2 SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex – France	*(For National Authority Use only)*
Name of finished product: Not applicable. **Name of active ingredient:** S95011	
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. Protocol No.: CL2-95011-001 CTIS No.: NCT04605978 INDA No.: 147638	
Main investigator: Not applicable	
Number of study centers and countries: Overall, 7 countries and 19 centers recruited patients; in Australia, 1 center enrolled 5 patients; in France, 5 centers enrolled 5 patients; in Germany, 2 centers enrolled 8 patients; in Spain, 3 centers enrolled 9 patients; in Hungary, 3 centers enrolled 13 patients; in the UK, 3 centers enrolled 6 patients; and in USA, 2 centers enrolled 2 patients.	
Studied period: Initiation date: 03 August 2021 Completion date: 02 May 2023	
Phase of development of the study: Phase II	
Publication (reference): Not applicable.	
Background and rationale for the study: This study was a proof-of-concept, phase IIa study designed to evaluate preliminary therapeutic efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of multiple intravenous infusions of 750 mg of S95011 in patients with primary Sjögren's Syndrome (pSS). The study was conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and the applicable regulatory requirements. Following negative efficacy results of this phase IIa clinical trial with S95011 in patients with pSS, the Sponsor has decided to stop the S95011 development in the Sjögren indication. In this context, an **abbreviated clinical study report** was written.	

Objectives and endpoints:

Objectives	Endpoints
Primary objective: 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).	**Primary endpoint:** Change from baseline in ESSDAI total score to W013
Secondary objectives:	**Secondary endpoints:**
- 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)	- ESSDAI score by domain and total score at each visit (value and change) - ESSPRI score by symptom and total score at each visit (value and 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 - Proportion of patients with a Sjögren's Syndrome Tool for Assessing Response (STAR) total score ≥5 at each visit (value) - Proportion of patients with a Composite of relevant Endpoints in Sjögren's Syndrome (CRESS) total score ≥3 at each visit (value)
• 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 NRS	- Fatigue (MFI), QoL (SF-36), phGA and PGA of the disease activity (NRS) at each visit (value and change)
• Tear gland function using the Schirmer test • Tear gland function using Ocular Staining Score (OSS)	- Tear gland function: Schirmer's test and in OSS at each visit (value and change)
• Salivary gland function measured by sialometry under unstimulated and stimulated conditions	- Salivary gland function: unstimulated and stimulated salivary flow rate at each visit (value and change)
- To assess the safety and tolerability of multiple intravenous infusions of S95011	- The safety and tolerability assessed by incidence of adverse events (AEs), change over time in safety parameters (vital signs, electrocardiogram [ECG], biological laboratory) and incidence of abnormal safety parameters throughout the study

- 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.	- Pharmacokinetics of S95011 in serum samples: • Predose (before the start of the Investigational medicinal product [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. - RO of S95011 in blood samples: • Predose (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. • At W013, W019, W028. - Incidence of ADA in serum samples: • Predose (before the start of the infusion) at W000, W002, W004, W007 and W010. • At W013, W019, W028.

Number of patients (Planned and Analyzed):
Planned: 45 patients (30 patients with S95011; 15 patients with placebo).
Analyzed: 48 patients.
A total of 48 patients were included in the study:
- Safety Set (SS): 48 patients (31 patients with S95011; 17 patients with placebo)
- Biomarker Set (BMKS): 48 patients (31 patients with S95011; 17 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 (ie, systemic manifestations).
Main inclusion criteria were:
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-Sjögren's Syndrome A (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 were:
Prior administration of belimumab or rituximab or other B cell depleting agents or abatacept or tumor necrosis factor inhibitors or tocilizumab or cyclophosphamide (or any other alkylating agent) or cyclosporine (except for eye drops), or tacrolimus, or sirolimus, or mycophenolate mofetil, or azathioprine, or leflunomide in the past 3, 6, 12, or 24 months (depending on the drug agent) and Janus kinase (JAK) inhibitors in the past 1 week prior to randomization (W000);
Corticosteroids > 10 mg/day oral prednisone (or equivalent) and any change or initiation of dose of oral prednisone (or equivalent) within 4 weeks prior to W000; any change or
initiation of new dose of antimalarials (eg, 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 Q2W for the first month (W000, W002, W004) and then Q3W until W010 (W007, W010).

Duration of treatment:
Active treatment period: 13 weeks

Statistical methodology:

Analysis Sets:

- Randomized Set (RS): All included patients to whom a therapeutic unit (TU) was randomly assigned using Interactive Web Response System (IWRS).
- SS: All patients who had taken at least one dose of IMP.
- BMKS: All patients of the RS having at least one available result for any biomarker.

Study patients (disposition, baseline characteristics and follow-up): Descriptive statistics were provided in the RS by treatment group, to assess their comparability, and overall.

Efficacy analysis (primary analysis): Change from baseline in ESSDAI total score to W013 was performed in patients of the RS. A General Linear Model including the fixed, categorical effect of treatment and randomization stratification factors as well as the continuous fixed covariate of baseline value was used. The randomization stratification factors were baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (yes/no).

Safety analysis: All safety analyses were performed by treatment group on the W000-W013 and W000-W028 periods in all patients of the SS.

Autoantibody analysis: All autoantibody analysis were described in a contingency table comparing modalities at baseline with modalities at W013. RF was described as value at baseline and W013 and change from baseline to W013.

Biomarker analysis: Marker was expressed in terms of concentration at baseline and at each post-baseline visit and relative change from baseline to each post-baseline visit. The percentage of values of the marker in each class was described overall, in the BMKS. All markers were analyzed on W000-W013 period except for IL7 (ie, analyzed on both treatment periods of W000-W013 and W000-W028).

PK analysis: Serum concentrations of S95011 were listed and subsequently summarized using descriptive statistics.

Summary of results and Conclusions

Disposition of patients:

A total of 75 patients were screened for the study. Of them, 48 patients were included and randomly assigned to one of the treatment groups: 31 patients in the S95011 group and 17 in placebo group. The overall disposition of patients is presented in **Table 1.**

Table 1 – Overall patient disposition (W000-W028) – Randomized Set (N=48)

Status		S95011 (750 mg) (N = 31)	Placebo (N = 17)	All (N = 48)
Included	**Nobs**	**31**	**17**	**48**
In conformity with the protocol	n (%)	25 (80.6)	10 (58.8)	35 (72.9)
With a protocol deviation before or at inclusion	n (%)	6 (19.4)	7 (41.2)	13 (27.1)
Withdrawn due to	**n (%)**	**3 (9.7)**	**2 (11.8)**	**5 (10.4)**
Lost to follow-up	n (%)	0	0	0
Adverse event	n (%)	2 (6.5)	1 (5.9)	3 (6.3)
Major worsening of pSS	n (%)	0	0	0
Withdrawal nonmedical reason	n (%)	1 (3.2)	1 (5.9)	2 (4.2)
Protocol violation	n (%)	0	0	0
Other	n (%)	0	0	0
Completed	**n (%)**	**28 (90 3)**	**15 (88.2)**	**43 (89.6)**
In conformity with the protocol	n (%)	11 (35 5)	7 (41.2)	18 (37.5)
With a protocol deviation(s) after inclusion	n (%)	17 (54.8)	8 (47.1)	25 (52.1)
Entering follow-up period	**n (%)**	**31 (100.0)**	**16 (94.1)**	**47 (97.9)**
Withdrawn from follow-up period due to	**n (%)***	**0**	**1 (6.3)**	**1 (2.1)**
Lost to follow-up	n (%)*	0	0	0
Adverse event	n (%)*	0	0	0
Major worsening of pSS	n (%)*	0	0	0
Withdrawal nonmedical reason	n (%)*	0	1 (6.3)	1 (2.1)
Protocol violation	n (%)*	0	0	0
Other	n (%)*	0	0	0
Completed follow-up period	**n (%)***	**31 (100.0)**	**15 (93.8)**	**46 (97.9)**
In conformity with the Protocol	n (%)*	10 (32 3)	6 (37.5)	16 (34.0)
With protocol deviation(s) after Inclusion	n (%)*	21 (67.7)	9 (56.3)	30 (63.8)

Nobs number of observations, pSS primary Sjögren's Syndrome
N number of patients by group
n number of patients
Percentages were based on Nobs
** Percentages were based on number of patients entering the follow-up period.*

Each of the 3 analysis sets (RS, SS, and BMKS) consisted of 48 patients, with 31 patients in the S95011 group and 17 patients in the placebo group.

Baseline characteristics:

Baseline characteristics were generally similar across both groups and are therefore presented below in the overall population. The mean age of the patients was 53.7 ± 12.4 years (median = 52.5 years), and the majority of the patients were female (87.5%), race of white (91.7%), and not Hispanic or Latino ethnicity (95.8%). Baseline disease characteristics and medical history were similar across both the treatment groups. The mean disease duration since diagnosis was 7.2 ± 7.3 years (median = 5.0 years). A total of 46 patients (95.8%) reported with at least one medical history other than pSS. At least one surgical or medical procedure was reported in 33 patients (68.8%). The most commonly reported surgical and medical procedures were cholecystectomy, hysterectomy, and tonsillectomy (5 patients, 10.4%; each). A total of 11 patients (22.9%) reported with at least one previous treatment specific to pSS with lower frequency in the S95011 group (5 patients, 16.1%) versus the placebo group (6 patients, 35.3%). The most common previous treatment by pharmacological classes was Corticosteroids for systemic use and Immunosuppressants (4 patients, 8.3%, each). At baseline, the mean ESSDAI total score was 12.1 ± 5.2 (median = 11.5) and the mean ESSPRI total score was 7.04 ± 1.60 (median = 7.30).

Extent of exposure:

Overall, 43 patients (89.6%) received 5 infusions during treatment period (W000-W013) with similar frequency in each group (28 patients [90.3%] in the S95011 group and 15 patients [88.2%] in the placebo group). Remaining patients received 1 and 2 infusions (1 patient [5.9%] each) in the placebo group; 3 infusions (1 patient [3.2%]), and 4 infusions (2 patients [6.5%]) in the S95011 group.

Efficacy results:

- Primary efficacy endpoint: mean change from baseline in ESSDAI total score to W013

Primary analysis results:

Among the 48 patients in the RS, at least one intercurrent event (IE) occurred for 5 patients in the S95011 group and 4 in the placebo group.

From only observed values before IEs, the mean change (SD) in ESSDAI total score from baseline to W013 was -3.77 (4.55) in the S95011 group and -5.54 (4.89) in the placebo group. The values post IE were imputed using a multiple imputation by treatment group for the primary analysis (only inferential results). There was no statistically significant difference in the change from baseline between the S95011 group and the placebo group at W013. The estimate (standard error) of the difference between adjusted treatment groups means obtained using General Linear Model was 2.44 (1.55) with a one-sided p-value of 0.942.

Pharmacokinetic results:

Following 750 mg IV administration of S95011 in pSS patients, mean S95011 serum concentrations were comparable to results of previously published literature data in healthy volunteers.

Safety results:

NOTE: The results presented below are for the overall study period selection visit [ASSE] - W028. Results over the ASSE-W013 period were included in the ASSE-W028 period, and results were consistent during these 2 periods.

- Treatment-emergent adverse events (TEAEs)

Main results for AEs in the SS are described in **Table 2.**

Table 2 - Overall summary of treatment-emergent adverse events – Safety Set (N=48)

		S95011 (N = 31)	Placebo (N = 17)
Patients having reported at least one:			
TEAE	n (%)	24 (77.4)	11 (64.7)
Treatment-related TEAE	n (%)	6 (19.4)	2 (11.8)
Severe (Grade ≥3) TEAE	n (%)	5 (16.1)	1 (5.9)
Severe treatment-related TEAE	n (%)	2 (6.5)	0
Serious AE	n (%)	3 (9.7)	1 (5.9)
Serious TEAE	n (%)	2 (6.5)	1 (5.9)
Serious treatment-related TEAE	n (%)	1 (3.2)	0
Serious TEAE leading to treatment withdrawal	n (%)	0	0
Non-serious TEAE leading to treatment withdrawal	n (%)	2 (6.5)	1 (5.9)
AE of special interest	n (%)	6 (19.4)	0
Patients who died	n (%)	0	0

AE adverse event, TEAE treatment-emergent adverse event
N number of patients by group
n number of patients
Percentage were based on N

The ***most frequently affected system organ classes (SOCs)***, in ≥10% of the patients, in the S95011 group were Infections and infestations (45.2%), Blood and lymphatic system disorders (16.1%), Gastrointestinal disorders and Investigations (both SOCs, 12.9%) and in the placebo group were Infections and infestations (35.3%), Musculoskeletal and connective tissue disorders (17.6%), General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Injury, poisoning and procedural complications, and Gastrointestinal disorders (all SOCs, 11.8%). A between-group difference was observed for the SOC Blood and lymphatic system disorders mainly due to the AE of lymphopenia (16.1% in the S95011 group and 5.9% in the placebo group).

The percentage of patients with at least one TEAE was similar across groups with 77.4% in the S95011 group and 64.7% in the placebo group. The ***most commonly reported TEAEs by preferred term (PT)***, in ≥10% of the patients, in the S95011 group were COVID-19 and lymphopenia (both, 16.1%) and in the placebo group was COVID-19 (11.8%). No TEAE of lymphopenia was reported in the placebo group.

The majority of TEAEs reported during the study period that were either Grade 1 (S95011 group: 35 [52.2%] and placebo group: 13 [40.6%]) or Grade 2 intensity (S95011 group: 24 [35.8%] and placebo group: 18 [56.3%]). Overall, the total of 8 TEAEs (11.9%) in S95011 group and one TEAE (3.1%) in the placebo group were reported with Grade 3 intensity, while no TEAEs were reported with Grade 4 or Grade 5 intensity in either group. In the overall study period (ASSE-W028), severe TEAEs were more frequently reported in the S95011 group (5 patients [16.1%]) than in the placebo group (1 patient [5.9%]). The ***most commonly reported severe TEAE*** (in at least 2 patients) was lymphopenia (3 patients [9.7%]) in the S95011 group; all other severe TEAEs were reported by one patient each.

The percentage of patients with at least one TEAE considered to be related to IMP was slightly higher frequency in the S95011 group (19.4%) versus placebo group (11.8%). In the overall study period (ASSE – W028), the ***most commonly reported treatment-related TEAEs by SOCs*** (in at least 2 patients) were Gastrointestinal disorders (2 patients [6.5%]) and Infections and infestations (2 patients [6.5%]) and both were occurred in the S95011 group.

No deaths occurred during the study.

A total of 3 patients experiencing at least one ***serious TEAE*** during the treatment period: 2 patients in the S95011 group (6.5%) with a total of 2 serious TEAEs, and one patient in the placebo group (5.9%) with a total

of 2 serious TEAEs. In the overall study period (ASSE – W028), one patient (3.2%) reported ***serious treatment -related TEAE*** in the S95011 group (PT: herpes zoster).

The percentage of patients with at least one ***TEAE leading to treatment discontinuation*** was similar in each group (2 patients [6.5%] in the S95011 group and one patient [5.9%] in the placebo group). No clinically meaningful trend was observed.

In the overall study period (ASSE-W028), a total of 6 patients (19.4%) experienced at least one ***AE of special interest*** in the S95011 group: lymphopenia (4 patients [12.9%]), herpes zoster (1 patient [3.2%]), and lymphocyte count decreased (1 patient [3.2%]). No TEAEs of special interest were reported in the placebo group.

- Laboratory tests

Hematology
Emergent abnormal values (high and/or low) were reported in both treatment groups with no obvious clinically trends in hematological parameters. Of note, there was the same percentage of patients in both groups presenting with at least one abnormal low emergent value for lymphocyte count on treatment.
Emergent Potentially Clinically Significant Abnormal (PCSA) hematological values were sparse in all groups and for each parameter, except for Low leukocytes (10^9/L): 5 patients (16.1%) in the S95011 group and 2 (11.8%) in placebo group.
There was a trend to decrease in lymphocyte counts over the course of the study in patients receiving S95011 as compared to patients in the placebo group. At baseline, the mean (SD) lymphocytes count was 1.301 ± 0.637 (median = 1.100) in the S95011 group and 1.117 ± 0.397 (median = 1.070) in the placebo group. At W028, the mean (SD) lymphocytes count was 1.073 ± 0.606 (median = 0.840) in the S95011 group and 1.267 ± 0.452 (median = 1.320) in the placebo group.

Biochemistry
Emergent abnormal values (high and/or low) were reported in both treatment groups with no obvious clinically trends in biochemical parameters.
Emergent PCSA biochemical values were sparse in all groups and for each parameter, except for Bicarbonate (mmol/L): 6 patients (19.4%) in the S95011 group and 3 (17.6%) in the placebo group.

Coagulation
Emergent abnormal values (high and/or low) were more frequent in S95011 group compared to placebo group. The most frequent emergent abnormal values (reported in ≥15% of the patient in either treatment groups) was observed for the following parameter: High prothrombin time (%): 5 patients (16.1%) in the S95011 group.

- Other safety evaluation

Vital signs and clinical examination

During overall study period (ASSE-W028), no clinically relevant changes in mean values over time were detected for weight, blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), heart rate, BMI, and body temperature.

Conclusion:

The primary efficacy objective of the study was the mean change in ESSDAI total score from baseline to end of treatment. From only observed values before IEs, the mean change (SD) in ESSDAI total score from baseline was -3.77 (4.55) in the S95011 group and -5.54 (4.89) in the placebo group. There was no statistically significant difference in the change from baseline between the S95011 group and the placebo group.

The safety profile of S95011 was generally acceptable and similar to that of placebo. No safety concerns were observed in terms of TEAEs, clinical laboratory evaluations, or vital signs. Similar percentages of patients reported at least one TEAE in the S95011 group (77.4%) and the placebo group (64.7%). The most commonly reported TEAEs were COVID-19 and lymphopenia (16.1% each) in the S95011 group and COVID-19 (11.8%) in the placebo group. No lymphopenia was reported in the placebo group. No deaths occurred during the study. A total of 3 patients reported serious TEAEs, 2 patients (6.5%) in the S95011 group and 1 patient (5.9%) in the placebo group. The percentage of patients with at least one TEAE leading to treatment discontinuation was similar in each group. Emergent PCSA hematological and biochemistry values were similar in both groups.

All TEAEs of lymphopenia were in the S95011 group versus 0 in the placebo group. There was a trend to decrease in lymphocyte counts over the course of the study in patients receiving S95011 as compared to patients in the placebo group. However, the percentage was the same in both groups for at least one abnormal low emergent value on treatment group. No clear conclusion on the impact of S95011 on lymphocytes count could be drawn; the Data and Safety Monitoring Board (DSMB) concluded similarly.

Following 750 mg IV administration of S95011 in pSS patients, mean S95011 serum concentrations were comparable to results of previously published literature data in healthy volunteers and maximum target engagement was achieved in blood at this dose level.

Following negative efficacy results of this phase IIa clinical trial with S95011 in patients with pSS, the Sponsor decided to stop S95011 development for the Sjögren indication. This decision was not a consequence of any safety concerns.

Date of the report: 21 November 2023