Sponsor: Sanofi **Drug substance(s):** SAR444559	**Study Identifiers**: U1111-1278-4028; ACTRN12622001387718 **Study code:** SAD17442/MAD17443

Title of the study:

A randomized, double-blind, placebo-controlled, Phase 1, single center, first-in-human, two-part study to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single (SAD17442) and multiple (MAD17443) ascending, subcutaneous doses of SAR444559 in healthy adult participants

Study center(s):

This study was conducted at a single center that randomized participants in Australia.

Study period:

Date first study participant enrolled: 28 November 2022 (first participant first visit)

Date last study participant completed: 07 December 2023 (last participant last visit)

Study Status: Terminated

The study was terminated early after completion of the SAD Cohort 5 due to an unanticipated safety issue of acute myopic shift reported in 2 participants.

Phase of development: Phase 1

Objectives:

Primary objectives:

• To assess the safety and tolerability of SAR444559 after single and multiple ascending subcutaneous (SC) doses in healthy adult participants

Secondary objectives:

• To assess the pharmacokinetic (PK) parameters of SAR444559 after single and multiple ascending SC doses

• To assess immunogenicity after single and multiple ascending SC doses of SAR444559

Methodology:

This SAD study (SAD17442) was part of the first-in-human study for SAR444559 and included sequential ascending single dose cohorts of healthy participants.

The SAD study (Part 1) enrolled 5 dose level cohorts (8 participants each: 6 active and 2 placebo).

Each dose cohort in Part 1 was divided into 2 subgroups:

• The first subgroup (the “sentinel group”) included 2 participants who were dosed on Day 1. As 1 participant received placebo and 1 participant received SAR444559, no restrictions for inter-participant dosing time were defined for sentinel dosing.

• The second subgroup (remaining participants) was dosed at least 48 hours later with inter-participant dosing spaced at least 30 minutes apart.

The starting dose in Part 1 was 0.03 mg SAR444559, a dose expected to only weakly deplete highly-expressing cluster of differentiation (CD38) cells including plasmablasts and natural killer (NK) cells, ie, by less than 25%, which was considered to be within physiological intra-individual variation. Dose escalation from cohort "n" to the next cohort "n+1" was based on the following data in at least 6 out of 8 participants:

• Safety and tolerability data of dose cohort "n".

- up to at least 2 weeks after injection (Day 15) to escalate up to SAD Cohorts 2 to 6.

- up to at least 4 weeks after injection (Day 29) to escalate to SAD Cohorts 7 to 9.

• PK data up to at least 2 weeks after injection (Day 15) of dose cohort "n-1".

• If the following data were available:

- Immunophenotyping, including plasmablasts, plasmacytoid dendritic cells (pDCs), NK cells, B and T cells, and other immune cell subtypes obtained from flow cytometry analyses of peripheral whole blood collected from 6 participants in dose level "n" until Day 5 post dose, and any other PK data available prior to the dose escalation meeting.

The treatment period and duration of end of study (EOS) follow-up was approximately 7 weeks including a 4-day in-house period after the single dose administration.

Number of study participants:

Part 1 (SAD17442): Approximately 72 participants with 8 participants per dose cohort (6 active and 2 placebo) and an expected number of 9 SAD cohorts were planned.

In total for Part 1 (SAD), 42 participants were randomized to study intervention (in 5 SAD cohorts) of whom 40 participants were exposed to study intervention as follows:

・0.03 mg SAR444559: 7 participants were randomized with 6 participants receiving study intervention. One participant did not complete the study period and discontinued from the study prior to receiving study intervention due to an adverse event (AE; not related to coronavirus disease of 2019 [COVID-19]).

・0.10 mg SAR444559: 7 participants were randomized with 6 participants receiving study intervention. One participant did not complete the study period and discontinued from the study prior to receiving study intervention due to a reason reported as 'Other' (not related to COVID-19).

・0.30 mg SAR444559: 6 participants were randomized and received study intervention with all participants completing the study.

・0.90 mg SAR444559: 6 participants were randomized with 6 participants receiving study intervention of whom 1 participant chose to withdraw.

・2.00 mg SAR444559: 6 participants were randomized and received study intervention with all participants completing the study.

・Placebo: 10 participants were randomized and received study intervention with all participants completing the study.

In total, 40 participants were exposed to study intervention and included in the Safety and PD populations, with 30 participants included in the PK population (placebo treated participants were excluded). In total, 42 participants were included in the "Without trial impact (disruption) due to COVID-19" population.

Part 2 (MAD17443) was not conducted as the study was terminated early after completion of the SAD Cohort 5 (2.00 mg) due to an unanticipated safety issue of acute myopic shift reported in 2 participants.

