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

Summary

EudraCT number	2020-000511-77
Trial protocol	DE BE HU
Global end of trial date	09 February 2024

Results information

Result version number	v1 (current)
This version publication date	21 February 2025
First version publication date	21 February 2025

Trial information

Trial identification

Sponsor protocol code	ACT16618

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04572841
WHO universal trial number (UTN)	U1111-1244-2266

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis Recherche & Développement
Sponsor organisation address	82 Avenue Raspail, Gentilly, France, 94250
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Développement, Contact-US@sanofi.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	04 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the therapeutic efficacy of 1 dose level of SAR441344 versus placebo over 12 weeks in adult participants with primary Sjögren's syndrome (pSjS), assessed by the change of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI).

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. During the course of the trial, participants were provided with individual participant cards indicating the nature of the trial the participant is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	84
EEA total number of subjects	26

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)	76
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 35 centers in 12 countries. A total of 234 participants were screened from 12 November 2020 to 10 August 2023, of which 150 were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 84 participants were randomized in a ratio of 1:1 to either placebo or SAR441344 (frexalimab) arm. Randomization was stratified by Baseline EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score greater than or equal to (≥) 5 versus less than (<) 5.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a single intravenous (IV) loading dose of placebo matched to SAR441344 on Day 1, followed by a subcutaneous (SC) dose of placebo matched to SAR441344 administered once every 2 weeks (q2w) at Weeks 2, 4, 6, 8 and 10.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Placebo matched to SAR441344 was administered via IV infusion on Day 1, followed by an SC injection administered q2w at Weeks 2, 4, 6, 8 and 10.

Arm title	SAR441344

Arm description:

Participants received a single IV loading dose of SAR441344 1200 milligram (mg) on Day 1, followed by an SC dose of SAR441344 600 mg administered q2w at Weeks 2, 4, 6, 8 and 10.

Arm type	Experimental
Investigational medicinal product name	SAR441344
Investigational medicinal product code	
Other name	Frexalimab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

SAR441344 1200 mg was administered via IV infusion on Day 1, followed by an SC injection of SAR441344 600 mg administered q2w at Weeks 2, 4, 6, 8 and 10.

Number of subjects in period 1	Placebo	SAR441344
Started	42	42
Completed	39	40
Not completed	3	2
Consent withdrawn by subject	2	1
Adverse event	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) loading dose of placebo matched to SAR441344 on Day 1, followed by a subcutaneous (SC) dose of placebo matched to SAR441344 administered once every 2 weeks (q2w) at Weeks 2, 4, 6, 8 and 10.	
Reporting group title	SAR441344
Reporting group description:	
Participants received a single IV loading dose of SAR441344 1200 milligram (mg) on Day 1, followed by an SC dose of SAR441344 600 mg administered q2w at Weeks 2, 4, 6, 8 and 10.	

Reporting group values	Placebo	SAR441344	Total
Number of subjects	42	42	84
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	47.8	49.2	
standard deviation	± 12.9	± 11.1	-
Sex: Female, Male			
Units: participants			
Female	40	40	80
Male	2	2	4
Race/Ethnicity, Customized			
Units: Subjects			
White	34	28	62
Black or African American	1	4	5
Asian	5	4	9
American Indian or Alaska Native	1	6	7
Missing/Not reported	1	0	1
EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) Score			
ESSDAI:validated and established outcome measurement for therapeutic efficacy in Sjögren's syndrome, evaluating disease activity mainly on extra-glandular manifestations, and consisted of 12 organ-specific domains(constitutional,lymphadenopathy,glandular,articular,cutaneous,pulmonary, renal,muscular,peripheral and central nervous system,hematological,biological), scored based on organ-specific items in 3 to 4 different severity grades (0=no to 3=high). These scores were summed up in weighted way to summarize into total score ranging from 0-123. Higher scores=worse outcome.			
Units: score on a scale			
arithmetic mean	10.38	8.43	
standard deviation	± 3.64	± 3.88	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received a single intravenous (IV) loading dose of placebo matched to SAR441344 on Day 1, followed by a subcutaneous (SC) dose of placebo matched to SAR441344 administered once every 2 weeks (q2w) at Weeks 2, 4, 6, 8 and 10.	
Reporting group title	SAR441344
Reporting group description:	
Participants received a single IV loading dose of SAR441344 1200 milligram (mg) on Day 1, followed by an SC dose of SAR441344 600 mg administered q2w at Weeks 2, 4, 6, 8 and 10.	

Primary: Change From Baseline to Week 12 in ESSDAI Score

End point title	Change From Baseline to Week 12 in ESSDAI Score
End point description:	
ESSDAI:validated,established outcome measurement for therapeutic efficacy in Sjögren's syndrome evaluating disease activity on extra-glandular manifestations.Score includes 12 organ-specific domains(constitutional,lymphadenopathy,glandular,articular,cutaneous,pulmonary,renal,muscular,peripheral and central nervous system,hematological,biological), scored based on organ-specific items in 3-4 severity grades(0=no to 3=high).Scores are summed up in weighted way(severity grades multiplied with weights 1-6) to summarize into total score(0-123).Higher scores=worse outcome.Negative change from baseline=improvement.Baseline=Day 1 assessment value.Efficacy population=all randomly assigned participants who received at least 1 complete dose of IMP with at least 1 post-IMP administration measurement with available Baseline assessment of ESSDAI.Least squares(LS) mean is calculated using mixed models for repeated measures (MMRM).Observed values after occurrence of intercurrent events are excluded.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to Week 12	

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: score on a scale				
least squares mean (standard error)	-5.60 (± 0.60)	-5.29 (± 0.59)		

Statistical analyses

Statistical analysis title	Placebo Versus SAR441344
Statistical analysis description:	
Analysis was performed for change from baseline using a mixed model for repeated measures with visit, intervention group (SAR441344 and Placebo), and visit by intervention group interaction as fixed categorical effects, and participant specific baseline ESSDAI as continuous covariate.	
Comparison groups	Placebo v SAR441344

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Square Mean Difference
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	2.02
Variability estimate	Standard error of the mean
Dispersion value	0.85

Secondary: Change From Baseline to Week 12 in European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) Score

End point title	Change From Baseline to Week 12 in European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) Score

End point description:

The ESSPRI is a validated and established outcome measurement, reported by participants, which rates the key disease manifestations: fatigue, dryness, and pain, based on a numeric scale ranging from 0 to 10, where 0 is defined as no symptoms and 10 as maximum imaginable complaints. The total score is the mean score of the 3 scales and ranges from 0 to 10. Higher scores indicates worse outcome. A negative change from baseline indicates improvement. Baseline is defined as Day 1 assessment value. LS mean is calculated using MMRM. Observed values after occurrence of intercurrent events are excluded. Efficacy population includes all randomly assigned participants who actually received at least 1 complete dose of IMP with at least 1 post-IMP administration measurement, with available Baseline assessment of the ESSDAI. Only participants with data collected for this endpoint are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 12

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: score on a scale				
least squares mean (standard error)	-2.21 (± 0.34)	-1.92 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in Multidimensional Fatigue Inventory (MFI) General Fatigue Subscale and Other Subscales Score

End point title	Change From Baseline to Week 12 in Multidimensional Fatigue Inventory (MFI) General Fatigue Subscale and Other Subscales Score

End point description:

MFI is validated,20 item self-report instrument to evaluate fatigue by investigating subscales: general fatigue,physical fatigue,mental fatigue,reduced motivation,reduced activity. Each subscale consists of 4 items that are scored from 1 (yes, this is true) to 5 (no, this is not true) on which participants indicate how listed statements applied to their current fatigue situation. Item scores are summed to create individual subscale score (4-20).Higher score=higher degree of fatigue.Negative change from baseline=improvement.Baseline=Day 1 assessment value.LS mean is calculated using ANCOVA. Observed values after occurrence of intercurrent events are excluded.Efficacy population=all randomly assigned participants who received at least 1 complete dose of IMP with at least 1 post-IMP administration measurement, with available Baseline assessment of ESSDAI. Only participants with data collected for this endpoint are reported. n=number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 12

