Clinical trial results:
A randomized, double-blind, placebo-controlled, proof of concept study assessing the efficacy and safety of the RIPK1-inhibitor SAR443122 in patients with moderate to severe subacute or discoid/chronic cutaneous lupus erythematosus

Summary

EudraCT number	2020-004703-14
Trial protocol	HU PL IT
Global end of trial date	26 June 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	ACT16404

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04781816
WHO universal trial number (UTN)	U1111-1246-6784

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91385
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	21 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of SAR443122 in cutaneous lupus erythematosus (CLE).

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 trail, 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	01 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	India: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	78
EEA total number of subjects	24

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	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 50 centers in 15 countries. A total of 132 participants were screened from 01 April 2021 to 01 March 2023, of which 54 were screen failures. Screen failures were mainly due to not meeting the eligibility criteria.

Pre-assignment

Screening details:

A total of 78 participants were randomized in a ratio of 1:1 to either SAR443122 or placebo arm. The randomization was stratified by subtype of CLE (discoid lupus erythematosus [DLE] or subacute cutaneous lupus erythematosus [SCLE]), baseline use of hydroxychloroquine/chloroquine (HCQ/CQ) and by region.

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 placebo matched to SAR443122 orally twice a day (BID) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to SAR443122 was administered orally BID for 12 weeks.

Arm title	SAR443122

Arm description:

Participants received SAR443122 300 mg orally BID for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Eclitasertib
Investigational medicinal product code	
Other name	DNL758
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

SAR443122 300 mg was administered orally BID for 12 weeks.

Number of subjects in period 1	Placebo	SAR443122
Started	40	38
Completed	38	35
Not completed	2	3
Adverse event, non-fatal	-	1
Not Related to Coronavirus Disease 2019	1	1
Withdrawal by Subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to SAR443122 orally twice a day (BID) for 12 weeks.	
Reporting group title	SAR443122
Reporting group description:	
Participants received SAR443122 300 mg orally BID for 12 weeks.	

Reporting group values	Placebo	SAR443122	Total
Number of subjects	40	38	78
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	46.3	45.6	
standard deviation	± 9.8	± 10.7	-
Sex: Female, Male Units:			
Female	29	33	62
Male	11	5	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	3	7
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	31	30	61
More than one race	0	1	1
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to SAR443122 orally twice a day (BID) for 12 weeks.	
Reporting group title	SAR443122
Reporting group description:	
Participants received SAR443122 300 mg orally BID for 12 weeks.	

Primary: Percent Change From Baseline in Cutaneous Erythematosus Disease Area and Severity Index – Activity (CLASI-A) Sub-Score at Week 12

End point title	Percent Change From Baseline in Cutaneous Erythematosus Disease Area and Severity Index – Activity (CLASI-A) Sub-Score at Week 12

End point description:

The CLASI is a clinician rated scale designed to assess the disease activity and damage in CLE in adults. It is composed of 56 items covering 2 dimensions: the disease activity (CLASI-A) and the disease damage (CLASI-D). CLASI-A disease activity covers the domains: erythema, scale/hypertrophy, recent hair loss/alopecia, and mucous membrane lesions. CLASI-A sub-score ranges for 0 to 70, where 0-9 indicates mild disease, 10-20 indicates moderate disease, and 21-70 indicates severe disease. Higher score indicates a more severe skin disease. Baseline was defined as the Day 1 assessment value. Efficacy population included all randomized participants exposed to the investigational medicinal product (IMP), with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Only participants with data collected at Week 12 are reported.

End point type	Primary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: percent change				
least squares mean (standard error)	-37.05 (± 5.31)	-42.76 (± 5.42)		

Statistical analyses

Statistical analysis title	SAR443122 Versus Placebo

Statistical analysis description:

Analysis was performed using mixed model with repeated measurements (MMRM) including fixed effects for baseline CLASI-A, post-baseline visit, geographical region, disease subtype, baseline use of CQ/HCQ, intervention group, visit-by- intervention group interaction, and visit-by-baseline-CLASI-A interaction.

Comparison groups	Placebo v SAR443122

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Square Mean Difference
Point estimate	-5.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.26
upper limit	6.85
Variability estimate	Standard error of the mean
Dispersion value	7.53

Secondary: Change From Baseline in Participants Reported Daily Worst Itch Using Peak Pruritus Numerical Rating Scale (Itch-NRS) at Week 12

End point title	Change From Baseline in Participants Reported Daily Worst Itch Using Peak Pruritus Numerical Rating Scale (Itch-NRS) at Week 12

End point description:

Peak Pruritus NRS (itch-NRS) is single item patient reported outcomes (PRO) tool that participants used to report intensity of their pruritus (itch) during daily recall period. Participants were asked to rate their worst itch on 0 (no itch) to 10 (worst itch imaginable) NRS by answering following question: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during previous 24 hours?". Total score on scale ranges from 0 (no itch) to 10 (worst itch imaginable). Higher score indicates more severe skin disease. Baseline was defined as average of daily non-missing scores obtained during the week prior to Day 1. Efficacy population included all randomized participants exposed to the IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Only participants with data collected at Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	36		
Units: score on a scale				
least squares mean (standard error)	-0.62 (± 0.37)	-2.16 (± 0.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Physician's Global Assessment of Disease Activity (PhysGA– Disease Activity) of 0 or 1 (Disease Free or Almost Disease Free) at Week 12

End point title	Percentage of Participants With Physician's Global Assessment

	of Disease Activity (PhysGA– Disease Activity) of 0 or 1 (Disease Free or Almost Disease Free) at Week 12

End point description:

The PhysGA- disease activity is a 5 point-Lickert scale instrument designed to assess physician-reported disease activity. The investigators were asked the following question "How active would you say your patient's cutaneous lupus erythematosus is currently?" The total score on scale ranges from 0 (not active at all) to 4 (extremely active). Higher score indicates a more severe skin disease. Efficacy population included all randomized participants exposed to the IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: percentage of participants				
number (not applicable)	32.5	44.74		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of CLASI-A50 and CLASI-A75 Responders at Week 12

End point title	Percentage of CLASI-A50 and CLASI-A75 Responders at Week 12

End point description:

The CLASI is a clinician rated scale designed to assess the disease activity and damage in CLE in adults. It is composed of 56 items covering 2 dimensions: the disease activity (CLASI-A) and the disease damage (CLASI-D). CLASI-A disease activity covers the domains: erythema, scale/hypertrophy, recent hair loss/alopecia, and mucous membrane lesions. CLASI-A sub-score ranges for 0 to 70, where 0-9 indicates mild disease, 10-20 indicates moderate disease, and 21-70 indicates severe disease. Higher score indicates a more severe skin disease. The CLASI-A50/75 responder was defined as a participant who achieved a decrease by at least 50%/75% of CLASI-A sub-score from baseline. Efficacy population included all randomized participants exposed to the IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: percentage of responders				
number (not applicable)				
CLASI-A50	45	44.74		
CLASI-A75	10	23.68		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CLASI Components' Score Over Time

End point title	Change From Baseline in CLASI Components' Score Over Time

End point description:

CLASI is clinician rated scale composed of 56 items covering disease activity(CLASI-A);disease damage(CLASI-D). CLASI-A disease activity covers erythema, scale/hypertrophy, recent hair loss/alopecia, mucous membrane lesions. Sub-score ranges 0-70 (0-9=mild disease,10-20=moderate disease,21-70=severe disease). CLASI-D disease damage covers dyspigmentation,scarring/atrophy/panniculitis,clinically judged scarring of scalp(including scarring alopecia). Scale ranges 0(absence of disease damage) to 56(severe disease damage) using parameters of dyspigmentation and scarring. For CLASI-A and CLASI-D, higher score=more severe skin disease. Baseline=Day 1 assessment value. Efficacy population=all randomized participants exposed to IMP, with available Baseline assessment of CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Only participants with data collected at Weeks 4, 8, 12, and 16 for each specified category are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Weeks 4, 8, 12, and 16

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: score on a scale				
arithmetic mean (standard deviation)				
Erythema: Weeks 4 (n=40, 37)	-2.33 (± 3.24)	-2.14 (± 3.02)		
Erythema: Weeks 8 (n=38, 36)	-3.37 (± 4.48)	-3.42 (± 3.80)		
Erythema: Weeks 12 (n=35, 35)	-4.97 (± 4.89)	-4.17 (± 4.15)		
Erythema: Weeks 16 (n=34, 33)	-5.09 (± 4.00)	-4.18 (± 4.38)		
Scale/Hypertrophy: Week 4 (n=40, 37)	-0.83 (± 1.32)	-1.86 (± 2.47)		
Scale/Hypertrophy: Week 8 (n=38, 36)	-1.34 (± 2.34)	-2.72 (± 3.19)		
Scale/Hypertrophy: Week 12 (n=35, 35)	-2.03 (± 2.99)	-3.17 (± 3.34)		
Scale/Hypertrophy: Week 16 (n=34, 33)	-2.12 (± 2.58)	-3.30 (± 3.54)		
Scarring/Atrophy/Panniculitis: Week 4 (n=40, 37)	-0.13 (± 0.88)	-0.16 (± 0.83)		
Scarring/Atrophy/Panniculitis: Week 8 (n=38, 36)	-0.08 (± 1.08)	-0.25 (± 0.87)		

Scarring/Atrophy/Panniculitis: Week 12 (n=35, 35)	-0.06 (± 1.37)	-0.06 (± 1.26)		
Scarring/Atrophy/Panniculitis: Week 16 (n=34, 33)	-0.24 (± 1.48)	-0.18 (± 1.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Participants Reported Daily Worst Pain Using Peak Pain Numerical Rating Scale (Pain-NRS) at Week 12

End point title	Change From Baseline in Participants Reported Daily Worst Pain Using Peak Pain Numerical Rating Scale (Pain-NRS) at Week 12

End point description:

Peak Pain NRS (Pain-NRS) is single item PRO tool that participants used to report intensity of their CLE-related pain (skin, oral, genital) during daily recall period. Participants were asked to rate their worst pain on 0 (no pain) to 10 (worst pain imaginable) NRS by answering following question: "On a scale of 0 to 10, with 0 being 'no pain' and 10 being 'worst pain imaginable', how would you rate your pain at worst moment due to your lupus during previous 24 hours?". Total score on scale ranges from 0 (no pain) to 10 (worst pain imaginable). Higher score indicates more severe skin disease. Baseline was defined as average of daily non-missing scores obtained during week prior to Day 1. Efficacy population included all randomized participants exposed to IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Only participants with data collected at Week 12 are reported.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	36		
Units: score on a scale				
least squares mean (standard error)	-0.93 (± 0.32)	-1.72 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Investigator's Global Assessment of Cutaneous Lupus Erythematosus (IGA-CLE) Score of 0 or 1 (Clear Or Almost Clear) at Week 12

End point title	Percentage of Participants With Investigator's Global Assessment of Cutaneous Lupus Erythematosus (IGA-CLE) Score of 0 or 1 (Clear Or Almost Clear) at Week 12

End point description:

IGA-CLE is a clinician reported outcome (ClinRO) that allows for clinicians to assess overall disease activity of CLE using 5-point scale: 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). Severity of CLE is determined by descriptions of combination of 3 plaque characteristics: erythema,

scale, elevation. Erythema is primary characteristic that influenced the rating, with other characteristics considered secondarily. Telangiectatic change is not considered in rating. The assessment did not require presence of all 4 characteristics, severity was averaged over observed characteristics. Total score on scale ranges from 0 to 4. Higher score indicates a more severe skin disease. Efficacy population included all randomized participants exposed to IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement. Only participants with data collected at Week 12 are reported.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	34		
Units: percentage of participants				
number (not applicable)	15.79	26.47		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in the Oral Health Impact Profile 14-Item Version (OHIP-14) for Participants With Oral Lesions at Baseline

End point title	Change From Baseline to Week 12 in the Oral Health Impact Profile 14-Item Version (OHIP-14) for Participants With Oral Lesions at Baseline

End point description:

OHIP-14 is PRO questionnaire composed of 14 items that assess 7 dimensions. Each of 14 items has set of possible answers distributed in Likert scale(0 =never,1=hardly ever,2=occasionally,3=fairly often,4=very often)which represents frequency that individual perceives impact of oral health on 7 dimensions:functional limitation(2 items),physical pain(2 items),psychological discomfort(2 items),physical disability(2 items),psychological disability(2 items),social disability(2 items),handicap(2 items).OHIP-14 scores range 0-56 and calculated by summing the ordinal values for 14 items.Domain scores ranges 0-8.Higher OHIP-14 scores=worse oral-health-related quality of life. Baseline=Day 1 assessment value.Efficacy population=all randomized participants exposed to the IMP,with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement.Only participants with data collected at Week 12 are

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	13		
Units: score on a scale				
arithmetic mean (standard deviation)	-2.90 (± 7.68)	-0.15 (± 4.79)		

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 (AESIs)

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

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 study treatment, whether or not considered related to the study treatment. TEAEs were defined as adverse events that occurred from the time of the first IMP administration up to the end of study visit. Serious adverse events (SAE): Any AE that at any dose: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. 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 Investigator to 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 study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: participants				
Any TEAE	18	22		
Any TESAE	1	0		
Any AESI	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SKINDEX-29+3 Total Score at Week 12

End point title	Change From Baseline in SKINDEX-29+3 Total Score at Week 12

End point description:

Skindex 29+3 is PRO measure designed to assess effects of skin disease on participants' health-related quality of life in adults.It contains following domains:emotions(10 items),symptoms(7 items), functioning(12 items),lupus-specific issues(3 questions),and 1 item about treatment that is not part of

the total score. Recall period is during the past week. Each item is rated on 5-point Likert scale (never, rarely, sometimes, often, all the time). These responses are then transformed to linear scale (0-100) in 25-point increments, where 100=maximal disability. Total score is average of participants' responses to items in given domain, ranging from 0-100, where higher scores indicate a greater impact on health-related quality of life. Baseline=Day 1 assessment value. Efficacy population=all randomized participants exposed to IMP, with available Baseline assessment of the CLASI-A who actually received at least 1 complete dose of IMP and with at least 1 post IMP administration measurement.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: score on a scale				
least squares mean (standard error)	-9.09 (± 2.31)	-11.09 (± 2.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Hematology Parameters

End point title	Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) in Hematology 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: 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; Platelets <100 x 10^9 per liter (/L) or ≥ 700 x 10^9/L; Erythrocytes ≥ 6 x 10^12/L; Leukocytes < 3 x 10^9/L (Non-Black [NB]); < 2 x 10^9/L (Black[B]); or ≥ 16 x 10^9/L; Neutrophils < 1.5 x 10^9/L (NB); < 1 x 10^9/L (B); Lymphocytes > 4 x 10^9/L; 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 range (ULN) (if ULN ≥ 0.5 x 10^9/L). 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 study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: participants				
Hb: ≤ 115 g/L (M); ≤ 95 g/L (F)	0	1		
Hb: ≥ 185 g/L (M); ≥ 165 g/L (F)	0	0		
Decrease from baseline ≥ 20 g/L	0	0		

Platelets < 100 x 10^9/L	0	0		
Platelets ≥ 700 x 10^9/L	0	0		
Erythrocytes ≥ 6 x 10^12/L	0	0		
Leukocytes < 3 x 10^9/L (NB); < 2 x 10^9/L (B)	3	0		
Leukocytes ≥ 16 x 10^9/L	0	0		
Neutrophils < 1.5 x 10^9/L (NB); < 1 x 10^9/L (B)	3	0		
Lymphocytes > 4 x 10^9/L	0	0		
Monocytes > 0.7 x 10^9/L	1	3		
Basophils > 0.1 x 10^9/L	6	5		
Eosinophils > 0.5 x 10^9/L or > ULN	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Clinical Chemistry

End point title	Number of Participants With PCSA in Clinical Chemistry

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:Glucose≤3.9 millimoles per liter(mmol/L) and <lower limit of normal range(LLN) or ≥11.1 mmol/L(unfasted);≥7 mmol/L(fasted);Creatine Kinase>3 ULN;Sodium≤129 mmol/L or ≥160 mmol/L; Potassium<3 mmol/L or ≥5.5 mmol/L;Creatinine≥150 micromoles per liter(µmol/L)(Adults) or ≥30% change from baseline or ≥100% change from baseline;Creatinine Clearance≥60-<90 milliliters per minute(mL/min)(mild decrease in glomerular filtration rate[GFR]) or ≥30-<60 mL/min(moderate decrease in GFR) or ≥15-<30 mL/min(severe decrease in GFR) or <15 mL/min(end stage renal disease);Alanine Aminotransferase>3ULN or >5ULN;Aspartate Aminotransferase>3ULN or>5ULN;Alkaline Phosphatase>1.5ULN;Total Bilirubin>1.5ULN.Safety population=all randomized participants exposed to IMP(regardless of amount of treatment administered).

End point type	Secondary

End point timeframe:

From first dose of study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: participants				
Glucose ≤ 3.9 mmol/L and < LLN	4	1		
Glucose ≥11.1 mmol/L(unfasted); ≥7mmol/L(fasted)	1	3		
Creatine Kinase > 3 ULN	0	0		
Sodium ≤ 129 mmol/L	0	0		
Sodium ≥ 160 mmol/L	0	0		
Potassium < 3 mmol/L	0	0		
Potassium ≥ 5.5 mmol/L	2	0		
Creatinine ≥ 150 µmol/L (Adults)	0	0		
Creatinine ≥ 30% change from baseline	2	1		

Creatinine ≥ 100% change from baseline	0	0		
Creatinine Clearance ≥ 60 - < 90 mL/min	10	8		
Creatinine Clearance ≥ 30 - < 60 mL/min	0	0		
Creatinine Clearance ≥ 15 - < 30 mL/min	0	0		
Creatinine Clearance < 15 mL/min	0	0		
Alanine Aminotransferase > 3 ULN	1	2		
Alanine Aminotransferase > 5 ULN	0	0		
Aspartate Aminotransferase > 3 ULN	1	0		
Aspartate Aminotransferase > 5 ULN	0	0		
Alkaline Phosphatase > 1.5 ULN	5	0		
Total Bilirubin > 1.5 ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Electrocardiogram (ECG)

End point title	Number of Participants With PCSA in Electrocardiogram (ECG)

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: Heart Rate (HR) < 50 beats/min (bpm) or < 50 bpm and decrease from baseline ≥ 20 bpm or < 40 bpm or > 90 bpm; PR Interval > 200 milliseconds (msec) or > 200 msec and increase from baseline ≥ 25% or > 220 msec; QRS Interval > 110 msec or 110 msec and increase from baseline ≥ 25% or > 120 msec; QT Interval > 500 msec; corrected QT (QTc) Interval > 450 msec or > 480 msec or increase from baseline [30-60] msec or increase from baseline > 60 msec. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered). Only participants with data collected for each specified category at Week 16 are reported.

End point type	Secondary

End point timeframe:

From first dose of study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: participants				
HR < 50 bpm	2	1		
HR < 50 bpm and decrease from baseline ≥ 20 bpm	0	0		
HR < 40 bpm	0	0		
HR > 90 bpm	2	1		
PR Interval > 200 msec	2	0		
PR Interval >200 msec;increase from baseline ≥25%	0	0		
PR Interval > 220 msec	0	0		
QRS Interval > 110 msec	0	2		

QRS Interval >110 msec;increase from baseline≥25%	0	0		
QRS Interval > 120 msec	0	0		
QT Interval > 500 msec	1	0		
QTc Interval > 450 msec	1	1		
QTc Interval > 480 msec	0	0		
QTc Interval: Increase from baseline [30-60] msec	4	0		
QTc Interval: Increase from baseline > 60 msec	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Urinalysis

End point title	Number of Participants With PCSA in Urinalysis

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: pH ≤ 4.6 or ≥ 8. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered). Only participants with data collected for each specified category at Week 16 are reported.

End point type	Secondary

End point timeframe:

From first dose of study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: participants				
pH ≤ 4.6 (n=39, 38)	0	0		
pH ≥ 8 (n=39, 38)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With PCSA in Vital Signs

End point title	Number of Participants With 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: Diastolic Blood Pressure (DBP) ≤ 45 millimeters of mercury (mmHg) and decrease from baseline ≥ 10 mmHg or ≥ 110 mmHg and increase from baseline ≥ 10 mmHg; Pulse Rate (PR) ≤ 50 bpm and decrease from baseline ≥ 20 bpm or ≥ 120 bpm and increase from baseline ≥ 20 bpm; Systolic Blood Pressure (SBP) ≤ 95 mmHg and decrease from baseline ≥ 20 mmHg or ≥ 160 mmHg and increase from

baseline ≥ 20 mmHg; Weight ≥ 5% decrease from baseline or ≥ 5% increase from baseline. Safety population included all randomized participants exposed to the IMP (regardless of the amount of treatment administered). Only participants with data collected for each specified category at Week 16 are reported.

End point type	Secondary

End point timeframe:

From first dose of study treatment (Day 1) up to end of study (Week 16)

End point values	Placebo	SAR443122		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	38		
Units: participants				
DBP≤45 mmHg;decrease from baseline≥10mmHg(n=40,38)	0	1		
DBP≥110mmHg;increase from baseline≥10mmHg(n=40,38)	0	0		
PR≤50 bpm; decrease from baseline≥20 bpm(n=40,38)	0	0		
PR≥120 bpm; increase from baseline≥20 bpm(n=40,38)	0	0		
SBP≤95 mmHg;decrease from baseline≥20mmHg(n=40,38)	0	1		
SBP≥160mmHg;increase from baseline≥20mmHg(n=40,38)	0	0		
Weight ≥ 5% decrease from baseline (n=38,38)	3	5		
Weight ≥ 5% increase from baseline (n=38,38)	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of SAR443122

End point title	Maximum Plasma Concentration (Cmax) of SAR443122[1]

End point description:

Blood samples were collected at the specified timepoints. Cmax was assessed by a Bayesian analysis using the population PK model. PK population included all randomized and treated participants for whom the PK data are considered interpretable. Participants with data collected at Day 1, 57, and 85 are reported.

End point type	Secondary

End point timeframe:

2-5 hours post first morning dose on Days 1, 57, and 85; 1 hour before morning dose on Days 57 and 85; 7-10 hours after morning dose on Day 57

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 SAR443122 arm were analyzed in this endpoint.

End point values	SAR443122			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=36)	3334 (± 1365)			
Day 57 (n=33)	4875 (± 1541)			
Day 85 (n=31)	4896 (± 2013)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (tmax) of SAR443122

End point title	Time to Reach Maximum Plasma Concentration (tmax) of SAR443122[2]

End point description:

Blood samples were collected at the specified timepoints. tmax was assessed by a Bayesian analysis using the population PK model. PK population included all randomized and treated participants for whom the PK data are considered interpretable. Participants with data collected at Day 1, 57, and 85 are reported. -9999 signifies that some tmax values were not calculable for participants with a low compliance, because all concentrations were below the lower limit of quantification.

End point type	Secondary

End point timeframe:

2-5 hours post first morning dose on Days 1, 57, and 85; 1 hour before morning dose on Days 57 and 85; 7-10 hours after morning dose on Day 57

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 SAR443122 arm were analyzed in this endpoint.

End point values	SAR443122			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: hours				
median (full range (min-max))				
Day 1 (n=36)	2.80 (-9999 to 4.90)			
Day 57 (n=33)	2.60 (-9999 to 4.35)			
Day 85 (n=31)	2.55 (-9999 to 4.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time 0 to 12 Hours (AUC0-12) of SAR443122

End point title	Area Under the Curve From Time 0 to 12 Hours (AUC0-12) of

	SAR443122[3]

End point description:

Blood samples were collected at the specified timepoints. AUC0-12 was assessed by a Bayesian analysis using the population PK model. PK population included all randomized and treated participants for whom the PK data are considered interpretable. Participants with data collected at Day 1, 57, and 85 are reported.

End point type	Secondary

End point timeframe:

2-5 hours post first morning dose on Days 1, 57, and 85; 1 hour before morning dose on Days 57 and 85; 7-10 hours after morning dose on Day 57

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 SAR443122 arm were analyzed in this endpoint.

End point values	SAR443122			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)				
Day 1 (n=36)	30151 (± 14926)			
Day 57 (n=33)	40194 (± 15831)			
Day 85 (n=31)	44489 (± 19232)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-Life (t1/2z) of SAR443122

End point title	Terminal Elimination Half-Life (t1/2z) of SAR443122[4]

End point description:

Blood samples were collected at the specified timepoints. t1/2z was assessed by a Bayesian analysis using the population PK model. PK population included all randomized and treated participants for whom the PK data are considered interpretable. Participants with data collected at Day 85 are reported.

End point type	Secondary

End point timeframe:

1 hour before morning dose and 2-5 hours post first morning dose on Day 85

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 SAR443122 arm were analyzed in this endpoint.

End point values	SAR443122			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: hours				
arithmetic mean (standard deviation)	7.62 (± 2.28)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study treatment (Day 1) up to end of study (Week 16)	
Adverse event reporting additional description:	
Analysis was performed on safety population.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to SAR443122 orally BID for 12 weeks.	
Reporting group title	SAR443122
Reporting group description:	
Participants received SAR443122 300 mg orally BID for 12 weeks.	

Serious adverse events	Placebo	SAR443122	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (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: 0 %

Non-serious adverse events	Placebo	SAR443122	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 40 (45.00%)	22 / 38 (57.89%)	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 40 (5.00%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Influenza Like Illness			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Peripheral Swelling			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast Mass			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Oropharyngeal Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 40 (2.50%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Neutrophil Count Decreased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	

Urine Protein/Creatinine Ratio Increased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 40 (5.00%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
Procedural Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Tooth Fracture			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Accidental Overdose			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Cardiac disorders			
Coronary Artery Stenosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Tension Headache			
subjects affected / exposed	1 / 40 (2.50%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
Syncope			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Maculopathy			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Pain Lower			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Odynophagia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 40 (0.00%)	2 / 38 (5.26%)	
occurrences (all)	0	2	
Onychoclasis			

subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Dry Skin			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Dermatitis Contact			
subjects affected / exposed	1 / 40 (2.50%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
Dermatitis Allergic			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Cutaneous Lupus Erythematosus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 40 (7.50%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
Neck Pain			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Muscular Weakness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Bone Cyst			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Back Pain			

subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Covid-19			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Vulvovaginal Mycotic Infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Tooth Abscess			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Tinea Pedis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis Viral			

subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Herpes Zoster			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nail Infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 40 (2.50%)	3 / 38 (7.89%)	
occurrences (all)	1	3	
Oral Candidiasis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Oral Herpes			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported