Sponsor: Sanofi **Drug substance(s):** SAR444656	**Study Identifiers:** EU trial number: 2024-515621-28 WHO: U1111-1307-7447 **Study code:** BDR17530

Title of the study:

A 2-part, randomized, open-label, single-dose Phase 1 study to investigate the relative bioavailability of the SAR444656 test formulation (Part 1) and evaluate the food effect on the SAR444656 test formulation (Part 2) in healthy adult participants.

Study center(s):

This study was conducted at one center in Belgium where 15 participants were randomized.

Study period:

Date first study participant enrolled: 17/April/2025

Date last study participant completed: 20/June/2025

Early study termination date: 24/June/2025

Study Status: Terminated. The study was terminated following the Sponsor's decision to prematurely stop the study, which was not linked to any safety concerns.

Phase of development: Phase 1

Objectives:

Primary

- Part 1: To determine the relative bioavailability of 200 mg dose of SAR444656 in the test tablet formulation versus current tablet formulation (reference) under fasted condition

  Part 2: To evaluate the food effect on SAR444656 PK (Pharmacokinetics) after a single dose of SAR444656 in the test tablet formulation

Secondary

- To assess the tolerability and safety of SAR444656 after a single oral 200 mg in the test tablet formulation under fasted condition (Part 1) or a single oral dose of the test tablet formulation under fasted and fed conditions (Part 2)
- Part 1: To assess the tolerability and safety of SAR444656 after a single oral 25 mg in the test tablet formulation under fasted condition
- Part 1: To assess the PK of SAR444656 after a single oral 25 mg in the test tablet formulation under fasted condition

Methodology:

This was a Phase 1, single-center study planned to be conducted in 2 parts in healthy adult participants.

Part 1 was a single-center, open-label, randomized, 3-sequence, 3-period, 3-treatment cross-over (among Treatment A, Treatment B, and Treatment C) study with 12 to 14 days of washout period between 2 consecutive investigational medicinal product (IMP) administrations. The primary goal of Part 1 was to determine the relative bioavailability of 200 mg SAR444656 in the test tablet formulation versus reference formulation under fasted conditions.

Three treatments were as follows:

- Treatment A: 200 mg SAR444656 - reference formulation in fasted condition
- Treatment B: 200 mg SAR444656 - test formulation in fasted condition
- Treatment C: 25 mg SAR444656 - test formulation in fasted condition

Part 2 was planned to be an open-label, randomized, 3-sequence, 3-period, 3-treatment cross-over study part to perform a preliminary assessment of the food effect on SAR444656 PK of single dose of SAR444656 in the test tablet formulation. However, the study was early terminated after the completion of Part 1 for reasons not related to safety.

Number of study participants:

Planned: 15 healthy participants in each Part 1 and Part 2 (30 healthy participants in total) were planned to be randomized to study intervention.

Enrolled/Randomized: 15 participants were randomized and exposed to study intervention in Part 1. Part 2 was not conducted, due to early termination of the study decided by the Sponsor.

Diagnosis and criteria for inclusion:

Male and female participant, between 18 and 55 years of age, inclusive, at the time of signing the informed consent form (ICF), who were certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination), and with body weight between 50.0 and 100.0 kg (inclusive), body mass index between 18.5 and 30.0 kg/m^2 (inclusive) were randomized in the study.

Study products

Investigational medicinal product(s):

Treatment A: SAR444656 Reference formulation

Formulation/Form & composition: Tablet

Route(s) of administration: Oral

Dose regimen: Single dose of 200 mg under fasted condition on Day 1 of Period 1, 2, and 3 in Part 1

Treatment B: SAR444656 Test formulation

Formulation/Form & composition: Tablet

Route(s) of administration: Oral

Dose regimen: Single dose of 200 mg under fasted condition on Day 1 of Period 1, 2, and 3 in Part 1

Treatment C: SAR444656 Test formulation

Formulation/Form & composition: Tablet

Route(s) of administration: Oral

Dose regimen: Single dose of 25 mg under fasted condition on Day 1 of Period 1, 2, and 3 in Part 1

Duration of treatment/participation:

Single administration on Day 1 of Periods 1, 2, and 3 in Part 1 with 12 to 14 days between 2 consecutive single dosing of SAR444656. Follow-up: up to end-of-study (EOS) at Day 13 to 15 of Period 3. Total study duration is approximately 11 weeks as maximum, including screening and EOS.

Criteria for evaluation:

Primary

- Plasma PK parameters C_{max} (maximum plasma concentration observed), AUC_{last} (area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last}), and AUC (area under plasma concentration versus time curve extrapolated to infinity)

Secondary

- Assessment of adverse events, treatment-emergent adverse events, clinical laboratory evaluation, vital signs, and ECG (electrocardiogram)
- Assessment of adverse events, treatment-emergent adverse events, clinical laboratory evaluation, vital signs, and ECG
- Plasma PK (pharmacokinetic) parameters C_{max}, AUC_{last}, and AUC

Statistical methods:

A detailed description of the statistical methods is provided in the clinical study protocol and the statistical technical document. Due to early termination of the study, the analysis was limited to Part 1. Only statistical analyses conducted on the primary endpoints for bioavailability, secondary PK endpoints and safety assessment are provided in this report.

Primary endpoint (Pharmacokinetics):

Part 1

- Area under the curve extrapolated to infinity (AUC), AUC_{last}, and the maximum plasma concentration (C_{max}) of SAR444656 parameters were summarized by formulation and dose using descriptive statistics. Formulation ratios (same dose test vs reference) were listed by participant, gender and sequence and summarized.
- For log-transformed C_{max}, AUC_{last}, and AUC, the relative bioavailability of SAR444656 compound between formulations (test vs. reference formulation) were assessed using the following linear mixed model:
  Log(Parameter) = Sequence + Period + Gender + Formulation + Error, with fixed terms for sequence, period, formulation, gender, and with an unstructured 3-by-3 matrix of formulation-specific variances and covariances for participant within sequence-by-gender blocks using SAS Proc Mixed®

- For Cmax, AUClast, and AUC, point estimates and 90% CIs for the geometric means ratio of formulation (test 200 mg/reference) were obtained by computing point estimates and 90% CIs for the differences between formulation means within the linear model framework, and then converting to ratios by the antilog transformation.

- Within-participant and total standard deviations were estimated for log-transformed C_{max}, AUC_{last}, and AUC of SAR444656, by equating observed and expected means squares within the following linear model framework with a homogeneous variance components structure:
  Log (Parameter) = Sequence + Period + Gender + Formulation + Participant (Sequence × Gender) + Error with fixed terms for sequence, period, gender and formulation, and with a random term for participant-within-sequence-by-gender. 90% CIs were computed using the simple Chi-square method for within-participant SD, and the Graybill-Wang procedure for the total SD.

Part 2

Not applicable. The study was terminated before the initiation of Part 2. No Part 2 data were collected; therefore, no analysis was performed.

Key secondary endpoints:

Part 1

Adverse events, clinical laboratory parameters, vital signs and electrocardiograms (ECGs) as well as PK parameters following the single dose administration of 25 mg test formulation, 200 mg test formulation and 200 mg reference formulation.

Pharmacokinetics:

The distribution of tmax values were represented by histogram plots separately for each formulation in Part 1. For Part 1 data histogram of differences in tmax between formulations (200 mg test minus reference, 25mg test minus reference, 25mg test minus 200mg test) were provided. The marginal homogeneity test to assess the formulation effect on tmax was not performed. Descriptive statistics of interval between administration time and the sampling time preceding the first concentration above the limit of quantification tlag, geometric mean terminal half-life (t1/2z), apparent total body clearance of a drug from the plasma (CL/F) and apparent volume of distribution at steady state (Vss/F) were provided. Dose proportionality assessment was provided for the test formulation.

Safety:

The safety evaluation was based upon the review of the individual values for assessment of adverse events, treatment emergent adverse events, clinical laboratory parameters, vital signs, and ECG. Potentially clinically significant abnormalities (PCSAs) in clinical laboratory parameters, vital signs, and ECG were flagged and summarized by study intervention using frequency tables.

An overview of treatment emergent adverse events (TEAEs) and a summary of TEAEs presented by system organ class (SOC) and preferred term (PT) was provided by study intervention. The summary of TEAEs presented the number (%) of participants experiencing at least one event and number of events, sorted by the internationally agreed SOC order and decreasing frequency of PTs.

Part 2

Not applicable. The study was terminated before the initiation of Part 2. No Part 2 data were collected; therefore, no analysis was performed.

Summary Results:

Population characteristics:

Among the15 participants, 7 (46.7%) were male and 8 (53.3%) were female, with the age between 32 and 55 years (mean [SD] 43.3 [7.5]). All participants were White. Baseline body weight ranged from 56.1 kg to 98.1 kg (mean [SD] 74.71 [10.23]). Baseline BMI ranged from 19.8 kg/m^2 to 29.9 kg/m^2 (mean [SD] 24.89 [2.98]) with 8 (53.3%) participants landed in the category ranged from 18.5 kg/m^2 to 25 kg/m^2 (exclusive), and 7 (46.7%) participants were in the category ranged from 25 kg/m^2 (included) to 30 kg/m^2 (exclusive).

Exposure:

15 participants were exposed to IMPs of SAR444656 in Periods 1, 2, and 3 as planned in Part 1.

Safety results:

Adverse events:

Overall, 9 participants after receiving 200 mg reference formulation, 10 participants after receiving 200 mg test formulation, and 7 participants after receiving 25 mg test formulation experienced at least 1 TEAE, all with the intensity of Grade 1 or 2. The most common TEAEs (occurring in 2 or more participants for a single intervention group) were nasopharyngitis, headache, diarrhea, myalgia and fatigue. There were no Grade ≥3 TEAEs, deaths, serious AEs, AEs of special interest or TEAEs leading to study/treatment discontinuation reported by the investigator during the study.

Potentially clinically significant abnormality: ECG and vital signs

The PCSAs observed for ECGs and vital signs were scattered across all treatments and not associated with TEAEs.

Potentially clinically significant abnormality: Laboratory parameters

The PCSAs observed for laboratory parameters were scattered across all treatments and not associated with TEAEs.

Pharmacokinetic results:

The summary of descriptive statistics of PK parameters is presented in Table 1.

Table 1 - Pharmacokinetic parameters of SAR444656 following a single oral dose of SAR444656 reference formulation (200 mg) and test formulation (25 mg or 200 mg) in healthy participants

	Treatment		
	200 mg SAR444656 - reference formulation[c] (Treatment A, Reference)	200 mg SAR444656 - test formulation (Treatment B, Test)	25 mg SAR444656 - test formulation (Treatment C, Test)
Parameter (Unit)	**N, Mean ± SD, (Geometric Mean) [CV%]**		
C_{max} (ng/mL)	15	15	15
	11.8 ±4.77	9.04 ±3.94	3.21 ±2.07
	(11.2) [40]	(8.38) [44]	(2.74) [65]
AUC_{last} (h*ng/mL)	15	15	15
	565 ±189	412 ±152	116 ±73.6
	(533) [34]	(386) [37]	(97.6) [63]
AUC (h*ng/mL)	15	15	14[b]
	599 ±205	437 ±153	134 ±72.8
	(564) [34]	(412) [35]	(119) [54]
t_{max} (h)[a]	15	15	15
	6.08	6.00	6.00
	(6.00 - 24.00)	(6.00 - 12.00)	(4.00 - 48.00)
$t_{1/2z}$ (h)	15	15	15
	35.3 ±4.96	35.2 ±4.90	33.3 ±6.77
	(35.0) [14]	(34.8) [14]	(32.7) [20]
CL/F (L/h)	15	15	14[b]
	378 ±148	519 ±221	236 ±125
	(354) [39]	(485) [43]	(210) [53]
Vss/F (L)	15	15	14[b]
	18300 ±6340	26200 ±9910	11000 ±4780
	(17300) [35]	(24400) [38]	(10100) [43]
t_{lag} (h)[a]	15	15	15
	0.00	0.00	0.00
	(0.00 - 1.00)	(0.00 - 1.00)	(0.00 - 1.02)

a Median (Min – Max)

b For one participant who received Treatment C: 25 mg SAR444656 - test formulation in fasted condition in Period 1, AUC_{ext} exceeded the threshold (20%), therefore, AUC, CL/F and Vss/F of this participant were excluded for statistical analysis.

c One participant, who vomited at approximately 9 h post dosing, <= 2 x median t_{max} of the 200 mg SAR444656 reference formulation group and >6 h after dosing, was included in the statistical analysis.

Following a single oral dose administration of 200 mg SAR444656 as Treatment A (reference formulation), 200 mg SAR444656 as Treatment B (test formulation), or 25 mg SAR444656 as Treatment C (test formulation) under fasted conditions, a median t_{max} of 6.00 hours was observed for 3 treatments.

Following a single oral administration of SAR444656 test formulation tablets under fasted conditions over the dose range between 25 mg and 200 mg, PK exposures increased in a less-than-dose-proportional manner, with approximately 3- to 4-fold increase in C_{max}, AUC_{last}, and AUC for an 8-fold increase in dose.

Relative bioavailability of 200 mg SAR444656 represented by the parameters C_{max} and AUC_{last} and AUC point estimates of treatment geometric means ratio (test vs. reference) with 90% CI are presented in Table 2.

Table 2 - Relative bioavailability of 200 mg SAR444656 C_{max}, AUC_{last} and AUC - Point estimates of treatments geometric means ratio with 90% confidence interval

Comparison	Parameter	Point estimate	90% CI
Treatment B vs. Treatment A	C_{max}	0.75	(0.62 to 0.90)
	AUC_{last}	0.72	(0.60 to 0.87)
	AUC	0.73	(0.61 to 0.87)

Treatment A: 200 mg SAR444656 - reference formulation; Treatment B: 200 mg SAR444656 - test formulation

All formulations were given in fasted condition

The test (Treatment B)/reference (Treatment A) treatment geometric mean ratio (90% CI) was 0.75 (0.62 to 0.90) for C_{max}, 0.72 (0.60 to 0.87) for AUC_{last}, and 0.73 (0.61 to 0.87) for AUC. The bioavailability of the SAR444656 test formulation (Treatment B) was lower (on average 25 to 28%) than the reference formulation (Treatment A) under fasted conditions in healthy participants (Table 2).

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