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: score on a scale				
least squares mean (standard error)				
General Fatigue Scale Score (n=38, 38)	0.37 (± 0.30)	-0.18 (± 0.30)		
Mental Fatigue Scale Score (n=38, 38)	0.26 (± 0.36)	0.37 (± 0.36)		
Physical Fatigue Scale Score (n=38, 38)	0.27 (± 0.36)	-0.30 (± 0.36)		
Reduced Activity Scale Score (n=37, 38)	0.22 (± 0.31)	0.29 (± 0.31)		
Reduced Motivation Scale Score (n=37, 38)	0.30 (± 0.30)	0.26 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Concentration of SAR441344

End point title	Mean Plasma Concentration of SAR441344[1]

End point description:

Blood samples were collected for the measurement of plasma concentrations of SAR441344. Pharmacokinetic (PK) population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population. Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

At end of infusion and 4 hours post-infusion on Day 1; pre-dose at Weeks 2, 4, 6, 8, 10, and at Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: microgram per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Day 1 (end of infusion) (n=21)	466.10 (± 93.86)			
Day 1 (4 hours post-infusion) (n=36)	427.22 (± 102.07)			
Week 2 (pre-dose) (n=39)	139.98 (± 28.30)			
Week 4 (pre-dose) (n=39)	132.91 (± 36.21)			
Week 6 (pre-dose) (n=38)	135.18 (± 46.39)			
Week 8 (pre-dose) (n=38)	141.34 (± 44.85)			
Week 10 (pre-dose) (n=38)	142.25 (± 48.80)			
Week 12 (n=36)	151.59 (± 56.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Plasma Concentration of SAR441344

End point title	Median Plasma Concentration of SAR441344[2]

End point description:

Blood samples were collected for the measurement of plasma concentrations of SAR441344. PK population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population. Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

At end of infusion and 4 hours post-infusion on Day 1; pre-dose at Weeks 2, 4, 6, 8, 10, and at Week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: mcg/mL				
median (full range (min-max))				
Day 1 (end of infusion) (n=21)	479.06 (302.4 to 652.2)			
Day 1 (4 hours post-infusion) (n=36)	408.37 (253.1 to 623.6)			
Week 2 (pre-dose) (n=39)	132.21 (98.3 to 203.1)			

Week 4 (pre-dose) (n=39)	133.01 (45.6 to 236.5)			
Week 6 (pre-dose) (n=38)	127.32 (60.2 to 237.5)			
Week 8 (pre-dose) (n=38)	135.10 (76.9 to 284.9)			
Week 10 (pre-dose) (n=38)	134.39 (58.0 to 268.1)			
Week 12 (n=36)	148.11 (64.4 to 306.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of SAR441344

End point title	Maximum Plasma Concentration (Cmax) of SAR441344[3]

End point description:

Blood samples were collected at the specified timepoints for the measurement of plasma concentrations of SAR441344. Cmax was assessed by a Bayesian approach using the population PK model. PK population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population. Only participants with data collected for this outcome measure are reported.

End point type	Secondary

End point timeframe:

After the last SC dose on Week 10 up to 336 hours post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: mcg/mL				
arithmetic mean (standard deviation)	190 (± 54.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t1/2z) of SAR441344

End point title	Terminal Half-life (t1/2z) of SAR441344[4]

End point description:

Blood samples were collected at the specified timepoints for the measurement of plasma concentrations of SAR441344. t1/2z was assessed by a Bayesian approach using the population PK model. PK population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population.

End point type	Secondary

End point timeframe:

Week 10 to Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: hours				
median (full range (min-max))	662 (374 to 997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (tmax) of SAR441344

End point title	Time to Maximum Plasma Concentration (tmax) of

End point description:

Blood samples were collected at the specified timepoints for the measurement of plasma concentrations of SAR441344. tmax was assessed by a Bayesian approach using the population PK model. PK population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population. Only participants with data collected for this outcome measure are reported.

End point type	Secondary

End point timeframe:

After the last SC dose on Week 10 up to 336 hours post-dose

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: hours				
median (full range (min-max))	89.1 (76.8 to 139)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve Over the Dosing Interval (AUC0-tau) of SAR441344

End point title	Area Under the Curve Over the Dosing Interval (AUC0-tau) of

	SAR441344[6]

End point description:

Blood samples were collected at the specified timepoints for the measurement of plasma concentrations of SAR441344. AUC0-tau was assessed by a Bayesian approach using the population PK model. PK population included all randomized and treated participants (safety population) with adequate PK results. Participants who received only placebo were not a part of the PK population. Only participants with data collected for this outcome measure are reported.

