE visit is performed more than 14 days before W000, blood samples for blood cell count and CRP must be repeated (central or local) within a maximum of two weeks before W000. These tests repeated should be obtained within the allowed screening period, and must be considered for the patient inclusion.

All safety samples will be destroyed after analysis or at the latest at study end.

The central lab will provide the investigators with a copy of the results and of reference values corresponding to the central measurements. A fully identified copy of the laboratory results print-out will be evaluated, dated and signed by the investigator and kept in the investigator binder. In case of a lost sample, or technical problem or if necessary for a clinical reason, a re-test can also be ordered by the investigator.

Laboratory results will be assessed by the investigator for clinical significance as soon as they become available and he/she will contact the patient if an unfavourable change is observed.

Clinically significant abnormalities will be recorded on the relevant medical history e-CRF page prior to first dosing and on the Adverse Events page thereafter. Abnormal laboratory values or tests constitute AEs or medical history only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease.

Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

- **Serum biochemistry and ESR:** will be performed at ASSE, W000 , W002, W004, W007, W010, W013, W019, W028.
- **Serum Haematology** will be performed at ASSE, W000, W002, W004, W007, W010, W013, W019, W028.

At W000, W002, W004, W007, W010, W013, W019 and W028 visits, serum biochemistry samples will be performed after 10 hours fasting.

- **Urinalysis:** A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

  Urinalysis will be performed at ASSE, W000, W002, W004, W007, W010, W013, W019, W028.
- **Coagulation test:** will be performed at ASSE, W000, W002, W004, W007, W010, W013, W019, W028.
- **Serum pregnancy test:** will be performed in WOCBP locally at ASSE.
- **Urinary pregnancy test:** will be performed in WOCBP at W000, W002, W004, W007, W010, W013, W019, W028.

8.3. Definition of Adverse events

An adverse event is defined as any untoward medical occurrence in a patient participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the patient signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (*e.g.* run-in period) are also concerned).

An adverse event can therefore be:
- any unfavourable and unintended sign (including an abnormal finding from an additional examination such as lab tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator,
- any symptom or disease,
- any worsening during the study of a symptom or a disease already present when the patient entered the study (increase in frequency and/or intensity),

  and detected during a study visit or at an additional examination or occurred since the previous study visit.

Of note:
Any **hospitalisation for social reasons, educational purpose** (*e.g.* learning of diabetes management by the patient) or routine check-up should not be considered as an adverse event and should not be reported in the CRF.
The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the e-CRF and kept in the source data (or patient file)**:
- Therapeutic procedures related to a non-aggravated medical history (*e.g.* cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study),
- Prophylactic procedures (*e.g.* sterilisation, wisdom teeth removal),
- Comfort procedures (*e.g.* cosmetic surgery),
- Control procedures of a pre-existing condition without aggravation (*e.g.* colonoscopy to control the remission of colon cancer).

Symptoms related to the studied pathology (pSS):
Symptoms of pSS occurring prior to first dosing have not to be reported in the medical history page of e-CRF. Only aggravations or new occurrence of pSS symptoms from first dosing will be reported as adverse event. In case of major worsening of Primary Sjögren's syndrome, the patient could be prematurely withdrawn according to the judgement of the investigator. (see Sections 5.6.1 and 8.9.2.4).

8.4. Definition of Serious adverse events

Any adverse event that at, any dose:
- Results in death,
- Is life-threatening[(1)],
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Is medically significant[(2)],
- Results in persistent or significant disability/incapacity[(3)],
- Is a congenital anomaly/birth defect[(4)].

[(1)] Life-threatening in this context 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.

[(2)] Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

[(3)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

[(4)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of Overdose

This refers to any intake or administration of a quantity of IMP which is above the maximum dose recommended in the study protocol, independently of the occurrence of any adverse event.

The quantity should be considered *per* administration or cumulatively regarding the maximum dose recommended in the study protocol (750 mg).

8.6. Definition of Adverse event of special interest

An adverse event of special interest (AEOSI) is one of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation with detailed information such as hospital records is required. It may be a serious or non-serious AE that may require further investigation in order to characterize and understand.

AEOSI include:
- Allergic reaction grade 3 or higher according to CTCAE/v5.0 grading including infusion related reaction (Note: Humans administered foreign proteins are at risk of developing allergic reactions, including anaphylaxis).
- Cytokine release syndrome: No cytokine release has been observed in FIH study (IFNγ, IL12p70, IL4, IL5, IL6, IL8, TNFα), however, given the risk of cytokine release syndrome observed in certain therapeutic monoclonal antibodies, this event will be systematically collected and closely monitored in patients treated with S95011). In case of suspiscion of cytokine release syndrome, a blood sample for cytokines assay will be performed and analysed locally.
- Infections grade 3 or higher according to CTCAE/v5.0 grading (Note: IL 7 receptor inhibition may induce immunomodulation, so patients should be monitored clinically for manifestations of infectious disease, and, if necessary, appropriately treated [*e.g.* with antibiotics]).
- Lymphopenia <500x10^6/L (grade 3 or higher according to CTCAE v5.0 Criteria)

No safety concern with S95011 (See Investigator's Brochure) has been identified in preclinical studies and phase I study.

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (*i.e.* without delay and within 24 hours at the latest) to the sponsor if it is:
- A serious adverse event,
- An AEOSI, as defined in Section 8.6.
- An overdose of the IMP even if asymptomatic,
- Any intake of the IMP by a person around the patient,
- A pregnancy (patient or patient's partner).

8.8. Classification of an adverse event (seriousness, intensity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an adverse event and the IMP. This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event, the causality and the seriousness (See Section 8.9.3).

The Seriousness should be evaluated according to international guidances (see definition Section 8.4, in accordance with ICH Topic E2A and the DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April).

The Intensity of AEs should be graded using the modified Common Terminology Criteria for Adverse Events CTCAE v5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in the table below.

Grading of Adverse Event Intensity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Fatal	Death-related AE

* *Activities of Daily Living (ADL) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

** *Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical intensity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

The causal relationship to the IMP or to the experimental procedures must be assessed when reporting the AE in the AE form. Cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the mechanism of action of the IMP…), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and drug is at least reasonably possible (*i.e.* the relationship cannot be ruled out) it is to be considered as "related".

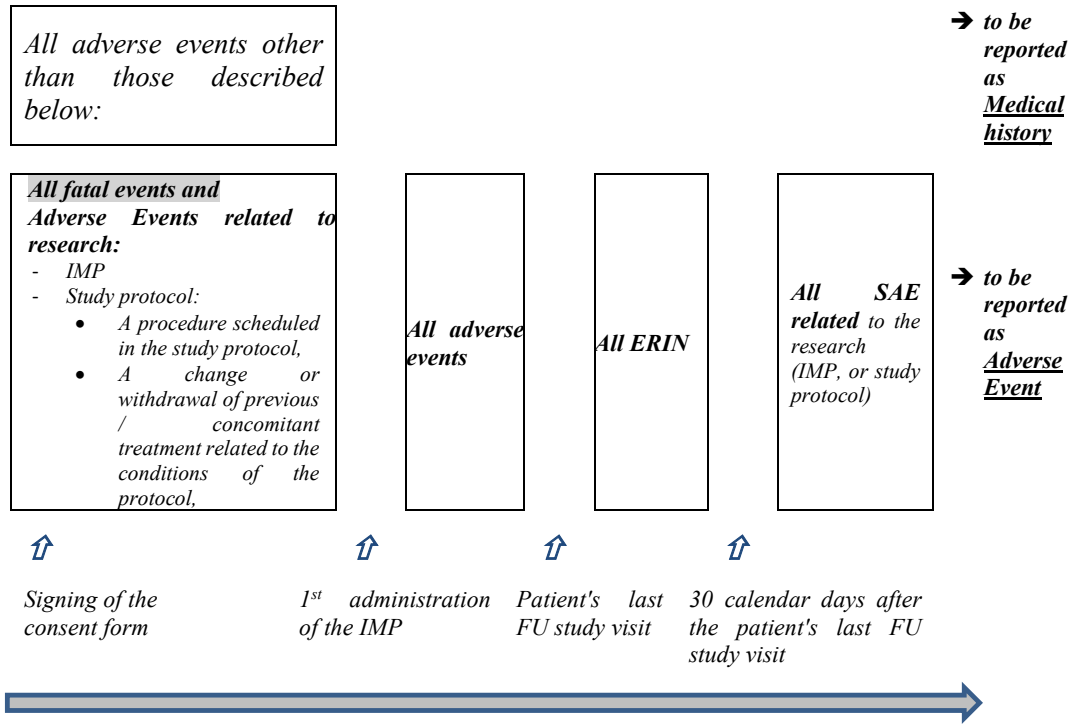
8.9. Reporting procedures

8.9.1. Time frame for AE reporting

Any event meeting the above mentioned definitions (see Sections 8.3 to 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- Before the first administration of the IMP, **for fatal events and events related to the research.**
- At any time after the first administration of the IMP up to the patient's last study visit for all events,
- After the patient's last Follow-up study visit:
  - Up to 30 calendar days after the patient's last study visit for all ERIN, regardless of the supposed role of the research (IMP, or experimental procedure).
  - Irrespective of the time of onset in case of serious adverse event related to the research (IMP, or experimental procedure).

Of note, events occurring between the signature of the informed consent and the first administration of the IMP for which the investigator does not consider an association with the research must be reported as **medical history** in the dedicated form of the e-CRF. ***Fatal events, related or not to the research, occurring after ICF signature and before first IMP intake, must be reported on AE form.***



8.9.2. Responsibilities of the investigator

For any adverse event and special situation mentioned above the investigator must:

- **Note in the patient's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the patient or a third person, …) and any other relevant information which he/she has learned of the event,
- **Assess** the event in terms of seriousness, intensity and causality,
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately),
- **Document** the event with additional useful information,
- Ensure the **follow-up** of the event,
- **Fulfill his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. In particular for ERIN or related withdrawal adverse event, he/she should provide the sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis or the autopsy report, if autopsy is performed.

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the patient is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be written up in a new complete evaluation of the event documented on an “Adverse event” page previously created for the event.

If the adverse event has not resolved at the patient's final visit in the study, the patient must be followed up suitably and any information on the outcome of the event will be noted on the « Adverse Event » page previously created for the event (e-CRF). The information will be recorded at a follow-up visit.

If the follow-up of the patient is not done by the investigator him/herself (hospitalisation, followed by a specialist or the patient's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the patient.

8.9.2.3. Special situations (pregnancy, overdose, IMP intake by a person around the patient)

Pregnancy

If a female patient in the study becomes pregnant, the investigator must:
- Stop immediately the IMP,
- Report it on an « Adverse Event » page in the e-CRF as well as on the specific paper pregnancy form (1st page) to be notified immediately (ERIN),
- Contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).
- If the partner of a patient becomes pregnant during the course of the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP
- In case of overdose, the investigator should report it on an "Adverse Event" page in the e-CRF to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - Dose details (number of units, duration,…) and, if multiple overdose, details regarding other medicinal products or substance ,
  - Context of occurrence, *i.e.* intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage),
  - Related signs and symptoms ("No related adverse events" to be reported otherwise),
  - Outcome.
- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP by a person around the participant

This event should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording Methods in the e-CRF

Adverse events must be documented on the « Adverse Event » page of the e-CRF.

In case of chronic disease:
- if the disease is known when the patient enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event,
- if the disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the « Adverse Event » page previously created for the event (e-CRF) which will clearly describe the diagnosis.
- **In the specific case of Sjögren's syndrome,** new occurence of symptoms or aggravations will be reported in the e-CRF as adverse events. Description of the symptoms will be recorded in the description of these AE.

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:
- **Immediately** after being informed of this event, **fill in** the **patient's medical file** as well as the **« Adverse Event » page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into the e-CRF, an e-mail will be immediately and automatically sent to the sponsor,
- Ensure medical oversight of the SAE reporting by attesting the authenticity of the data (see Section 14.1),
- Provide the sponsor (person designated in the contact details provided in the investigator's study file), as they become available, with anonymized copies of the documents which provide additional useful information,
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC in accordance with local regulations.

If an adverse event initially non-serious worsens and becomes serious (ERIN), this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:
- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page,
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page,
- Immediately send them by fax or by e-mail to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line is +33.1.55.72.60.00.
- As soon as the e-CRF becomes available, the investigator should enter these data in the « Adverse Event » page of the e-CRF.

8.9.3. Responsibilities of the sponsor

In accordance with international guidances, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of documents providing useful information such as reports of further consultations, laboratory tests reports, reports of other examination aiding diagnosis may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.Independently of the regulatory obligations of the investigator, and according to the requirements stated in ICH Good Clinical Practice guidelines and local regulations, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product to the appropriate Authorities and to all the investigators involved. Any new safety finding likely to affect the benefit /risk balance of the product will be also notified to the trial patients involved - through the investigators - as mentioned in Section 13.4 "Modification of the information and consent form".

The concerned Authorities will be notified as soon as possible by the Sponsor of the Data Safety Monitoring Board (DSMB) recommendations if any, where relevant for the safety of patients (*i.e.* modification or discontinuation of the study).

8.10. Responsabilities of Data Safety Monitoring Board

In accordance with the DSMB charter and the rules for DSMB functioning (refer to Section 12.4), the independent external DSMB is responsible for reviewing the safety data on a regular basis, and providing written recommendations to the Sponsor regarding the conduct of the study (continuation as per protocol, modification, temporary halt or premature discontinuation).

Unscheduled DSMB meetings may be organized at any time should patient safety issues or other unanticipated problems arise.

The DSMB charter will define the data to be received by the DSMB on a regular basis, as well as the data/events to be received without delay and may trigger urgent DSMB meeting.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments related to inclusion/exclusion criteria

- **Body Height (m)**
  Patients must have a body mass index (BMI)* between 18 (exclusive) and 40 (inclusive) at inclusion
  BMI = Body weight (kg)/Body height^2 (m^2)
- **Auto-antibody panel:** Anti-nuclear antibody (ANA), extractable nuclear antigens (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), and RF, will be measured during screening period for patient eligibility (diagnosis of primary Sjögren's Syndrome based on 2016 ACR-EULAR criteria and positive anti-SSA (Ro) antibodies or anti-nuclear antibodies (ANA) ≥1:320 or rheumatoid factor (RF) >20 IU/ml). (see Section 9.5.1)
- **Infectious disease panel:** Hbs Ag, anti-HBc, anti-HBs, anti HCV, and HIV antibodies will be measured during the screening period to exclude patients with HIV, HBV or HCV infections (see Section 5.2).
- **HbA1c assay** will be performed at screening for eligibility criteria (HbA1c should be ≤ 8%) (see Section 8.1).
- **CD19 B cell count** performed **locally** to check criterion n°30 (rituximab or other B cell depleting agent).

- **Interferon Gamma Release assay (IGRA) tuberculosis test (Quantiferon or T-Spot):** performed during the screening period to exclude patients with Tuberculosis infection.
- **Chest X-Ray:** obtained during the screening period or anytime within 90 days prior to signing the ICF in order to exclude any current active infection (*e.g.* TB), malignancy, or clinically significant abnormalities (unless due to pSS).

The results of these exams should be available for the inclusion/exclusion criteria assessment at inclusion visit (W000).

All samples will be destroyed after analysis or at the latest at study end.

9.2. Measurement of drug concentration

For all patients, blood samples (3 mL/time-point) will be collected to determine S95011 serum concentrations and characterize S95011 PK profile:

- Pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007, and W010
- Right after the end of the IMP infusion and in the [1-3h] interval after the end of the IMP infusion at W000 and W010
- Between W011 and W012, and at W013, W016, W019 and W028.

The determination of the concentration of S95011 will be analysed by a bioanalytical laboratory under the responsibility of the Sponsor, using a validated bioanalytical method (ELISA-like ECLIA/MSD method). The bioanalytical procedure will be described in a separate bioanalytical protocol.

The randomisation list will be sent to the bioanalytical lab in order to select the samples to be analysed.

The details for sampling, handling, storage and shipping of the samples will be described in the laboratory manual.

All samples should be collected at the time specified and properly labelled. Samples missed or lost for any reason should be recorded.

For each sample, the exact dates and times of serum sample collection will be reported in the requisition form.
PK samples will be destroyed after their analysis or at the latest at study end, PK back-up samples will be stored in the biorepository if agreed by the patient (specific optional informed consent signed) (See Section 9.5.3)

9.3. PK/PD analyses: Receptor occupancy (RO)

For all patients, blood samples (1 mL/time-point) will be collected to determine RO.

RO will be measured in blood samples taken pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007 and W010, right after the end of the infusion of the IMP at W000 and W010, and at W013, W019, W028.

The determination of the receptor occupancy will be analysed by a bioanalytical laboratory under the responsibility of the Sponsor, using a validated bioanalytical method. The analytical procedure will be described in a separate bioanalytical protocol. The randomisation list will be sent to the bioanalytical lab in order to select the samples to be analysed.

The details for sampling, handling, storage and shipping of the samples will be described in laboratory manual. All samples should be collected at the time specified and properly labelled. Samples missed or lost for any reason should be recorded.

For each sample, the exact dates and times at which the IMP is lastly administered should be reported in the requisition form in addition to the exact dates and times of serum sample collection.

All RO samples will be destroyed after analysis or at the latest at study end.

9.4. Measurement of anti-drug antibodies (ADA)

To determine the incidence of anti-drug antibodies (ADA) formation, blood samples (3 mL/time-point) will be collected for all patients:

ADA will be measured in serum samples taken pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007 and W010, and at W013, W019, W028.

ADA formation will be determined using S95011-specific ADA assays, by a bioanalytical laboratory under the responsibility of the Sponsor, using a validated bioanalytical method. The bioanalytical procedure will be described in a separate bioanalytical protocol. The randomisation list will be sent to the bioanalytical centre in order to select the samples to be analysed.

All the procedures for sampling, labelling, handling, storage and shipment will be described separately in a laboratory manual. All samples should be collected at the time specified and properly labelled. Samples missed or lost for any reason should be recorded.

For each sample, the theoretical and exact dates and times at which the study drug is lastly administered should be reported in the requisition form in addition to the exact dates and times of serum sample collection.

ADA samples will be destroyed after their analysis or at the latest at study end. ADA back- up samples will be stored in the biorepository, if agreed by the patient (specific optional informed consent signed) (See Section 9.5.3).

9.5. Exploratory biological parameters in blood

In order to improve the knowledge of the study drug, the following blood samples will be performed for:

- Lymphocytes subsets,
- Other proteins involved in pSS physiopathology: IL-7, cytokines and specific proteins, cytokine release panel.
- Immune panel, auto-antibody panel and β2 microglobulin.

9.5.1. Assessments in blood

Participation in the CL2-95011-001 study implies a systematic participation in the mandatory investigation. All patients will have to consent to this investigation by signing the main information and consent form for participation in the study.

In addition, in case of consent withdrawal, related samples will be destroyed after mandatory assessment is completed and at the latest at study completion.

Lymphocytes subsets (PBMC):

Lymphocytes subsets will be measured on PBMC at W000, W004, W007, W013.

The lymphocytes subsets panels analysis will be subcontracted to a central laboratory. The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual.

Results will be directly transferred in the sponsor database by the central laboratory, without communication to the investigator.

PBMC samples will be destroyed after their analysis or at the latest at study end. PBMC back-up samples will be stored in the biorepository, if agreed by the patient (specific optional informed consent signed) (See Section 9.5.3).

IL-7, cytokines and other proteins involved in pSS physiopathology

IL-7 and some cytokines (for instance may include but not limited to and according to the analytical assays used IL-12/IL-23p40, IL-15) will be measured at W000, W002, W004, W007, W010, W013, W019, W028.

Other specific proteins (may include but not limited to and according to the analytical assays used CXCL13, IFN-γ, IL-2 IL-4, IL-6, IL-17, TNFα,….) will be measured at W000, W004, W013.

Cytokine release panel: IFN-γ, IL-2, IL 6, IL-8, IL-10, TNF-α concentrations and may include other proteins according to the analytical assays used.

Will be performed at W000, W002:

- One pre-dose sample (before IMP)
- and one post-dose sample right after the end of the IMP infusion.

The exploratory protein and cytokine panels analysis will be subcontracted to a central laboratory. The exact list of the proteins measured, the details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual. In order to limit the amount of blood collected, the same sampling will be used for assessing several proteins.

Results will be directly transferred in the sponsor database by the central laboratory, without communication to the investigator.

Cytokines samples will be destroyed after their analysis or at the latest at study end. Cytokines back- up samples will be stored in the biorepository, if agreed by the patient (specific optional informed consent signed) (See Section 9.5.3).

Immune panel: C3 and C4 complement fractions, CH50 (or CH100), quantitative immunoglobulins, protein electrophoresis and immunofixation.

Immune panel will be measured at: ASSE, W000, W004, W013.

Immune panel analysis will be subcontracted to a central laboratory. The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual. The central laboratory will provide the investigators with a copy of the results and of reference values corresponding to the central measurements. A fully identified copy of the laboratory results print-out will be evaluated, dated and signed by the investigator and kept in the investigator binder. In case of a lost sample, or technical problem or if necessary for a clinical reason, a re-test can also be ordered by the investigator.

Laboratory results will be assessed by the investigator for ESSDAI assessment at each visit (see Section 7.1).

All Immune Panel samples will be destroyed after analysis or at the latest at study end.

Autoantibody panel: Anti-nuclear antibodies, extractable nuclear antigens (anti-SS-A, anti-SS-B, anti-Smith/anti-ribonuclear protein), RF.

Autoantibody panel will be measured at ASSE, W013.

Autoantibody panel analysis will be subcontracted to a central laboratory. The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual. The central lab will provide the investigators with a copy of the results and of reference values corresponding to the central measurements **for ASSE results only** (eligibility criteria) (See Section 9.1).

A fully identified copy of the ASSE antibody panel results print-out will be evaluated, dated and signed by the investigator and kept in the investigator binder. For W013 sampling, results will be directly transferred in the sponsor database by the central laboratory, without communication to the investigator.

All Autoantibody Panel samples will be destroyed after analysis or at the latest at study end.

β2 microglobulin: β2 microglobulin will be measured at W000, W004, W013.

β2 microglobulin analysis will be subcontracted to a central laboratory. The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual.

Results will be directly transferred in the sponsor database by the central laboratory, without communication to the investigator.

All samples should be collected at the time specified and properly labelled. Samples missed or lost for any reason should be recorded.

The accurate sampling times must be recorded in the CRF.

All β2 microglobulin samples will be destroyed after analysis or at the latest at study end.

9.5.2. Labelling and transfer to analytical centre

Labelling and shipping to analytical centres will be described in a specific document (laboratory manual).

9.5.3. Transfer of analytical results

Final analytical results will be transferred to Data Management according to Section 14.3.

All mandatory samples will be destroyed after analysis or at the latest at study end. However, if agreed by the patient (specific optional informed consent signed), optional samples may be stored in suitable conditions after study completion in a central bio-repository for a maximum duration of 25 years (except for ADA back-up samples which will be stored up to 15 years maximum): Indeed, after the end of the study, if a specific optional informed consent form is signed, the samples may be used for other parameters assessments in relation to the study drug or to pSS in light of scientific knowledge or technology unknown today but that may appear in the literature in the coming years or extend the search for the potential of other relevant biomarkers. After the trial, in addition to the biomarkers specified above, exploratory biomarker research may be conducted on any remaining and /or back up samples collected for PBMCs and blood investigations. In particular, it may concern PBMCs samples, samples collected for the PK, ADA, IL7 analyses and samples dedicated to other proteins investigations.

Back-up samples for anti-drug antibodies (ADA) will be stored for a maximal period of 15 years to allow complementary analyses as part of the drug immunogenicity assessment. This could include ADA reanalysis with a modified bioanalytical method, new methods to characterize pre-existing ADA or the neutralizing potential of ADA or any other method used to study ADA or their impact on safety or efficacy.

9.6. Exploratory measurements in salivary glands

- **Lip biopsy for salivary glands collection** will be used to evaluate S95011 concentration and exploratory biomarkers assessments may be assessed (as focus score, T and B cells number, germinal centers, histological markers, and potential genomic analyses, if appropriate) **(optional):**

Participation in the CL2-95011-001 study does not imply a mandatory or systematic participation in the lip biopsies for salivary glands collection. All voluntary patients will have to sign a specific informed consent form. This consent given can be withdrawn at any moment without compromising the participation in the overall clinical study investigations.

If accepted by the patient, a lip biopsy will be performed to obtain minor salivary glands at W013:

Once incision is performed, as much glands as possible are collected (ideally, 3 to 6, but 1 or 2 glands are accepted). Once collected, the glands can be rested on sterile gauze (slightly damp with physiological solution or sterile water) prior preparation of samples in frozen conditions or in formalin (refer to the specific procedures manual for details).

Local anaesthetics are permitted and the patients will be closely followed after the biopsies.

The lip biopsy must not be performed before the sialometry.

The biopsy will be performed by an experienced physician in such a procedure.

A specific procedure manual will be provided.

Of note: **if deemed more convenient, lip biopsy can be performed the day before and up to 2 days after the scheduled visit's date (but the lip biopsy must always be performed after the sialometry).**

In addition, for patients who agreed to perform salivary glands biopsy at W013, **if histological results of a previously documented lip biopsy* are available (focus score, determination of germinal center, number of T and B cells and ratio T/B), these results will be documented in the e-CRF.**

**The previous biopsy should have been performed within 1 year before W000, and the patient should not have received any biological therapy between the time of the biopsy and W000; and the biopsy must have been collected after 5 half-lives of a prior biological treatment.*

The biopsy samples may be used after the end of the study for other parameters assessments in relation to the study drug or to pSS in light of scientific knowledge or technology unknown today but that may appear in the literature in the coming years or extend the search for the potential of other relevant biomarkers.

9.7. Biocollections (Optional)

Set of PBMC, extracted RNA and blood (serum and plasma) biocollections:

Participation in the CL2-95011-001 study does not imply a mandatory or systematic participation in the biocollection sampling. All voluntary patients will have to sign a specific informed consent form. This consent given can be withdrawn at any moment without compromising the participation in the overall clinical study investigations.

During the trial, exploratory research may be conducted on blood (serum & plasma), PBMC and extracted RNA from blood for transcriptomic analyses. These investigations would extend the search for the potential of relevant biological parameters for S95011 effect and/or safety. This may also include research to help develop ways to detect, monitor and/or treat Sjögren's disease.

The details for sampling, handling, storage and shipping of the samples will be described in a laboratory manual.

Samples for serum and plasma biocollection (10 ml of blood /sample) will be performed at W000, W004, W013.

Samples for PBMC biocollection (16 mL of blood/sample) will be performed at W000, W010.

Samples for extracted RNA biocollection (5 mL of blood/ sample) will be performed at W000, W004, W013.

The samples collected for the **optional procedures** (lip biopsies and biocollections) will be destroyed within a maximum of 25 years after the end of the study or earlier if requested. Samples may be stored in suitable conditions after study completion in a central bio-repository.

10. STATISTICS

10.1. Statistical analysis

Statistical analysis will be performed by the I.R.I.S. Pole of Expertise Methodology and Data Valorisation.

The main analysis of the study concerns the ASSE-W13 period and will be performed as soon as all efficacy and safety data of the ASSE-W13 period are available and the mandatory steps defined in section 14.2. "Data Management" have been performed. The descriptive analysis including data after W13 will be performed subsequently when all data are available.

A Statistical Analysis Plan dealing with the main analysis of the study (ASSE-W13 period) and the follow-up period will be written and completed at the latest before study unblinding, with associated templates for Tables, Listings and Graphs. These specifications will detail the implementation of associated statistical analyses in accordance with the main characteristics stated in the protocol.

10.1.1. Analysis sets / Treatment groups

10.1.1.1. Analysis sets

- **Randomised Set (RS)**:

  All patients to whom a therapeutic unit was randomly assigned using IWRS.

- **Safety Set (SS):**

  All patients having taken at least one dose of IMP.

Definition of analysis sets will be updated if necessary, before study unblinding.

10.1.1.2. Treatment groups

Treatment groups considered will be S95011 and placebo.

They will correspond to randomised treatment except for safety analyses for which treatment taken at inclusion visit will be considered.

10.1.2. Statistical methods

10.1.2.1. General considerations

The following descriptive statistics will be provided depending on the nature of considered data:

- **Qualitative data**: number of observed values, number and percentage of patients per class.
- **Quantitative data**: number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.

10.1.2.2. Disposition and baseline characteristics

Disposition of patients, including reasons for withdrawal, protocol deviations will be described in the RS.

Demographic data and other baseline characteristics such as prognostic factors and baseline value of endpoints will be described by treatment group, to assess their comparability, and overall in the RS.

10.1.2.3. Treatments of patients

Extent of exposure and treatment compliance, as well as concomitant treatments will be summarized by treatment group in the RS and the SS (if different).

10.1.2.4. Efficacy analysis

10.1.2.4.1. Primary estimand based on the ESSDAI

The primary estimand of interest is the effect of the initially randomised treatments on the clinical disease activity in all patients assuming non-occurrence of intercurrent events. The motivation for this choice is to assess at this proof-of-concept stage the full efficacy potential, that is, the pharmacologic effect of the S95011 if all patients adhere to it (without any intercurrent events).

The attributes of the primary estimand are defined as follow:

- Treatment: S95011 or placebo
- Population: RS
- Variable: change in ESSDAI total score from baseline to W13 (primary efficacy endpoint).
- Summary measure: difference in means between treatments.
- Intercurrent events (IE):
  - change or initiation of unauthorised medication
  - study drug discontinuation for major worsening of primary Sjögren's syndrome or AE related to study drug
  - study drug discontinuation for other reasons (non-medical reason, AE not-related…)
  - unexpected others events having a major impact on the pharmacologic effect evaluation (They will be defined at the latest in the final version of the SAP).

The rate of IEs is assumed to be below 10%. They will be handled by a hypothetical strategy to estimate what the outcome would have been at the designated time point if no IE would have occurred through that time point, considering that patients with IE would have efficacy outcomes as patients, in their treatment group, who continue their randomised treatment without IE.

10.1.2.4.1.1. Primary analysis

The primary analysis for the primary estimand will be conducted using only data obtained prior to IEs. Values post IE will not be taken into account and will be imputed according to the MAR assumption (multiple imputation by treatment group). This is aligned with the primary estimand and the hypothetical strategy.

S95011 will be compared to placebo on the primary efficacy endpoint in the RS, using a General Linear Model including the fixed, categorical effect of treatment and randomisation stratification factors (*rando_factor*) as well as the continuous fixed covariate of baseline value.

GENERAL LINEAR MODEL: change = baseline rando_factors treatment

The assumptions underlying the model, as for instance, the normality and homoscedasticity of residuals and detection of outliers, will be checked.

Missing data (not linked to intercurrent events) will be imputed according to the MAR assumption with a multiple imputation by treatment group.

The hypotheses to be tested are:
Let μ_0 and μ_1 be the population means of the change from baseline in ESSDAI score at W13 (primary endpoint) under placebo and S95011, respectively. The statistical hypotheses that will be tested are:

$$H0: \mu_0 \geq \mu_1 \text{ (S95011 is not superior to placebo)}$$
$$\text{versus}$$
$$H1: \mu_0 < \mu_1 \text{ (S95011 is superior to placebo)}$$

The type I error of the statistical tests will be set at 10% for unilateral situation, which is consistent with the objective of demonstrating the superiority versus placebo.

The following elements will be provided in a summary table:
- Estimate (standard error) of the difference between adjusted treatment group means.
- Two-sided 80% CI of the estimate
- Two-sided 95% CI of the estimate.
- One-sided p-value

10.1.2.4.1.2. Sensitivity analyses

In order to assess the sensitivity to the missing at random (MAR) assumption, values post the following IEs:
- change or initiation of unauthorised medication,
- study drug discontinuation for major worsening of primary Sjögren's syndrome or AE related to study drug,

will not be taken into account and will be imputed according to the missing not at random (MNAR) assumption. The values of outcome will be imputed using a reference based multiple imputation ("copy increments in placebo" approach) for S95011 group and using multiple imputation for the placebo group. This approach assumes that patients from S95011 will exhibit an evolution of the disease similar to patients in the placebo group but starting from the benefit already obtained (Carpenter *et al*, 2013). The imputed value will reflect the fact that these IEs are considered a moderately bad outcome. The others IEs and missing data will be handled as in the primary analysis.

10.1.2.4.1.3. Supplementary analyses

Responders ESSDAI at W13 defined as patients having improvement from baseline in ESSDAI total score of at least:
- 3 points
- 5 points
- 7 points

will be analysed separately using a logistic regression model including the fixed, categorical effect of treatment and randomisation stratification factors (*rando_factor*) as well as the continuous fixed covariate of baseline value. The handling of IEs and missing data will be the same as the primary and sensitivity analysis.

10.1.2.4.2. Secondary estimand based on the ESSPRI

The secondary estimand of interest is the effect of the randomised treatments on symptoms reported by the patients in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.
Compared to the primary estimand, only the *variable* attribute is different and is defined as the change in ESSPRI total score from baseline to W13 (secondary efficacy endpoints).
The other attributes, main and sensitivity analyses are the same as for the primary estimand.
In the same line as for the primary estimand, the supplementary analyses will be performed on the responders ESSPRI at W13 defined as patients having improvement from baseline in ESSPRI total score of at least:
- 1 point
- 2 points
- 3 points.

using the same model as for responders ESSDAI.

10.1.2.4.3. Additional estimands based on ESSDAI and ESSPRI

Treatment policy estimands

Treatment policy estimands are defined in order to assess the treatment effect on the clinical disease activity (ESSDAI) and also on the symptoms reported by the patients (ESSPRI) regardless of whether or not the IE occurs.

The attributes of the additional estimands are defined as follow:
- Treatment: S95011 or placebo, regardless of whether or not the IE occurs
- Population: RS
- Variable 1: change in ESSDAI total score from baseline to W13
- Variable 2: change in ESSPRI total score from baseline to W13
- Summary measure: difference in means between treatments.
- Intercurrent events: The occurrence of IEs (see list in primary estimand) is irrelevant in defining the treatment effect of interest. All observed values will be used regardless of occurrence of an IE.

Main and supplementary analyses are the same as for the primary estimand.

Other estimand
This estimand of interest is the effect of the randomised treatments on the composite response to treatment taking into account a double dimension - clinical disease activity from ESSDAI and symptoms reported by the patients from ESSPRI - in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of this estimand are defined as follows:
- Treatment: S95011 or placebo.
- Population: all randomised patients (RS).
- Variable: Number of responders defined as patients with ≥ 3 points of improvement in ESSDAI and with ≥ 1 point of improvement in ESSPRI from baseline at W013.
- Summary measure: difference in proportion between treatments.

- Intercurrent events (IE):
  - change or initiation of unauthorised medication
  - study drug discontinuation for major worsening of primary Sjögren's syndrome or AE related to study drug
  - study drug discontinuation for other reasons (non-medical reason, AE not-related…)
  - unexpected others events having an major impact on the pharmacologic effect evaluation (They will be defined at the latest in the final version of the SAP)

S95011 will be compared to placebo on the responders in the RS using a logistic regression model including the fixed, categorical effect of treatment and randomisation stratification factors (*rando_factor*) as well as the continuous fixed covariate of baseline value. The handling of IEs and missing data will be the same as the primary analysis of the primary estimand.

10.1.2.4.4. Additional estimands based on other efficacy endpoints

These estimands of interest are the effect of the randomised treatments on fatigue (MFI), quality of life (SF-36), global assessments of the disease activity reported by the physician (PhGA) and by the patient (PGA), and tear and salivary glands function (Schirmer test, OSS and salivary test), in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of these estimands are defined as follows:
- Treatment: S95011 or placebo
- Population: RS
- Variable 1: change in SF-36 physical score from baseline to W13
- Variable 2: change in SF-36 mental score from baseline to W13
- Variable 3: change in MFI total score from baseline to W13
- Variable 4: change in PhGA score from baseline to W13
- Variable 5: change in PGA total score from baseline to W13
- Variable 6: change in Schirmer test from baseline to W13
- Variable 7: change in OSS from baseline to W13
- Variable 8: change in stimulated salivary flow score from baseline to W13
- Variable 9: change in unstimulated salivary flow score from baseline to W13
- Summary measure: difference in means between treatments.
- Intercurrent events (IE):
  - change or initiation of unauthorised medication
  - study drug discontinuation for major worsening of primary Sjögren's syndrome or AE related to study drug
  - study drug discontinuation for other reasons (non-medical reason, AE not-related…)
  - unexpected others events having an major impact on the pharmacologic effect evaluation (they will be defined at the latest in the final version of the SAP).

Main analyses are the same as for the primary estimand. Sensitivity and supplementary analyses are not planned for these estimands.

10.1.2.4.5. Descriptive analyses

For all efficacy endpoints, descriptive statistics will be provided at each visit, by treatment group and also for some efficacy endpoints, by treatment group according to the disease severity and background therapy in RS.

10.1.2.5. Safety analysis

All safety analyses will be performed by treatment group in the Safety Set.

10.1.2.5.1. Adverse events

Number of events, number and percentage of patients reporting at least one event, presented by primary system organ class and/or preferred term (depending on the analysis), will be provided for:

- Serious AE over the analysed period according to the investigator or sponsor opinion,
- Treatment Emergent AE (TEAE), TEAE leading to IMP withdrawal, TEAE requiring new treatment or increase of on-going treatment, TEAE requiring surgical or medical procedure, TEAE related to IMP, serious TEAE, TEAE of Grade 3-4 intensity, non serious TEAE over the corresponding treatment period.

TEAE will be described according to the seriousness, the intensity, the relationship with the IMP, the action taken regarding the IMP, the requirement of added therapy and the outcome.

10.1.2.5.2. Clinical laboratory evaluation

For each laboratory parameter, the following analyses will be performed:

- Descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and on change from baseline to last post-baseline value under treatment,
- Number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for PCSA values.
- Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and cut-offs, and using shift tables from baseline to the worst (high and/or low) values under treatment.

10.1.2.5.3. Vital signs, clinical examination and other observations related to safety

10.1.2.5.3.1. Vital signs and clinical examination

Vital signs and clinical examination will be described, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to each post baseline visit under treatment.

10.1.2.6. Exploratory markers analysis

Cell subsets:

The count of cell subsets will be described using value at each time point and by treatment group.

IL-7, cytokines, and other proteins in blood:

Concentration of circulating proteins will be described using value and by classes (< LLOD, [LLOD ; ULOD],> ULOD) at each time point and by treatment group. Proteins with concentration below LLOQ in more than 70% of all samples will be excluded from analysis

Immune panel, β2 microglobulin and on the auto-antibody panel:

Concentration of immune panel, β2 microglobulin and auto-antibody panel will be described using value at each time point and by treatment.

Salivary glands tissue:

Histological analyses and exploratory biomarkers will be described by treatment group.

10.1.2.7. Interim analysis

Only if the recruitment is much longer than expected, a blinded standard deviation reassessment could be planned when 30 patients will have completed the 13-week treatment period as detailed in Section 10.2.

10.2. Determination of sample size

The following efficacy criteria are defined:

- a statistically significant reduction in ESSDAI at Week 13 in the S95011 group compared to placebo, at the one-sided 10% significance level
- an estimated mean reduction in ESSDAI in the S95011 group to be 3 points or greater than placebo. The decrease of 3 points was chosen because it is considered as clinically minimal relevant (Seror *et al*, 2016).

Targeted sample size

With 45 patients in the primary analysis of the primary estimand (30 in the S95011 group and 15 in the placebo group), the study would have around 5% chance of having a false-positive result, *i.e.*, of meeting both the efficacy criteria when the true difference between S95011 and placebo is zero. Additionally, the chances of meeting both the efficacy criteria remain below 14% for true differences between S95011 and placebo of less than 1 point.
The study would have approximately 70% chance of meeting both the efficacy criteria, when the true difference between S95011 and placebo is 4 points. In case the true difference between S95011 and placebo is only 3 points, the study would have approximately 50% chance of meeting both the efficacy criteria. These calculations assume that the primary efficacy endpoint, change from baseline in ESSDAI, follows a normal distribution with a standard deviation of 6. This estimate of the standard deviation is based on some clinical studies (Fisher *et al*, 2020; UCB5857; RO5459072) in patients with primary Sjögren's syndrome in which the observed standard deviation ranged from around 4 to 6.

Blinded standard deviation reassessment

The similar operational characteristics (false-positive and right-positive rates) are obtained with 20 patients in S95011 group and 10 patients in placebo group under assumption of an overall standard deviation of primary efficacy endpoint of 5. So, only if the recruitment is much longer than expected, when 30 patients will have completed the 13-week treatment period, the overall standard deviation of the primary endpoint on non-comparative data could be calculated. If the value is less or equal to 5, the sponsor could stop the patient recruitment, considering that the number of patients is sufficient to meet both efficacy criteria. This potential adaptation has very little or no impact on the probability of having a false-positive result (Kieser, 2003).

10.3. Pharmacokinetic analysis and PK/PD analysis

Serum concentrations of S95011 will be analysed by a population modelling approach, described in a separated Data Analysis Plan (DAP), in order to assess the pharmacokinetics of the drug and to investigate potential sources of variability through a covariate analysis. This analysis will provide pharmacokinetic parameters and their associated variability in patients and will be the object of a separate report.
Exploratory assessment of the relationship between exposure and pharmacodynamics (as safety and efficacy) will be performed and if applicable, population pharmacokinetic-pharmacodynamic (PK/PD) models will be developed and a DAP will be set up and reported separately.

11. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).
Monitoring for this study will be performed by the structure mentioned in Section 1.
Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place in order to ensure compliance with the protocol requirements.

Training sessions may be organised for the investigators and/or instruction manuals may be given to the investigators.

12.1.2. During the study

The investigator will allow the monitor to:
- Review the study site's processes and procedures,
- Verify appropriate clinical investigator supervision of study site staff and third party vendors,
- Inspect the site, the facilities and the material used for the study,
- Meet all members of his/her team involved in the study,
- Consult the documents relevant to the study,
- Have access to the electronic case report forms,
- Check that the electronic case report forms have been filled out correctly,
- Directly access source documents for comparison of data therein with the data in the electronic case report forms,
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (*i.e.* audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:
- at the start of the study, to print the medical files of all patients allowing a reliable verification of the study criteria (*e.g.* medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol),
- during the study, to print in real time each data entry and each data change.

The investigator will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the patients. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the patients and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all patients. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the patients. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:
- All medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor,
- If the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system,
- All original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form...).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out during or after the end of the study.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:
- to inspect the site, facilities and material used for the study,
- to meet all members of his/her team involved in the study,
- to have direct access to study data and source documents,
- to consult all of the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the patients and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:

- give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all patients,
- provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory committees

DSMB recommendations will be forwarded to the IRB/IEC/ Regulatory Agencies only if relevant for the safety of patients.

All along the study, in order to ensure patients' safety, the DSMB will review patients' safety data, including ERIN and adverse events leading to individual premature IMP discontinuation. In addition, unscheduled urgent DSMB meetings will be triggered if required (see Sections 4.4.1 and 8.10).
The DSMB will treat all data as strictly confidential and will not disclose them to anyone else than members of the DSMB.

The role and organization of the DSMB are detailed in a separate DSMB charter, specifying the safety criteria for which the study should be discontinued.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators document, the insurance documents, the Investigator's Brochure of administered IMP will be submitted to (an) IRB(s)/IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (see Appendix 1) with the GCP and with the applicable regulatory requirements.

13.3. Patient information and informed consent

In any case, the patient (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is to collect written consent from each patient before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each patient of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.

The patient will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One, or two if required by local regulation, original information and consent form(s) must be completed, dated and signed personally by the patient and by the person responsible for collecting the informed consent.

If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. The patient must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The patient will be given one signed copy (or original if required by local regulation) of the information and consent form. A signed original will be kept by the investigator..

A copy of the information and consent form in the language(s) of the country is given in the "Participant information and consent form" document attached to the protocol.

All voluntary patients will have to sign specific and separate informed consent forms for participating in the optional lip biopsy assessments or biocollection blood samplings. These consents given can be withdrawn at any moment without compromising the participation in the overall clinical study investigations.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version of the information and consent form in the language(s) of the country will be given in the amendment to the "Participant Information and consent form".

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate risk to the study patients.

Each patient affected by the amendment or an independent witness must complete, date and sign two originals of the new version of the information and consent form together with the person who conducted the informed consent discussion. He/she will receive one signed original amendment to the information and consent form.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CRF Part 11-compliant electronic data capture system is going to be used for this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the patient's Medical File.

Upon entry, data will be transmitted *via* the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each patient visit, and all other documents provided by the sponsor (*e.g.* documents relating to the IMP management…).
The e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of Inform software, including date, reason for modification and identification of the person who has made the change.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.
Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed via a request to the sponsor.

To demonstrate the oversight on data reported and ensure the whole content 's accuracy, completeness and legibility in accordance with the GCP, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her user name and password :

- As soon as possible in case of SAE (and no later than 2 weeks after the date the SAE was reported in the e-CRF),
- Before each DSMB meeting,
- Before the interim analysis (if applicable),
- After the last visit of the participant of the treatment period and the follow-up period.

After the data base lock, the investigator or an authorized member of his/her team will have to download from the e-CRF an electronic file containing patient data of his/her centre for archiving it in the study file (see Section 14.3).

14.2. Data management

Data are collected *via* a CRF and stored in a secured database.

For data collected on the e-CRF, the Clinical Data Management of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from the centralised laboratories, e-COA, IWRS systems, the Clinical Data Management of I.R.I.S. is responsible for data transfer. Centralised laboratories, e-COA, IWRS provide electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Review Department of I.R.I.S. is responsible for data coding including:
- Medical / surgical history, adverse events and procedures using MedDRA,
- Medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

Before each database lock (one for ASSE-W13 period , and one at the end of the study when the FU period is finished), when data validation is achieved, a blind review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked. The IMP code will unblinded and made available for data analysis after the database lock of ASSE-W013 period.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator or an authorized member of his/her team will download an electronic copy of each patient's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

All data reported in electronic Clinical Outcome Assessment (e-COA) will be provided to the investigator's site. At the end of the study, the CRO provider will send a CD-ROM to each site with all data of their patients.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation are included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS – DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the study sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several centres and analysed under the responsibility of I.R.I.S. The investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. has been provided.

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, patient-level and/or study-level clinical trial data including clinical study reports (CSRs).

They can ask for all interventional clinical studies:

- Submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the United States (US).
- Where Servier or an affiliate are the Marketing Authorization Holders (MAH). The date of the first Marketing Authorization of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier's data sharing policy includes all interventional clinical studies in patients:
- sponsored by Servier,
- with a first patient enrolled as of 1 January 2004 onwards,
- for New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any Marketing authorization (MA) approval.

The datasets generated and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on www.clinicaltrials.servier.com within 12 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the patient, the investigator will inform the patient's general practitioner about his/her patient's participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by the coordinators and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, with the exception of a measure required to eliminate an immediate risk to the study patients.

When the submission is performed by the investigator or the coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the Competent Authorities in accordance with local regulations.

17.1.3. Final study report

The study report will be drafted by I.R.I.S. in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and the coordinators must mutually agree on the final version. One copy of the final report, must be dated and signed by the coordinators and the sponsor's representatives.

If the clinical trial is still on-going but ended in the European countries, the statistical analysis will not be relevant before the end of the study worldwide. Therefore the clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

17.2. Concerning the sponsor

The sponsor undertakes to:

- Supply the investigator with adequate and sufficient information concerning the IMP administered during the study to enable him/her to carry out the study,
- Supply the investigator with the investigator's brochure if the IMP is not marketed,
- Obtain any authorisation to perform the study and/or import licence for the IMP administered that may be required by the local authorities before the beginning of the study,
- Provide the coordinators annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).
- Take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non-exhaustive):
  - Management of authorisation to access to personal data (e-CRF)
  - Identification and authentication measures before accessing personal data (e-CRF)
  - Traceability measures for the access to and modification of personal data (e-CRF)
  - Secured data transfer
  - Time limit for storing personal data
- Handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to S95011 and study CL2-95011-001 are strictly confidential.
The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.
In case patient wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor (see Appendix 8).

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study patients. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A patient screening log and a full identification and enrolment list of each patient will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The patient screening log must be completed from the moment the investigator checks that a patient could potentially take part in the study (by assessment of patient medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (e.g ophthalmologist, ENT specialist, surgeon, pharmacist,…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the centre.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:
- To provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s),
- To provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured,
- To provide any other document required by local regulation (*e.g.* Food & Drug Administration 1572 form),
- To send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CVs of other members of the team involved in the study (if possible in English) will be collected during the course of the study (at least, members involved in the patients' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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ICH E9 - Statistical Principles for Clinical Trials - Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96/step 5

ICH E9 (R1) – Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials – Adopted by the Regulatory Members of the ICH Assembly step 4, November 2020.

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Clinical Investigators brochure S95011. Version No. 1 of 08 June 2020.

19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a

research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biocollections or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: ACR-EULAR classification for primary Sjögren's Syndrome (pSS) (Shiboski *et al*, 2017)

ACR-EULAR Classification Criteria for primary Sjögren's syndrome (pSS)

The classification of SS applies to any individual who meets the inclusion criteria,[1] does not have any condition listed as exclusion criteria,[2] and who has a score ≥ 4 when summing the weights from the following items:

Item	Weight / Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1.[3]	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterfeld score ≥ 4) on at least one eye[4]	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min[5]	1

[1] Inclusion criteria: these criteria are applicable to any patient with at least one symptom of ocular or oral dryness (defined as a positive response to at least one of the following questions: 1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2) Do you have a recurrent sensation of sand or gravel in the eyes? 3) Do you use tear substitutes more than 3 times a day? 4) Have you had a daily feeling of dry mouth for more than 3 months? 5) Do you frequently drink liquids to aid in swallowing dry food?); or suspicion of SS from ESSDAI questionnaire (at least one domain with positive item)

[2] Exclusion criteria: Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Active Hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Note: Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness

[3] The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and focus score count (based on number of foci per 4 mm^2) following a protocol described in Daniels et al 2011 (26)

[4] Ocular staining score described in Whitcher et al 2010 (30). van Bijsterfeld score described in van Bijsterveld 1969 (29)

[5] Unstimulated whole saliva described in Navazesh & Kumar, 2008 (27)

Appendix 3: ESSDAI

(Seror *et al,* 2015)

The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights

Domain [Weight]	Activity level	Description
Constitional [3]	No = 0	Absence of the following symptoms
Exclusion of fever of infectious origin and voluntary weight loss	Low = 1	Mild or intermittent fever (37.5-38.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight
	Moderate = 2	Severe fever (> 38.5°C)/night sweats and/or involuntary weight loss of > 10% of body weight
Lymphadenopathy and lymphoma [4]	No = 0	Absence of the following features
Exclusion of infection	Low = 1	Lymphadenopathy ≥ 1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥ 2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferate disorder
Glandular [2]	No = 0	Absence of glandular swelling
Exclusion of stone or infection	Low = 1	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular (≤ 2 cm) or lachrymal swelling (≤ 1 cm)
	Moderate = 2	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular (> 2 cm) or lachrymal swelling (< 1 cm)
Articular [2]	No = 0	Absence of currently active articular involvement
Exclusion of osteoarthritis	Low =1	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 2	1 – 5 (of 28 total count) synovitis
	High = 3	≥ 6 (of 28 total count) synovitis
Cutaneous [3]	No = 0	Absence of currently active cutaneous involvement
Rate as 'no activity' stable long lasting features related to damage	Low = 1	Erythema multiforma
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary [5]	No = 0	Absence of currently active pulmonary involvement
Rate as 'no activity' stable long-lasting features related to damage,or respiratory involvement not related to the disease (tobacco use, etc)	Low = 1	Persistent cough due to bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement,such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA Il) or abnormal lung function tests restricted to 70% > Dlco ≥ 40% or 80% > FVC ≥ 60 %
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA Ill, IV) or with abnorma l lung function tests Dlco < 40% or FVC < 60%

Domain [Weight]	Activity level	Description
Renal [5] *Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease.* *If biopsy has been performed, please rate activity based on histological features first*	No = 0	Absence of currently active renal involvement with proteinuria < 0.5 g/day , no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥ 60 mL/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR < 60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥ 60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria > 1.5 g/day or haematuria or renal failure (GFR < 60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement
Muscular [6] *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG, MRI or biopsy with no weakness and creative kinase (N ≤ CK ≤ 2N)
	Moderate = 2	Moderately active myositis proven by abnormal EMG, MRI or biopsy with weakness (maximal deficict of 4/5), or elevated creatine kinase (2N ≤ CK ≤ 4N)
	High = 3	Highly active myositis shown by abnormal EMG, MRI or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N)
PNS* [5] *Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia Proven small fibre neuropathy
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 3	Higly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤ 3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia
CNS*[5] *Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease*	No = 0	Absence of currently active CNS involvement
	Moderate = 2	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

Domain [Weight]	Activity level	Description
Haematological [2] *For anaemic, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of auto-immune cytopenia
	Low = 1	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm^3), and/or anaemia (10 < haemoglobin < 12 g/dL), and/or thrombocytopenia (100000 < platelets < 150000/mm^3) Or lymphopenia (500 < lymphocytes < 1000/mm^3)
	Moderate = 2	Cytopenia of auto-immmune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm^3), and/or anaemia (8 ≤ haemoglobin ≤ 10 g/dL), and/or thrombocytopenia (50000 ≤ platelets ≤ 100000/mm^3)
	High = 3	Or lymphopenia (≤ 500/mm^3) Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm^3), and /or anaemia (haemoglobin < 8 g/dL) and/or thrombocytopenia (platelets < 50000/mm^3)
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50**) and/or >hypergammaglobulinaemia or high IgG level between 16 and 20 g/l
	Moderate = 2	Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level >20g/l, and/or recent onset hypergammaglobulinaemia or recent decrease of IgG level (< 5g/l)

CIDP, chronic inflammatory demyelinating polyneuropathy; CK, creatine kinase, CNS, central nervous system, DLco, diffusing Co capacity; EMG, electromyogram; EULAR, European League Against Rheumatism; FVC, forced vital capacity; GFR, glomerular filtration rate; Hb, haemoglobin; HRCT, high-resolution computed tomography, IgG; Immunoglobulin G, NCS, nerve conduction studies; NHYA, New York Heart Association classification; Pit platelet; PNS, peripheral nervous system.

**Clinical investigator subjective scoring based on availability of concurrent clinical data.*

***CH100 may be used instead of CH50*

Appendix 4: The European League Against Rheumatism (EULAR) Sjögren's syndrome Patient Reported Index (ESSPRI)

Your physician has asked you to answer several questions relating to your disease. To answer to these questions, please take into account how bad your symptoms have been at their worst during the last two weeks only.
Please tick one box only that best reflects your response.

Example:

No pain ☐ ☐ ☐ ☐ ☐ ☐ ☒ ☐ ☐ ☐ ☐ Maximal imaginable pain

0 1 2 3 4 5 6 7 8 9 10

Evaluation scales

1) How severe has your **dryness** been during the last 2 weeks?

No dryness	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Maximal imaginable dryness

2) How severe has your **fatigue** been during the last 2 weeks?

No fatigue	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Maximal imaginable fatigue

3) How severe has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9 10	Maximal imaginable pain

Appendix 5A: MFI® MULTIDIMENSIONAL FATIGUE INVENTORY

® E. Smets, B.Garssen, B. Bonke (2013)

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**.
There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 no, that is not true

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

1	I feel fit.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
2	Physically, I feel only able to do a little.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
3	I feel very active.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
4	I feel like doing all sorts of nice things.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
5	I feel tired.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
6	I think I do a lot in a day.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
7	When I am doing something, I can keep my thoughts on it.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
8	Physically I can take on a lot.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
9	I dread having to do things.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
10	I think I do very little in a day.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
11	I can concentrate well.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
12	I am rested.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
13	It takes a lot of effort to concentrate on things.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
14	Physically I feel I am in a bad condition.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
15	I have a lot of plans.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
16	I tire easily.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
17	I get little done.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
18	I don't feel like doing anything.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
19	My thoughts easily wander.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**
20	Physically I feel I am in an excellent condition.	**yes, that is true**	❑1	❑2	❑3	❑4	❑5	**no, that is not true**

Appendix 5B: Short Form Health Survey (SF-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

(SF-36v2® Health Survey *Standard, United Kingdom (English))*

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

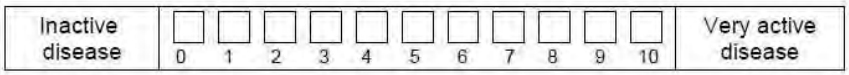
(SF-36v2® Health Survey *Standard, United Kingdom (English))*

Appendix 6: Numerical Rating Scales

Evaluation of disease activity

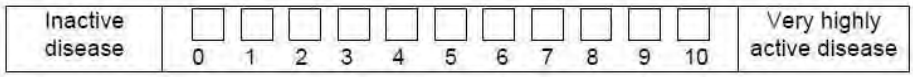
PGA : Patient Global Assessment

Considering now your symptoms **related to your Sjögren's syndrome** (your dryness, your fatigue, your pain and your mental fatigue), as well as their consequences on your professional or personal life, how severe was your Sjögren's syndrome during the last 2 weeks

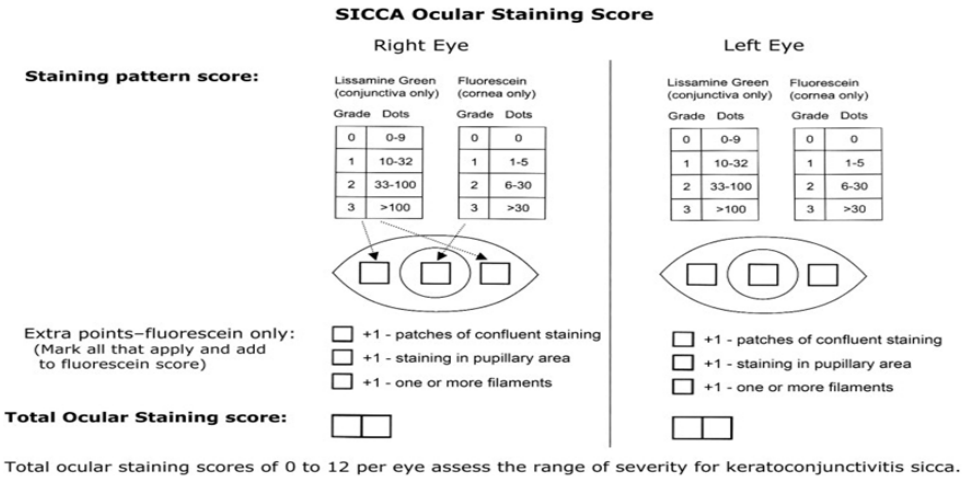


PhGA: Physician Global Assessment

Please indicate, according to your clinical experience, **the level of disease activity** in this patient using the following numerical scale



Appendix 7: SICCA Ocular Staining Score



Total ocular staining scores of 0 to 12 per eye assess the range of severity for keratoconjunctivitis sicca.

Appendix 8: Instructions to investigator for handling data rights requests

DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679)

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, *i.e.* may ask I.R.I.S. (as data controller) for:

- access to his/her data
- rectification of inaccurate/incomplete information
- restriction of processing of data
- objection to processing of data
- data portability (receiving his/her data in a readable format)

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.

Request for exercise of rights:
- has to be a **written** one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written)
- has to be sent **by you** by e-mail or by mail **to** I.R.I.S. (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a sponsor to know the identity of the participant

	I.R.I.S. responsibility	Investigator responsibility
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	

Appendix 9: Trial Conduct During National or International Public Health Emergency

It is recognized widely that the COVID -19 pandemic has impacted the conduct of clinical trials. The COVID 19 pandemic is still running and may again trouble the conduct of clinical trials in the coming months before any preventive treatment becomes available. The impact is unknown at this point. However, challenges may arise in the next months from COVID-19 or similar disease. It may cause for example, quarantines self-imposed or institute imposed or governmental imposed, site closures, travel limitations, interruptions in the supply chain for the study drugs, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures including administering the study drug or adhering to protocol-mandated visits and laboratory/diagnostic testing.
The Sponsor is providing the following exceptional options for study related patient management in the event of disruption to the conduct of the study during the pandemic/epidemic time:

1. If scheduled visits cannot be conducted in person at the study site, it should be performed remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, patients should be interviewed to collect safety data. Patients will also be questioned regarding general health status to fulfill physical examination requirements.
2. Study drug administrations are allowed only at site according to the procedure described in the protocol. In case of any issue with study administration schedule investigator must contact the Sponsor as indicated in Section 5.6.1.
3. Efficacy endpoint assessments should be performed if required and as feasible. If not, the sponsor should be contacted to advise the investigator on how to proceed.
4. Every effort should be made to adhere to protocol-specified assessments for patients on study intervention including follow-up. Safety laboratory assessment can be performed at the local laboratory near the patient, if possible.
5. In case of patient's withdrawal, if the withdrawal visit is done remotely, an on-site visit will be organized once the situation is stabilized.
6. Study sites should inform the Sponsor about modifications as soon as possible.
7. Missed assessment/visits should be captured as protocol deviations due to COVID-19.
8. Changes to study procedures should be documented in the source notes and in the e-CRF as advised by the Sponsor. Specific information for individual patients should be captured in the e-CRF that explains the basis for missing protocol-specified information in relationship to COVID-19, *i.e.,* from missed study visits or study discontinuations due to COVID-19.

I.R.I.S. as the Sponsor of the study will continue to monitor the conduct and progress of the clinical study during pandemic/epidemic scenario and any changes (*e.g.,* delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and to the Health Authorities according to local guidance. Modifications made to the study conduct as a result of disruption the COVID-19 pandemic/epidemic will be summarized in the Clinical Study Report. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of patients and site staff.