Diagnosis and criteria for inclusion:

Healthy male or female participants, 18 to 55 years of age (inclusive), with a body weight between 50 and 100 kg (inclusive), a body mass index (BMI) between 18 and 32 kg/m^2 (inclusive) and with medical/surgical history, vital signs, electrocardiogram (ECG), and laboratory parameters within the protocol defined ranges.

Study products

Investigational medicinal product(s):

SAR444559

- Formulation: SAR444559 is a powder lyophilizate, for solution for injection, supplied in a single-use glass vial (10R ISO vial).
- Route of administration: SC injection in the abdomen.
- Dose regimen (SAD): 9 ascending single doses of SAR444559 were planned (expected dose range: 0.03 mg to ⩽100 mg, ie, 0.03 mg, 0.10 mg, 0.30 mg, 0.90 mg, 2.50 mg, 7.00 mg, 19 mg, 50 mg, and 100 mg).

The actual dosages administered before study termination were: 0.03 mg, 0.10 mg, 0.30 mg, 0.90 mg, 2.00 mg.

Placebo

- Formulation: Placebo for SAR444559 is a liquid formulation, without drug substance, as a solution for injection supplied in single-use glass vial (2R ISO vial).
- Route of administration: Same as for SAR444559.
- Dose regimen: Same as for SAR444559.

Sterile syringes and needles were used for study intervention (SAR444559/placebo) preparation and administration.

Duration of treatment:

The anticipated overall study duration per participant was up to 12 weeks in Part 1 (SAD), which included a Screening period (Day -35 to Day -1]), Treatment period (Day 1 to Day 50) with institutionalization (already starting on the day before [Day -1] and lasting up to Day 4) and a single administration of study intervention on Day 1, and a Follow-up period (Day 5 to the EOS visit at Day 50 ±3 days).

Criteria for evaluation:

Primary endpoints:

- Assessment of adverse events (AEs)/ treatment-emergent adverse events (TEAEs)
- Clinical laboratory evaluations (hematology with differential, C-reactive protein [CRP], clinical chemistry, coagulation, urinalysis)
- Vital signs
- Electrocardiogram (ECG) intervals (heart rate, PR, QRS, QT, QTcF) derived from 12-lead ECG
- Comprehensive ophthalmic examination outcomes

Secondary endpoints:

- Plasma and/or whole blood/dried blood spot (DBS) parameters at least C_{max}, T_{max}, AUC_{last}, AUC (for SAD part)
- Anti-SAR444559 antibodies

Statistical methods:

The study sample size was based upon empirical considerations for this SAD study.

Analyses were performed with participants who received placebo pooled from the different dose cohorts.

Safety:

The safety analysis focused on the treatment-emergent (TE) period, defined as the time from the first study intervention administration up to the EOS visit (included).

Safety analysis (eg, AEs, treatment-emergent AEs [TEAEs], clinical laboratory evaluations [hematology with differential, C-reactive protein {CRP}, clinical chemistry, coagulation, urinalysis], vital signs, and ECG intervals) were based on the review of individual values and descriptive statistics.

The AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA; version 26.1). Their severity was graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0). The number (%) of participants experiencing TEAEs was summarized by dose level group.

Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs, and ECG were flagged and summarized by dose level group using frequency tables.

Number of participants experiencing injection site reactions were summarized by dose level group and severity (eg, mild, moderate, and severe).

Ophthalmologic examinations (introduced in the protocol amendment while the follow-up of the sentinel participants of SAD Cohort 5 [2.00 mg group] was ongoing), were only collected for the second subgroup (3rd to 8th participant) of the SAD Cohort 5. Ophthalmic parameters were listed.

Pharmacokinetics:

The PK parameters and concentration of SAR444559 were summarized by descriptive statistics by dose level.

Due to almost all analyzed plasma sample results being below the lower limit of quantification/detection limit (LLOQ), only descriptive statistics were performed on the PK samples. As a result, the distribution of time to maximum observed concentration (T_{max}) values as well as dose proportionality analyses on PK data were not performed. The PK analyses were performed only on the PK plasma samples, and not on PK dried blood spot samples, because collection of the additional PK dried blood spot samples was only begun following the protocol amendment and thus, only samples provided by the second subgroup (3rd to 8th participant) of the SAD Cohort 5.

Immunogenicity:

Since there was no indication of immunogenicity at the time of early termination, the planned antidrug antibody (ADA) sample analyses were not performed. As a result, the collected ADA samples were not analyzed and hence no ADA data statistical analyses were performed.

Pharmacodynamics:

Pharmacodynamic parameters were listed and summarized descriptively by intervention group and timepoint. Given the lack of quantifiable PK samples, no PK/PD analyses were performed.

Summary Results:

Demographic and other baseline characteristics:

A total of 42 participants were randomized to receive study intervention. However, 2 participants discontinued from the study prior to receiving the study intervention (and were subsequently replaced): 1 participant in the 0.03 mg group due to an AE of Grade 1 presyncope and 1 participant in the 0.10 mg group due to a reason reported as "Other reason: RCC was low at D-1 visit. remains low after repeat - PI has decided safest for participant to be excluded" (Note: RCC referring to red cell count and D-1 referring to Day -1).

A total of 40 randomized participants received study intervention with 39 participants completing the study period. One participant in the 0.90 mg group withdrew consent with the reason provided as "Other: the participant went overseas due to family reasons" after the penultimate study visit on Day 43.

Most randomized and exposed participants were either White (25 [62.5%] participants, ranging from 2 [33.3%] participants up to 6 [100.0%] participants in a dose group) or Asian (10 [25.0%] participants, ranging from 0 up to 3 [50.0%] participants in a dose group).

All participants in the safety population were from 18 up to 53 years in age, with a mean (standard deviation [SD]) age of 33.1 (10.1) years, weighing from 52.3 up to 96.0 kg, with a mean (SD) body weight of 72.10 (10.86) kg. Nineteen (47.5%) participants were male, and 21 (52.5%) participants were female. However, the distribution between dose groups was varied: mostly males in the 0.03 mg and 0.10 mg groups (4 [66.7%] participants in both groups), mostly females in the 0.30 mg, 0.90 mg, 2.00 mg groups (4 [66.7%] participants in each group), and an equal distribution in the placebo group (5 [50.0%] male and female participants).

The mean (SD) baseline BMI of all exposed participants was 25.18 (2.75) kg/m^2, ranging from 19.2 to 31.8 kg/m^2. Most participants were in the BMI categories of 18.5 to <25 kg/m^2 (20 [50.0%] participants) or 25 to <30 kg/m^2 (18 [45.0%] participants).

Exposure:

A total of 40 participants were exposed to either SAR444559 or placebo.

Safety results:

No deaths were reported during the study.

Overall, most participants who received SAR444559 reported at least 1 TEAE (5 [83.3%] participants [0.90 mg] and 6 [100%] participants [0.03 mg, 0.10 mg, 0.30 mg, and 2.00 mg, respectively]). Five (50.0%) participants who received placebo had a TEAE reported. No participants discontinued from the study due to a TEAE.

A TE serious AE (SAE) ("other medically important event") of myopia was reported for 1 (16.7%) participant in the SAR444559 2.00 mg group and was also considered an AESI. No SAE was reported in the other SAR444559 groups (0.03 mg, 0.10 mg, 0.30 mg, and 0.90 mg) or the placebo group.

Adverse events of special interest, both deemed Grade ≥3 TEAEs, were reported for 2 (33.3%) participants in the SAR444559 2.00 mg group and considered related to study intervention. One (16.7%) participant developed a ciliary body disorder (AE diagnosis: blurred vision due to myopic shift secondary to anterior rotation of the ciliary body) and the other (1 [16.7%] participant) developed myopia (AE diagnosis: blurred vision due to myopic shift) (also reported as an SAE). The events started in the morning after the dosing day or in the evening of the dosing day, respectively, and completely resolved after 10 days and 7 days, respectively. Diagnosis and full recovery were confirmed by an ophthalmologist in both cases.

No Grade ≥3 TEAEs were reported in the 0.03 mg, 0.10 mg, 0.30 mg, and 0.90 mg SAR444559 groups or the placebo group.

The incidence of TEAEs reported during the study was varied between the SAR444559 dose groups (0.03 mg [13 TEAEs], 0.10 mg [12 TEAEs], 0.30 mg [15 TEAEs], 0.90 mg [10 TEAEs], and 2.00 mg [19 TEAEs]) and was higher than in the placebo group (6 TEAEs). The most common reported TEAEs belonged to the SOC General Disorders and Administration Site Conditions (occurring in 6 [100%] participants [0.03 mg, 0.10 mg, and 0.30 mg groups]; 5 [83.3%] participants [0.90 mg group]; 4 [66.7%] participants [2.00 mg group] who received SAR444559 and in 1 [10.0%] participant who received placebo).

Overall, the most frequently reported TEAEs were:

• Injection site reaction with >1 injection site reaction symptom (SAR444559: 3 [50.0%] participants [0.03 mg], 6 [100%] participants [0.10 mg group], 5 [83.3%] participants [0.30 mg group], 1 [16.7%] participant [0.90 mg group], and 2 [33.3%] participants [2.00 mg group]; placebo: 0 participants).

• Injection site erythema (SAR444559: 1 [16.7%] participant [0.03 mg group], 0 participants [0.10 mg group], 0 participants [0.30 mg group], 4 [66.7%] participants [0.90 mg group], and 1 [16.7%] participant [2.00 mg group]; placebo: 0 participants).

Including 1 reported TEAE of injection site discoloration, 2 TEAEs of injection site pain and 6 TEAEs of injection site erythema, 26/30 (87%) participants receiving SAR444559 each reported 1 TEAE related to reaction at the injection site, which were all considered related to study intervention by the Investigator and deemed as either Grade 1 or Grade 2.

Other TEAEs in each of the SAR444559 groups were reported by ≤1 (16.7%) participant except for viral upper respiratory tract infection (0.03 mg group), musculoskeletal pain (0.10 mg group), upper respiratory tract infection (0.30 mg group), cytokine release syndrome (2.00 mg group), and headache (2.00 mg group), each of which were reported for 2 (33.3%) participants. In the placebo group all TEAEs were reported for 1 (10.0%) participant.

The total of 25/30 participants on SAR444559 with symptoms of injection site reaction during the first 4 days after study intervention administration is presented with symptoms by severity in Table 1. The 1 participant reporting discoloration at injection site was not included in this table as the onset of symptom was after Day 4.

Table 1 - Number (%) of participants with symptoms of injection site reaction by severity including all times of measurement during the first 4 days (D1-D4) - Safety population

		SAR444559				
Symptom of injection site reaction - Preferred term Severity, n(%)	**Placebo (N=10)**	**0.03 mg (N=6)**	**0.10 mg (N=6)**	**0.30 mg (N=6)**	**0.90 mg (N=6)**	**2.00 mg (N=6)**
Any class	0	5 (83.3)	6 (100)	6 (100)	5 (83.3)	3 (50.0)
Mild	0	3 (50.0)	3 (50.0)	4 (66.7)	5 (83.3)	1 (16.7)
Moderate	0	2 (33.3)	2 (33.3)	1 (16.7)	0	2 (33.3)
Severe	0	0	1 (16.7)	1 (16.7)	0	0
Erythema	0	4 (66.7)	6 (100)	3 (50.0)	5 (83.3)	3 (50.0)
Mild	0	2 (33.3)	3 (50.0)	1 (16.7)	5 (83.3)	1 (16.7)
Moderate	0	2 (33.3)	2 (33.3)	1 (16.7)	0	2 (33.3)
Severe	0	0	1 (16.7)	1 (16.7)	0	0
Tenderness	0	3 (50.0)	6 (100)	6 (100)	0	2 (33.3)
Mild	0	3 (50.0)	5 (83.3)	5 (83.3)	0	2 (33.3)
Moderate	0	0	1 (16.7)	1 (16.7)	0	0

Contusion	0	0	0	0	0	1 (16.7)
Mild	0	0	0	0	0	1 (16.7)
Pain	0	2 (33.3)	5 (83.3)	5 (83.3)	0	1 (16.7)
Mild	0	2 (33.3)	5 (83.3)	5 (83.3)	0	1 (16.7)
Pruritus	0	1 (16.7)	0	2 (33.3)	0	0
Mild	0	1 (16.7)	0	2 (33.3)	0	0
Swelling	0	4 (66.7)	5 (83.3)	3 (50.0)	0	0
Mild	0	4 (66.7)	5 (83.3)	2 (33.3)	0	0
Moderate	0	0	0	1 (16.7)	0	0

A participant having several grades of severity for "Any class" (i.e., over all symptoms of injection site reaction) at different times of measurement is counted once by selecting the worst grade

A participant having several grades of severity for the same symptom of injection site reaction at different times of measurement is counted once by selecting the worst grade

Note: Table sorted by decreasing frequency of preferred term (over all grades of severity) in SAR444559 2.00 mg group and then alphabetically

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An increase of the mean body temperature of 0.4°C at the 12-hour timepoint of Day 1 was noted in the SAR444559 0.03 mg group (SAD Cohort 1), and mainly driven by a participant with an AE of pyrexia (AE diagnosis: low-grade fever asymptomatic) (Grade 1, considered related to the study intervention by the Investigator), whose individual body temperature increased to a maximum of 37.9°C at 12 hours after dosing. In the SAR444559 0.10 mg group (SAD Cohort 2) and the placebo group there was no relevant change in mean body temperature.

A temporary and dose-dependent increase in mean body temperatures was observed in the three highest SAR444559 dose groups (0.30, 0.90 and 2.00 mg, SAD Cohorts 3, 4, and 5) at Day 1 to Day 2 at the longest. The maximal extent of the mean increase was the higher the dose (2.00 mg: 1.1°C; 0.90 mg: 0.9°C; 0.30 mg: 0.5°C). The individual increases in body temperatures from normal at baseline to maximum recorded were 36.6 to 38.8°C, 36.1 to 38.9°C, and 36.7 to 38.9°C, respectively, in the 3 participants with an AE of cytokine release syndrome, all Grade 1, that lasted from the afternoon/evening of Day 1 to end in the early afternoon of Day 2 at the longest.

Overall, a few participants (≤1/6 participants who received a planned SAR444559 dose or ≤1/10 participants who received placebo) had a PCSA reported in the vital signs parameters of supine systolic blood pressure, supine diastolic blood pressure, supine heart rate, and weight change during the TE period. However, ≥2/6 participants who received a planned SAR444559 dose had a PCSA reported for:

· Orthostatic systolic blood pressure:

- ≤-20 mmHg (SAR444559: 0/6 participants [0.03 mg group], 0/6 participants [0.10 mg group], 1/6 participants [0.30 mg group], 3/6 participants [0.90 mg group], and 1/6 participants [2.00 mg group]; placebo: 2/10 participants).

· Orthostatic diastolic blood pressure:

- ≤-10 mmHg (SAR444559: 0/6 participants [0.03 mg group], 1/6 participants [0.10 mg group], 1/6 participants [0.30 mg group], 4/6 participants [0.90 mg group], and 1/6 participants [2.00 mg group]; placebo: 1/10 participants).

Overall, a few participants (≤1/6 participants who received a planned SAR444559 dose or ≤1/10 participants who received placebo) had a PCSA reported in the ECG parameters of PR interval, aggregate; QRS duration, aggregate; QT interval, aggregate; and corrected QT interval by Fridericia (QTcF) interval, aggregate during the TE period. However, ≥2/6 participants who received a planned SAR444559 dose had a PCSA reported for:

· Heart rate

- <50 beats/min (SAR444559: 3/6 participants [0.03 mg group], 3/6 participants [0.10 mg group], 0/6 participants [0.30 mg group], 2/6 participants [0.90 mg group], and 1/6 participants [2.00 mg group]; placebo: 0/10 participants).
- The only other heart rate related PCSA occurred in only 1/6 participants who received SAR444559 0.90 mg who had a heart rate >90 beats/min and increase from baseline ≥20 beats/min.

Overall, 1/6 participants who received SAR444559 0.30 mg had a QTcF, aggregate, result of >450 msec while 1/6 participants each who received SAR444559 0.30 mg and 0.90 mg had an increase from baseline of]30-60] msec. No participant during the study had a QTcF result of >480 msec or an increase from baseline of >60 msec.

Overall, the laboratory results were varied over time and across the SAR444559 and placebo groups with no notable trends observed in most of the laboratory assessments.

There was a temporary decrease in mean creatine kinase values during the in-house period (baseline to Day 4) across all SAR444559 groups and the placebo group. Thereafter, fluctuations were observed in the mean creatine kinase values without a clear trend until the EOS.

Of the participants with elevated creatine kinase values, three participants had particularly high values: 1 participant each in the placebo group, and the 0.30 mg and 0.90 mg groups showed high creatine kinase values following physical exercise (766.0 IU/L [0.0-160.0], 631.0 IU/L [0.0-160.0], 1370.0 IU/L [0.0-200.0], respectively), and for the participant in the 0.90 mg group an AE of rhabdomyolysis (AE diagnosis: exercise related rhabdomyolysis, grade 1, not related to IMP), was reported, based on the creatine kinase values. The participant had not indicated any clinical symptoms.

Additionally, there appeared to be a dose-dependent increase in CRP mean and median values of the SAR444559 groups starting from the SAR444559 0.10 mg group with a maximal mean increase of 2.4 mg/L in the 0.10 mg group, 11.1 mg/L in the 0.30 mg group, 14.3 mg/L in the 0.90 mg group, and 17.3 mg/L in the 2.00 mg group.

The increased CRP value peaked at Day 4 for the two lower SAR444559 0.10 mg and 0.30 mg groups, while it already peaked at Day 2 for the two higher SAR444559 0.90 mg and 2.00 mg groups. (The mean increase of 4.4 mg/L in CRP at Day 15 in the 0.03 mg group was driven by 1 participant whose CRP increased to 24 mg/L (upper limit of normal [ULN] 3 mg/L) on Day 15, most likely following an AE of viral upper respiratory tract infection, with a reported onset on Day 10 and end date on Day 12. In the placebo group, there was no trend noted over time, with the largest mean increase of 1.2 mg/L occurring on Day 29.

Cytokine measurements (interleukin-6 [IL-6], Interferon-γ [IFN-γ], tumor necrosis factor alpha [TNF-α], and interleukin-8 [IL-8]) were performed during the first 4 days after administration of study intervention to substantiate whether a suspicious clinical event is a result of immune-mediated toxicity.

In the three highest SAR444559 dose groups (0.30 mg, 0.90 mg, and 2.00 mg) all participants reached IL-6 values above normal range. The mean values of IL-6 in these groups temporarily increased from the 2-hour timepoint at Day 1 up to the morning of Day 2 and reached 37.24 ng/L (approximately 7 × ULN) to 59.21 ng/L (approximately 11 × ULN). One of the participants with an AE of a cytokine release syndrome in the highest dose group reached a maximum IL-6 level of 222.23 ng/L (approximately 43 × ULN) in the afternoon of the dosing Day 1, and that was 5.68 ng/L (approximately back at ULN) at Day 4, 2 days after clinical resolution of the reported AE of cytokine syndrome (Grade 1).

Interferon-γ (IFN-γ) remained within the normal range in all participants, except for 4 participants of the highest SAR444559 (2.00 mg) dose group: 2 participants with cytokine release syndrome (up to 7.11 ng/L [474 × ULN]), a participant with myopia (AE diagnosis: blurred vision due to myopic shift), where the IFN-γ value increased (up to 0.67 ng/L [approximately 45 × ULN]) on Day

1 until the morning of Day 2, and the 4th SAD Cohort 5 participant with injection site reaction, Grade 2, occurring from Day 2 to 8 where IFN-γ increased (up to 0.91 ng/L [approximately 61 × ULN]) at Day 4.

No dose dependent trend was noted for IL-8, with only maximally 1 participant per dose group having out-of-range IL-8 values. No dose-dependent trend was noted for TNF-α with only 0, 1, or 2 participants per group with out-of-range TNF-α values.

Overall, a few participants had a PCSA reported for hemoglobin (decrease from baseline ≥20 g/L: 1 participant each in the placebo, 0.10 mg, 0.30 mg, and 0.90 mg groups), platelet counts (<100 × 10^9/L in 1 participant in the placebo group), white blood cells (leukocyte counts [<3 × 10^9/L {Non-Black}; <2 × 10^9/L {Black} in 1 participant in the placebo group], neutrophils [<1.5 × 10^9/L {Non-Black}; <1 × 10^9/L {Black} in 1 participant in the placebo group]), creatine kinase (>3 ULN: 1 participant each in the placebo, 0.30 mg, and 0.90 mg groups), electrolytes (potassium [≥5.5 mmol/L: 1 participant in the 0.30 mg group]) and renal function (creatinine [≥30% change from baseline: 1 participant in the 0.90 mg group], estimated creatinine clearance [Cockcroft-Gault equation] [≥60 to <90 mL/min {mild decrease in GFR}: 1 participant in the 0.90 mg group, ≥30 to <60 mL/min {moderate decrease in GFR}: 1 participant in the 2.00 mg group], estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration] [≥60 to <90 mL/min/1.73m^2 {mild decrease in GFR}: 1 participant in the placebo group, 2 participants in the 0.03 mg group, 1 participant in the 2.00 mg group]). None of these PCSAs were associated with clinical symptoms. Details related to the increases of creatinine kinase are indicated above.

For CRP, several participants in a SAR444559 group (up to all participants) or in the placebo group had a PCSA reported:
· >2 ULN or >10 mg/L (if ULN not provided): In the three highest SAR444559 dose groups (0.30, 0.90, and 2.00 mg), all (6/6) participants had a PCSA for CRP, while only 3/6 participants in the 0.03 mg group, 1/6 participants in the 0.10 mg group, and 4/10 participants in the placebo group had PCSA for CRP. The dose-dependent increase in CRP is detailed above.

No PCSAs were reported for eosinophils, glucose, sodium, and liver function.

Vaccination titer
A single dose of SAR444559 did not have an effect on tetanus and diphtheria antibody titers regardless of the SAR444559 dose: In 24 of the 30 participants receiving a dose of SAR444559 and who provided at least 1 Clostridium tetani toxoid IgG antibody titer, there was no change in titer between baseline and the EOS visit. One participant of the 0.30 mg group had a change in titer from positive (baseline) to indeterminate (EOS). In 3 participants of the 0.03 mg or 0.10 mg groups a change from negative (baseline) to indeterminate or to positive (EOS) was noted. One participant of the 0.90 mg group only provided a sample at baseline. One participant had a “missing” baseline titer, as the Day 1 sample only was collected around 2 hours after IMP administration. This sample was positive as well as the second sample at end of study.

In 24 of 30 participants receiving a dose of SAR444559 and who provided at least 1 Diphtheria toxin IgG antibody titer, there also was no change in titer between baseline and EOS visit. One participant of the 0.30 mg group had a change in titer from positive (baseline) to indeterminate (EOS). In 1 participant of both the 0.10 mg and 2.00 mg groups, a change from negative (baseline) to indeterminate (EOS) was noted. One participant of both the 0.03 mg and 2.00 mg groups had a change from either negative or indeterminate (baseline) to positive (EOS). One participant of the 0.90 mg group only provided a sample at baseline.

The timing of vaccination against tetanus or diphtheria is not available for any of the study participants, and for the participants whose titers had become positive at the EOS no AE related to either tetanus or diphtheria was reported during the study.

Pharmacokinetic results:

All blood samples were collected within ±15% of the sampling time specified in the protocol.

Two of the plasma concentrations at t = 6 hours were above the LLOQ of 0.35 ng/mL at the 2.00 mg SAR444559 dose (0.479 ng/mL and 0.467 ng/mL).

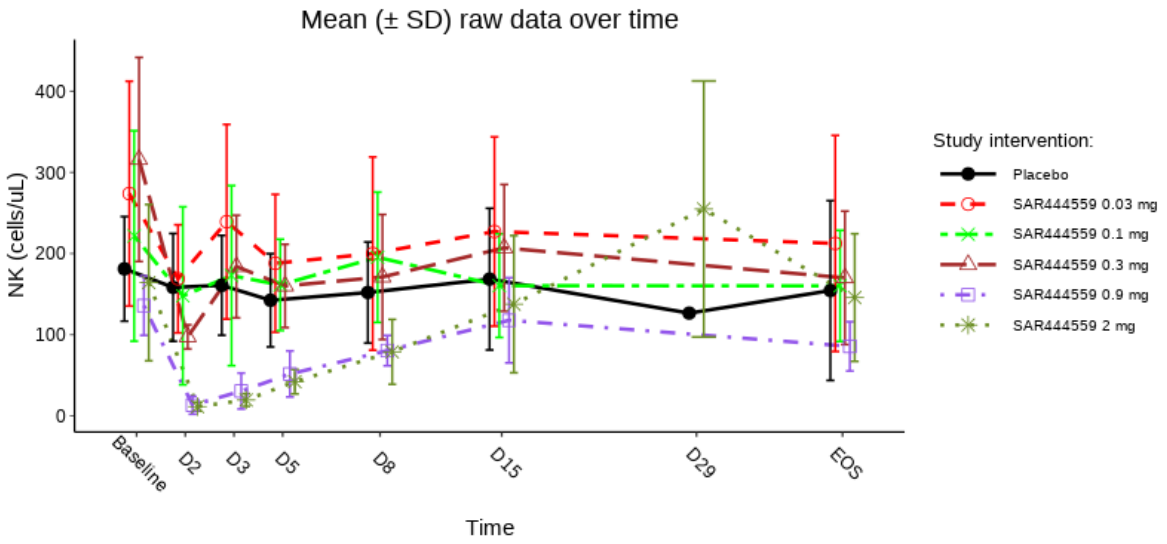
Pharmacodynamics results:

For each white blood cell subpopulation, data were obtained from all participants of the 5 SAD cohorts (at doses of 0.03 to 2.00 mg SAR444559, or placebo), ie, 30 participants on SAR444559 and 10 on placebo from Day 1 predose to Day 50.

The subpopulation of main interest was the NK cells, as they were considered the surrogate cell population to monitor the pharmacological activity effect of SAR444559.

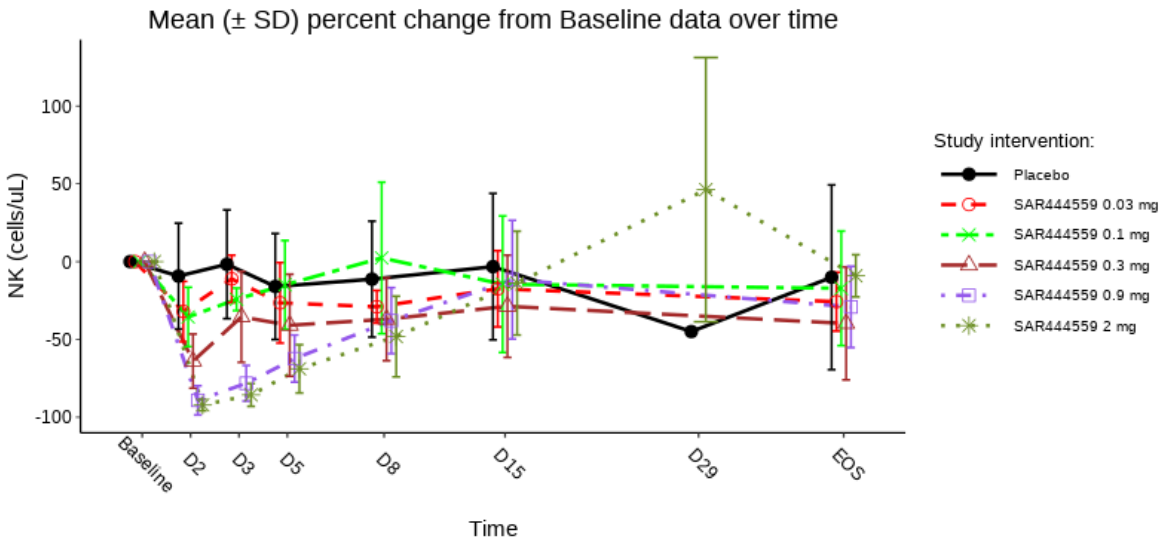
Overall, a substantial and dose-dependent decrease in NK cell count was observed in the participants on SAR444559, with peak depletion at Day 2 (-32% to -92%, from 0.03 mg to 2.00 mg, respectively). The return to baseline values was progressive (from Day 3 to Day 15) with a dose-dependent duration. Similar amplitude and duration were observed at 0.90 mg and 2.00 mg: full depletion at Day 2 (-89% and -92%, respectively) and recovery at Day 15 (-12% and -14%, respectively). No change in NK cell counts was observed over time in the placebo group. See Figure 1 and Figure 2 for more details.

Figure 1 - Time profile plots of mean ± standard deviation for raw data, by study intervention group and visit



Note: Day 29 is an additional timepoint post-amendment for cohort 5 (ROC).
PGM=PRODOPS/SAR444559/SAD17442/CSR/REPORT/PGM/bm_flowc_talisma_x.sas
OUT=REPORT/OUTPUT/bm_flowc_mean_wbcm1c1_p_f.png (15APR2024 09:19)

Figure 2 - Time profile plots of mean ± standard deviation for percent change from baseline, by study intervention group and visit



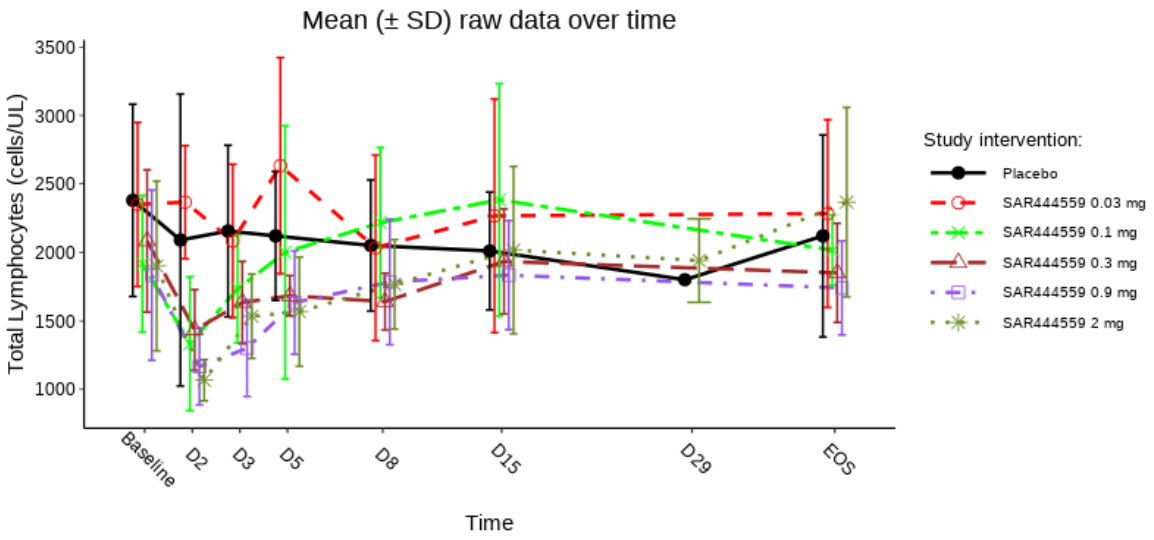
Note: Day 29 is an additional timepoint post-amendment for cohort 5 (ROC).
PGM=PRODOPS/SAR444559/SAD17442/CSR/REPORT/PGM/bm_flowc_talisma_x.sas
OUT=REPORT/OUTPUT//bm_flowc_mean_pchg_wbcm1c1_p_f.png (15APR2024 09:19)

No significant change in plasmablast/plasma cells or pDCs was observed across treatment groups or over time.

A transient decrease in total lymphocytes (Figure 3) was observed similarly in all cohorts.

The total B cells and total T cells were slightly and furtively decreased. Most of the decrease was driven by CD38+ cells (eg, after 2.00 mg SAR444559, up to -79% decrease at Day 2 for CD38+ B cells, while -14% in total B cells).

Figure 3 - Time profile plots of mean ± standard deviation for raw data, by study intervention group and visit



Note: Day 29 is an additional timepoint post-amendment for cohort 5 (ROC).
PGM=PRODOPS/SAR444559/SAD17442/CSR/REPORT/PGM/bm_flowc_talisma_x.sas
OUT=REPORT/OUTPUT//bm_flowc_mean_lymc1_p_f.png (15APR2024 09:19)

Issue date: 19-Jul-2024