End point type	Secondary

End point timeframe:

After the last SC dose on Week 10 up to 336 hours post-dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: microgram*hour per milliliter (mcg*h/mL)				
arithmetic mean (standard deviation)	57900 (± 18000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Adverse Events of Special Interest (AESI)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs), Treatment-emergent Serious Adverse Events (TESAEs), and Adverse Events of Special Interest (AESI)

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. TEAEs: AEs that occurred, worsened, or became serious during the TEAE period (time from the first IMP administration up to Week 24). Serious adverse events (SAE): Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent disability/incapacity, or was a congenital anomaly/birth defect. An AESI: an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor’s product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

From first dose of IMP (Day 1) up to end of follow-up period (Week 24)

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
Any TEAE	26	29		
Any TESAE	1	1		
Any AESI	5	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Discontinuation and Withdrawals due to TEAEs

End point title	Number of Participants With Treatment Discontinuation and Withdrawals due to TEAEs

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. TEAEs were AEs that occurred, worsened, or became serious during the TEAE period (time from the first IMP administration up to Week 24). Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

From first dose of IMP (Day 1) up to end of follow-up period (Week 24)

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
Treatment discontinuation due to TEAEs	4	4		
Treatment withdrawal due to TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Increase in Pain Intensity Compared to Pre-dose Pain Intensity at Injection Site by Verbal Descriptor Scale (VDS)

End point title	Number of Participants With Increase in Pain Intensity Compared to Pre-dose Pain Intensity at Injection Site by Verbal Descriptor Scale (VDS)

End point description:

For measurement of local tolerability, participants had a self-evaluation using VDS before IMP administration, after completion of IMP administration, and 2 hours post-administration. Participants were asked to report sensations at injection site and rated pain severity as following grading: 0= no

pain; 1= mild pain; 2= moderate pain, 3= severe pain, 4= very severe. Positive change in VDS score indicated higher pain severity compared to pre-dose pain. Numerical change provides number of grades the pain got worse (positive change) or improved (negative change). Total number of participants with pain intensity increase (change in VDS score of greater than or equal to 1) compared to pre-dose pain intensity are reported. Safety population included all randomized participants exposed to IMP (regardless of amount of treatment administered). Only participants with data collected at specified timepoints are reported. Here, n= number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

Pre-dose (within 24 hours prior IMP dosing), post-dose (up to 15 minutes after dosing) and 2 hours post-dose at Weeks 2, 4, 6, 8 and 10

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: participants				
Week 2: Post-dose versus (vs) pre-dose(n=42,40)	7	7		
Week 2: 2 hours post-dose vs pre-dose (n=42,40)	5	8		
Week 4: Post-dose vs pre-dose (n=39,40)	12	8		
Week 4: 2 hours post-dose vs pre-dose (n=39,40)	5	6		
Week 6: Post-dose vs pre-dose (n=41,38)	13	10		
Week 6: 2 hours post-dose vs pre-dose (n=41,38)	3	3		
Week 8: Post-dose vs pre-dose (n=39,38)	7	11		
Week 8: 2 hours post-dose vs pre-dose (n=39,38)	3	1		
Week 10: Post-dose vs pre-dose (n=37,38)	7	10		
Week 10: 2 hours post-dose vs pre-dose (n=37,38)	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs Related to Local Tolerability Findings

End point title	Number of Participants With AEs Related to Local Tolerability Findings

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. Local tolerability at injection site was assessed following IMP injection and findings at the site of injection such as injection site erythema, injection site reaction, and injection site pain were recorded. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 10

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
Injection site erythema	1	3		
Injection site reaction	2	0		
Injection site pain	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs

End point title	Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Vital Signs

End point description:

PCSA values were defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor. Criteria for PCSA: Sitting systolic blood pressure (SSBP) less than or equal to (≤)95 millimeters of mercury (mmHg) and decrease from baseline ≥20 mmHg; ≥160 mmHg and increase from baseline ≥20 mmHg; Sitting diastolic blood pressure (SDBP) ≤45 mmHg and decrease from baseline ≥10 mmHg, ≥110 mmHg and increase from baseline ≥10 mmHg; Sitting heart rate (HR) ≤50 beats per minute (bpm) and decrease from baseline ≥20 bpm, ≥120 bpm and increase from baseline ≥20 bpm; Weight ≥5% decrease from baseline, ≥5% increase from baseline. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
SSBP: ≤95 mmHg; decrease from baseline ≥20 mmHg	2	2		
SSBP: ≥160mmHg; increase from baseline ≥20mmHg	0	0		
SDBP: ≤45 mmHg; decrease from baseline ≥10 mmHg	0	0		
SDBP: ≥110 mmHg; increase from baseline ≥10 mmHg	0	0		
Sitting HR: ≤50bpm; decrease from baseline ≥20bpm	1	0		
Sitting HR: ≥120bpm; increase from baseline ≥20bpm	0	0		
Weight: ≥5% decrease from baseline	6	3		

Weight: ≥5% increase from baseline	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Electrocardiogram

End point title	Number of Participants With PCSA in Electrocardiogram

End point description:

PCSA values were defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor. Criteria for PCSA: HR <50 bpm, <40 bpm, >90 bpm, >90 bpm and increase from baseline ≥20 bpm, >100 bpm; PR interval, aggregate >200 milliseconds (msec), >200 msec and increase from baseline ≥25%, >220 msec, >220 msec and increase from baseline ≥25%, >240 msec, >240 msec and increase from baseline ≥25%; QRS duration, aggregate >110 msec, >110 msec and increase from baseline ≥25%, >120 msec, >120 msec and increase from baseline ≥25%; QT interval, aggregate >500 msec; corrected QT (QTc) correction method unspecified (CMU) >450 msec, >480 msec, increase from baseline [30-60] msec, increase from baseline >60 msec. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered). IFB= increase from baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
HR: <50 bpm	2	1		
HR: <40 bpm	0	0		
HR: >90 bpm	3	1		
HR: >90 bpm; IFB ≥20 bpm	1	0		
HR: >100 bpm	0	0		
PR interval, aggregate: >200 msec	4	2		
PR interval, aggregate: >200 msec; IFB ≥25%	1	0		
PR interval, aggregate: >220 msec	1	0		
PR interval, aggregate: >220 msec; IFB ≥25%	0	0		
PR interval, aggregate: >240 msec	1	0		
PR interval, aggregate: >240 msec; IFB ≥25%	0	0		
QRS duration, aggregate: >110 msec	2	0		
QRS duration, aggregate: >110 msec; IFB ≥25%	0	0		
QRS duration, aggregate: >120 msec	1	0		
QRS duration, aggregate: >120 msec; IFB ≥25%	0	0		

QT interval, aggregate: >500 msec	0	0		
QTc CMU: >450 msec	5	2		
QTc CMU: >480 msec	0	0		
QTc CMU: IFB [30-60] msec	3	7		
QTc CMU: IFB >60 msec	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Hematology Parameters

End point title	Number of Participants With PCSA in Hematology Parameters

End point description:

PCSA values were defined as abnormal values considered medically important by Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by Sponsor. Criteria for PCSA: Hemoglobin (Hb) ≤115 grams per liter (g/L) (Male [M]) or ≤95 g/L (Female [F]), ≥185 g/L (M) or ≥165 g/L (F), decrease from baseline ≥20 g/L; Hematocrit ≤0.37 volume per volume (v/v) (M) or ≤0.32 v/v (F), ≥0.55 v/v (M) or ≥0.5 v/v (F); Erythrocytes (red blood cells [RBC]) ≥6 x 10^12 per liter (/L); Platelets <100 x 10^9/L, ≥700 x 10^9/L; Leukocytes (white blood cells [WBC]) <3 x 10^9/L (Non-Black[NB]) or <2 x 10^9/L (Black[B]), ≥16 x 10^9/L; Neutrophils <1.5 x 10^9/L (NB) or <1 x 10^9/L (B); Lymphocytes >4 x 10^9/L, <0.5 x 10^9L; Monocytes >0.7 x 10^9/L; Basophils >0.1 x 10^9/L; Eosinophils >0.5 x 10^9/L or >upper limit of normal(ULN) (if ULN ≥0.5 x 10^9/L). Safety population included all randomized participants exposed to the IMP (regardless of amount of treatment administered).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
Hb: ≤115 g/L (M); ≤95 g/L (F)	0	1		
Hb: ≥185 g/L (M); ≥165 g/L (F)	0	1		
Hb: Decrease from baseline ≥20 g/L	2	2		
Hematocrit: ≤0.37 v/v (M); ≤0.32 v/v (F)	5	3		
Hematocrit: ≥0.55 v/v (M); ≥0.5 v/v (F)	0	1		
RBC: ≥6 x 10^12/L	0	1		
Platelets: <100 x 10^9/L	0	0		
Platelets: ≥700 x 10^9/L	0	0		
WBC: <3 x 10^9/L (NB); <2 x 10^9/L (B)	8	5		
WBC: ≥16 x 10^9/L	0	0		
Neutrophils: <1.5 x 10^9/L (NB); <1 x 10^9/L (B)	7	7		
Lymphocytes: >4 x 10^9/L	0	1		
Lymphocytes: <0.5 x 10^9L	2	0		
Monocytes: >0.7 x 10^9/L	1	2		

Basophils: >0.1 x 10^9/L	0	8		
Eosinophils: >0.5 x 10^9/L or >ULN	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Clinical Chemistry Parameters

End point title	Number of Participants With PCSA in Clinical Chemistry Parameters

End point description:

PCSA values:abnormal values considered medically important by Sponsor,according to predefined criteria/thresholds based on literature reviews;defined by Sponsor.Criteria for PCSA:Sodium≤129 millimoles per liter(mmol/L),≥160 mmol/L;Potassium<3 mmol/L,≥5.5 mmol/L;Glucose≤3.9 mmol/L and <lower limit of normal(LLN),≥11.1 mmol/L(unfasted);≥7 mmol/L(fasted); Creatine kinase(CK)>3 ULN,>10 ULN;Creatinine≥150 micromoles/L(adults),≥30% change from baseline,≥100% change from baseline;Creatinine clearance(CG)≥60-<90 milliliters per minute(mL/min)(mild decrease in glomerular filtration rate[GFR]),≥30-<60 mL/min(moderate decrease in GFR),≥15-<30 mL/min(severe decrease in GFR),<15 mL/min(end stage renal disease),Urea nitrogen≥17 mmol/L;Alkaline phosphatase(ALP)>1.5 ULN;Alanine aminotransferase(ALT)>3 ULN; ALT>3 ULN & bilirubin>2 ULN;Aspartate aminotransferase(AST)>3 ULN;Direct bilirubin>35% bilirubin & bilirubin>1.5 ULN;Total bilirubin>1.5 ULN,>2 ULN.Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
Sodium: ≤129 mmol/L	0	0		
Sodium: ≥160 mmol/L	0	0		
Potassium: <3 mmol/L	0	0		
Potassium: ≥5.5 mmol/L	1	0		
Glucose: ≤3.9 mmol/L and <LLN	3	5		
Glucose:≥11.1 mmol/L(unfasted); ≥7 mmol/L(fasted)	3	1		
CK: >3 ULN	0	1		
CK: >10 ULN	0	0		
Creatinine: ≥150 micromoles/L (Adults)	0	0		
Creatinine: ≥30% change from baseline	1	2		
Creatinine: ≥100% change from baseline	0	0		
CG: ≥60 - <90 mL/min	24	16		
CG: ≥30 - <60 mL/min	3	2		
CG: ≥15 - <30 mL/min	0	0		
CG: <15 mL/min	0	0		
Urea Nitrogen: ≥17 mmol/L	0	0		
ALP: >1.5 ULN	0	1		

ALT: >3 ULN	0	0		
ALT >3 ULN; Bilirubin >2 ULN	0	0		
AST: >3 ULN	0	0		
Direct Bilirubin>35% Bilirubin; Bilirubin>1.5 ULN	0	0		
Total Bilirubin: >1.5 ULN	0	1		
Total Bilirubin: >2 ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Urinalysis Parameters

End point title	Number of Participants With PCSA in Urinalysis Parameters

End point description:

PCSA values were defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor. Criteria for PCSA: Potential of hydrogen (pH) ≤4.6 or ≥8. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered).

