Clinical trial results:
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

Summary

EudraCT number	2020-001526-59
Trial protocol	GB HU DE
Global end of trial date	02 May 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	CL2-95011-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04605978
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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)

Protection of trial subjects:

The study was conducted in accordance with the protocol and with the following: Consensus ethical principles derived from international guidelines including the Declaration of Helsinki, 1964, as revised in Fortaleza, 2013; Applicable Good Clinical Practice (GCP) guidelines; Applicable laws and regulations.
The study was initiated only after the Ethics Committee's approval, in accordance with the local regulations in each of the countries.
Patients were to give freely their written informed consent (by signing the main study ICF [or screening ICF]) before the start of the screening process of the study.

Background therapy:

Those patients who were receiving permitted medications for pSS [oral corticosteroids (prednisone or equivalent), anti-malarials, methotrexate, NSAIDs, artificial tears and artificial saliva/salivary stimulants (e.g. cevimeline, pilocarpine), cyclosporine eye drops and lifitegrast], must be maintained on a stable regimen throughout the treatment period compared to baseline. These treatments are considered "usual" background therapy in the absence of recognized standard of care.

Evidence for comparator:

Matching placebo

Actual start date of recruitment	03 August 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 13
Worldwide total number of subjects	48
EEA total number of subjects	35

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	38
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 19 centers in 7 countries recruited patients.

Pre-assignment

Screening details:

The target population is male or female patients suffering from primary Sjögren's Syndrome with moderate to high activity disease level (ie, systemic manifestations): adults, male or female, diagnosed with primary Sjögren's Syndrome (pSS based) on 2016 American College of Rheumatology-EULAR criteria who fulfilled inclusion criteria of the study.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

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 were similar, in order to protect the blinding with regard to the patients and the investigators. Patients were randomised to S95011 or placebo in an overall 2:1 ratio by Interactive Web Response System (IWRS).

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental S95011

Arm description:

Subjects randomized to receive S95011 concentrate for solution for infusion. S95011 is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Arm type	Experimental
Investigational medicinal product name	S95011
Investigational medicinal product code	S95011
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

S95011 - Dose: 750 mg (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).

Arm title	Placebo

Arm description:

Subjects randomized to receive matching placebo concentrate for solution for infusion. Placebo is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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).

Number of subjects in period 1	Experimental S95011	Placebo
Started	31	17
Completed	28	15
Not completed	3	2
Adverse event, non-fatal	2	1
Withdrawal nonmedical reason	1	1

Baseline characteristics

Reporting groups

Reporting group title	Experimental S95011

Reporting group description:

Subjects randomized to receive S95011 concentrate for solution for infusion. S95011 is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to receive matching placebo concentrate for solution for infusion. Placebo is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Reporting group values	Experimental S95011	Placebo	Total
Number of subjects	31	17	48
Age categorical Units: Subjects			
18 to 75 years	31	17	48
Age continuous Units: years			
arithmetic mean	53.7	53.6	
standard deviation	± 12.6	± 12.5	-
Gender categorical Units: Subjects			
Female	26	16	42
Male	5	1	6

End points

End points reporting groups

Reporting group title	Experimental S95011

Reporting group description:

Subjects randomized to receive S95011 concentrate for solution for infusion. S95011 is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to receive matching placebo concentrate for solution for infusion. Placebo is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.

Primary: Change in ESSDAI Total Score from baseline to W013

End point title	Change in ESSDAI Total Score from baseline to W013

End point description:

Efficacy criterion Eular Sjögren Syndrome Disease Activity index (ESSDAI) is a physician-administered clinical index which has been validated to objectively assess systemic manifestations in Primary Sjögren's Syndrome patients. Scores range from 0 - 123, with a lower score representing less disease activity. Among 48 patients in the Randomized Set (RS), at least one Intercurrent event (IE) occurred for 5 patients in the S95011 group and 4 in the placebo group. Change in ESSDAI Total Score is computed only on observed values before occurrence of Intercurrent Events, therefore some participant data is missing.
Note: Due to the presence of missing data or intercurrent events before W013, the change from baseline to W013 was computed only on observed values, i.e.: 26 and 13 subjects respectively in S95011 and placebo groups.

End point type	Primary

End point timeframe:

From baseline to W013

End point values	Experimental S95011	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	17		
Units: unit of score				
median (standard deviation)				
From baseline to W013 (26:13 subjects analyzed)	-3.77 (± 4.55)	-5.54 (± 4.89)		

Statistical analyses

Statistical analysis title	Statistical Analysis: Change in ESSDAI Total Score

Statistical analysis description:

General Linear Model
This analysis was performed on all patients after imputation of missing data following several imputation strategies depending on the reason for missingness (already missing or set as missing post intercurrent event).

Comparison groups	Experimental S95011 v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.942
Method	General Linear Model
Parameter estimate	Mean difference (net)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	5.49
Variability estimate	Standard error of the mean
Dispersion value	1.55

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study period from Selection visit to W028.	
Adverse event reporting additional description:	
All patients who had taken at least one dose of IMP are included in the Safety Set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Experimental S95011
Reporting group description:	
Subjects randomized to receive S95011 concentrate for solution for infusion. S95011 is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomized to receive matching concentrate for solution for infusion. Placebo is administered by one IV infusion every 2 weeks for the first month and then every 3 weeks until W010.	

Serious adverse events	Experimental S95011	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	1 / 17 (5.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Vascular stent stenosis			

subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Experimental S95011	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 31 (77.42%)	11 / 17 (64.71%)	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	2	3	
Thermal burn			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 31 (6.45%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphopenia			

subjects affected / exposed	4 / 31 (12.90%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Neutropenia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Dry mouth			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Salivary gland pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	2 / 31 (6.45%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Acne			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	

Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Sjogren's syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 31 (16.13%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Parotitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Cystitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Sialoadenitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 17 (5.88%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2020	Amendment No. 1: • Implementation of a DSMB who would review the safety data and give recommendations regarding the conduct of the study. Removal of the stopping rules for premature discontinuation and temporary halt, since DSMB recommendations were to be followed instead • Addition of ECG at W010 • Extension of the screening period to 4 weeks • Addition of instructions on 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 eg, VAY736 • Modification of exclusion criterion No. 31 (ongoing medication) • Addition of a paragraph about rescue treatment • Modification of the AEs list leading to premature discontinuation of the IMP • Specification that adjustments and/or interruptions of IMP were not allowed in the study • Modification of the reporting rules regarding the symptoms related to pSS
24 March 2022	Amendment No. 2: • Update to the exclusion criteria No. 30 to allow rituximab or other B cell depleting agents if the CD19 B cell count was within normal range at randomization (W000) and to specify that prior administration of JAK inhibitors was forbidden • Update of exclusion criterion No. 17 (in case of participation in another clinical study) • Update of exclusion criterion No. 31 adding medications known to cause dry mouth/eyes • Update of the oversight of a physician on safety data collected on e-CRF

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported