NCT Number: NCT03236311

STATISTICAL TECHNICAL DOCUMENT

A randomized, double-blind, placebo-controlled parallel arm dose titration study to assess the effects of SAR4907899 in patients with microvascular angina and/or persistent stable angina despite angiographically successful percutaneous coronary intervention

SAR407899-ACT14656

STATISTICIAN: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AESI:	Adverse Event of Special Interest
CFR:	Coronary Flow Reserve
DBP:	Diastolic Blood Pressure
HR:	Heart Rate
PCSA:	Potentially Clinically Significant Abnormality
PD:	Pharmacodynamic
PK:	Pharmocokinetics
PL:	Physical Limitation
SAE:	Serious Adverse Event
SAQ:	Seattle Angina Questionnaire
SBP:	Systolic Blood Pressure
TEAE:	Treatment Emergent Adverse Event

1 STATISTICAL AND ANALYTICAL PROCEDURES

1.1 INTRODUCTION

The purpose of this document is to provide additional technical details.

A comprehensive and detailed description of strategy and statistical technique used to perform the analysis of data was provided in Section 11 of the protocol (amended clinical trial protocol no 03 dated 18-Apr-2018).

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 21.0).

Previous and concomitant medication records will be coded according to the World Health Organization Drug Dictionary (WHO-DD version 2018 MARCH 1).

1.2 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

At the time of the early study termination decided by the sponsor, only 10 patients were randomized in the study, and only 8 patients have a post baseline CFR assessed (primary efficacy endpoint) . The number of patients initially planned to be randomized in the study was 78, therefore with such few patients finally enrolled in the study, no formal statistical analysis will be performed. The analysis will be only descriptive, with few summary tables and some additional listings.

The following table gives the changes to the protocol statistical section.

Table 1 – Statistical analysis changes

Protocol version	Section number	Description of statistical changes
Amended no 03	11.4.1.2 Compliance	No summary table on compliance will be done. Instead listing with individual treatment intake, and compliance by visits interval will be provided.
	11.4.2.1 Analysis of primary efficacy endpoint	No model will be built. Only descriptive table and listing with information on the uncorrected global CRF will be provided
	11.4.2.2 Analysis of secondary efficacy endpoint	No model will be built for the SAQ-PL. Only descriptive table and listing will be provided
	11.4.2.3 Multiplicity considerations	Not applicable. All results presented are considered informative only.
	11.4.3.1 Adverse events	Incidence tables will be provided as planned. Only one listing will be provided for the treatment emergent adverse events with flag to identify SAE, TEAE leading to treatment discontinuation, AESI.
	11.4.3.2 Laboratory data	No summary statistics will be provided since only local laboratory data are retrieved in this study. Only the incidence of PCSA will be provided, as well as standard listings of patients with PCSAs
	11.4.3.4 Vital signs data	No summary statistics will be provided. Only the incidence of PCSA will be provided, as well as standard listings. In addition Individual graphs for SBP and HR could be provided if necessary
	11.4.3.5 Electrocardiogram data	No summary statistics will be provided. Only the incidence of PCSA will be provided, as well as standard listings
	11.4.4 Analysis of pharmacokinetic and pharmacodynamic variables	No PK nor PK/PD analysis will be performed

1.3 DATA HANDLING CONVENTIONS

This section describes the rules and conventions used in the presentation and analysis of data.

In the statistical appendices the following treatment label will be used:

SAR407899 or **Placebo.**

For parameters with possible several evaluations before administration, only the last observation will be used as baseline in descriptive statistics and derivations.

For clinical laboratory parameters with nonnumeric values, the imputed values used for the flags of PCSA will be determined by considering the following rules:

- If database value is '< X', the value used will be X/2
- If database value is '> X', the value used will be X

Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), standard error of the mean (SEM), minimum, maximum and median.

Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percent (%).

For vital signs parameters, the mean value of the three measures by time-points for the sitting SBP, DBP and HR will be used to determine the PCSA.

Windows for time points for vital signs

Vital signs analyzed by time point will be summarized using the time windows given below. If multiple valid values of a variable exist within a time window, the nearest from the targeted time point will be used. In case the time of the drug intake the day of the vital sign assessment is not reported in eCRF (possible when the vital sign assessment did not occur the first day or the last day of the kit number assigned), then the theoretical time will be used.

Table 2 – Time windows definition for vital signs

Time point	Targeted time	Time windows
T0H	Just before drug intake	6H00 to 0H00 before drug intake
T1H	1 hour after drug intake	0H30 to 2H00 after dug intake
T3H	3 hours after drug intake	2H01 to 6H00 after drug intake

Handling missing data for adverse events

In case of missing or inconsistent information, an adverse event will be counted as a treatment-emergent adverse event, unless it can clearly be ruled out that it is not a treatment-emergent adverse event (eg, by partial dates or other information).

Rules to derive SAQ summary scores

The rules used to derive the secondary endpoint SAQ-PL, and other summary SAQ summary scores are detailed in appendix B.

Angina episodes and short-acting nitrate intakes frequency

The weekly rate of angina episode and short-acting nitrate intakes will be derived as follows:

(Nb of angina episodes (respectively nb of short-acting nitrate intakes) reported during the recall period / duration of the recall period) * 7

For baseline, only the 7 days before randomization will be taken into account as recall period.

2 SOFTWARE DOCUMENTATION

The analysis of clinical data will be performed under the responsibility of Sanofi Biostatistics Department, using SAS® (SAS Institute, NC USA).

3 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities (PCSA) criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

[redacted]

[redacted]