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Week 24

End point values	Placebo	SAR441344		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: participants				
pH ≤4.6	0	0		
pH ≥8	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-drug Antibodies (ADA) to SAR441344

End point title	Number of Participants With Anti-drug Antibodies (ADA) to SAR441344[7]

End point description:

Serum samples were collected at the specified timepoints for the assessment of ADAs to SAR441344. Number of participants with treatment-emergent ADA defined as at least 1 treatment-induced/boosted ADA during the treatment-emergent period, i.e. from the time of the IMP administration up to the end of study visit are reported. Number of participants with positive ADA are reported. ADA population included all randomized participants treated with SAR441344 with at least 1 post-baseline ADA result (positive, negative or inconclusive). Here, n= number of participants analyzed for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 8, Week 12, and Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants in the SAR441344 arm were analyzed in this endpoint.

End point values	SAR441344			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: participants				
Baseline (n=42)	2			
Week 4 (n=41)	2			
Week 8 (n=38)	2			
Week 12 (n=42)	0			
Week 24 (n=41)	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of IMP (Day 1) up to end of follow-up period (Week 24)	
Adverse event reporting additional description:	
Analysis was performed on safety population.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	SAR441344
Reporting group description:	
Participants received a single IV loading dose of SAR441344 1200 mg on Day 1, followed by an SC dose of SAR441344 600 mg administered q2w at Weeks 2, 4, 6, 8 and 10.	
Reporting group title	Placebo
Reporting group description:	
Participants received a single IV loading dose of placebo matched to SAR441344 on Day 1, followed by an SC dose of placebo matched to SAR441344 administered q2w at Weeks 2, 4, 6, 8 and 10.	

Serious adverse events	SAR441344	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Product issues			
Device Breakage			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Osteomyelitis Acute			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SAR441344	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 42 (35.71%)	20 / 42 (47.62%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	4 / 42 (9.52%)	5 / 42 (11.90%)	
occurrences (all)	5	5	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 42 (7.14%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 42 (9.52%)	2 / 42 (4.76%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Injection Site Erythema			
subjects affected / exposed	3 / 42 (7.14%)	1 / 42 (2.38%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Infections and infestations			
Covid-19			
subjects affected / exposed	4 / 42 (9.52%)	4 / 42 (9.52%)	
occurrences (all)	4	4	
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	3 / 42 (7.14%)	
occurrences (all)	1	3	

Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	6 / 42 (14.29%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 August 2020	The purpose of the amendment was to have minor adjustments in the exclusion criteria E01, E11, E14, and E30 to address comments raised by the European Union participating National Competent Authorities during review of the clinical trial application, via the Voluntary Harmonisation Procedure. Clarification of minor discrepancies were also addressed, as well as minor editorial and document formatting revisions were made.
28 July 2021	The purpose of the amendment was to have an adjustment in the inclusion criterion I03 and to allow re-screening for I06 to better reflect the participant population to aid recruitment without compromising on safety requirements. Section 9.5 (Interim analysis) was extended with an early analysis after all participants have completed their End of Treatment/Week 12 visit, to allow for internal decision making. Section 6.2 was adapted to allow destruction of vials according to local regulations and a reference to the pharmacy manual was added. Clarification of discrepancies were also addressed, as well as minor editorial and document formatting revisions were made.
05 April 2022	The purpose of the amendment was to adapt inclusion/exclusion criteria I06, E17, E18, and E22 to better account for the required characteristics of Sjögren's syndrome (ESSDAI >5 and baseline treatment) to facilitate recruitment, without compromising safety requirements. The discontinuation due to Coronavirus Disease 2019 was adjusted. Section 9.5 (Interim analysis) was revised with an option of additional analysis. Discrepancies were also addressed, as well as minor corrections and clarifications were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported