STATISTICAL ANALYSIS PLAN

Protocol title:	**An open-label, first-in-human, dose-escalation/expansion study of SAR443579 administered as single agent by intravenous infusion in adult and pediatric participants with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL), high risk-myelodysplasia (HR-MDS), or blastic plasmacytoid dendritic cell neoplasm (BPDCN)**
Protocol number:	**TCD17197**
Compound number (INN/Trademark):	**SAR443579** **bexatamig/Not applicable**
Study phase:	**Phase 1/Phase 2**
Short title:	**First-in-human study of SAR443579**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**23-Jul-2025**

Regulatory agency identifier number(s):

IND:	153790
EudraCT:	2023-508357-58-00
NCT:	NCT05086315
WHO:	U1111-1266-7399

Total number of pages:45

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1

TABLE OF CONTENTS 2

LIST OF TABLES 4

VERSION HISTORY 5

1 INTRODUCTION 6

1.1 STUDY DESIGN 6

1.2 OBJECTIVES AND ENDPOINTS 7

2 ANALYSIS POPULATIONS 12

3 STATISTICAL ANALYSES 13

3.1 GENERAL CONSIDERATIONS 13

3.2 PRIMARY ENDPOINTS ANALYSIS 13

3.2.1 Definition of endpoints 13

3.2.2 Main analytical approach 14

3.2.3 Sensitivity analysis 15

3.2.4 Supplementary analyses 15

3.3 SECONDARY ENDPOINTS ANALYSIS 15

3.3.1 Key/Confirmatory secondary endpoint(s) 15

3.3.1.1 Definition of endpoint(s) 15

3.3.1.2 Main analytical approach 18

3.4 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS 18

3.5 MULTIPLICITY ISSUES 18

3.6 SAFETY ANALYSES 19

3.6.1 Extent of exposure 19

3.6.2 Adverse events 21

3.6.3 Additional safety assessments 25

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs) 25

3.7 OTHER ANALYSES 27

3.7.1 PK analyses 27

3.7.1.1 Observed PK parameters 27

3.7.1.2 Population PK analysis 27
3.7.1.3 Analyses endpoints for PK/PD 28
3.7.2 Immunogenicity analyses 28
3.7.3 [redacted] 30
3.7.3.1 [redacted] 31
3.7.3.2 [redacted] 31
3.7.3.3 [redacted] 32
3.7.3.4 [redacted] 32
3.7.3.5 [redacted] 32
3.8 INTERIM ANALYSES 32
3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES 33
4 SAMPLE SIZE DETERMINATION 34
4.1 DOSE ESCALATION PART 34
4.2 DOSE EXPANSION/OPTIMIZATION PART 34
5 SUPPORTING DOCUMENTATION 36
5.1 APPENDIX 1 LIST OF ABBREVIATIONS 36
5.2 APPENDIX 2 PARTICIPANTS DISPOSITIONS 37
5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS 38
5.3.1 Demographics, baseline characteristics, medical surgical history 38
5.3.2 Prior or concomitant medications (other than anti-cancer therapies) 39
5.3.3 Post anticancer therapies 40
5.4 APPENDIX 4 DATA HANDLING CONVENTIONS 40
5.4.1 Missing data 40
5.5 APPENDIX 5 SANOFI SPONSOR GENERIC RANGES FOR HEMATOLOGICAL AND BIOCHEMISTRY PARAMETERS 44
6 REFERENCES 45

LIST OF TABLES

Table 1 - Major changes in statistical analysis plan 5
Table 2 - Objectives and endpoints 7
Table 3 - Population for analyses 12
Table 4 - Summary of event or censoring time rules for EFS 17
Table 5 - Sorting of AE tables 22
Table 6 - Analyses of adverse events 22
Table 7 - [redacted] 33
Table 8 - Estimated composite complete remission (CRc) rate and 90% CI for dose expansion 35
Table 9 - Generic ranges for hematological parameters 44
Table 10 - Generic ranges for biochemistry parameters 44

VERSION HISTORY

This statistical analysis plan (SAP) for Study TCD17197 is based on the Protocol Amendment 09 dated 28-Jan-2025. This section summarizes major changes to the statistical analysis features in the SAP. This SAP is approved before database lock.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	14-Apr-2023	Not Applicable	Original version
2	23-Jul-2025	Section 1.1: updated the study design	Updated to align with the updated study design
		Section 1.2: updated the objectives and endpoints	To reflect the change in study design
		Section 2: removed “Exposed” and “Safety” populations in the table “Population for analyses”.	For clarity and to avoid redundancy
		Section 2: removed “Pharmacodynamic (PDy)” population in the table “Population for analyses”.	Removed as it is not needed in the analyses
		Sections 3.2 and 3.3: updated the endpoints and corresponding analyses	To reflect the change in study design
		Section 3.6: clarified and simplified the analyses	For clarity and simplification
		Section 4: updated the sample sizes according to the updated study design	To reflect the change in study design
		Section 5.2: clarified the analyses for dispositions and the analysis population for protocol deviations	For clarity
		Section 5.3: removed the analyses for last regimen received prior to study entry and premedications	To simplify the analyses due to the termination of the study
		Minor editorial and typographical error corrections throughout the document	Minor, therefore, have not been summarized

1 INTRODUCTION

There are no major changes to the analyses described in the protocol.

1.1 STUDY DESIGN

This is a Phase 1/Phase 2, open label, first in-human study to determine the maximum tolerated or maximum administered doses, and evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and anti-cancer activity of SAR443579 administered intravenously as a single agent in participants aged ≥1 years (France ≥2) with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), or high risk-myelodysplasia (HR-MDS).

SAR443579 will be administered IV in approximately three 28-day cycles in the Induction period. In the Induction period, IV administration will be twice or once weekly depending on the dose level and participant population. In the Maintenance period SAR443579 will be administered IV on Day 1 and D29 of each 56-day cycle for a Maintenance period up to 13 cycles. However, the dose and schedule for maintenance therapy may be refined based on clinical data.

The study includes adult and pediatric arms, which are divided in two parts: a dose escalation part and a dose expansion/optimization part.

During the adult arm dose escalation phase, the population to be treated are adults (≥18 years) with either relapsed or refractory AML or HR-MDS [redacted] In the pediatric arm dose escalation, the population (1 to <18 years) to be treated includes relapsed or refractory AML, B-ALL, or BPDCN [redacted]. Treatment for pediatric and adolescents arm will be conducted with access to a facility addressing the clinical needs of potential toxicity, which requires pediatric oncology expertise. The escalation part of the adult and pediatric arms aims to determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and preliminary Recommended Dose(s) for Expansion (RDEs) of SAR443579 based on the occurrence of dose-limiting toxicity (DLT) in Cycle 1. The dose escalation will be guided by a Bayesian logistic regression model (BLRM). At the end of dose escalation, preliminary RDEs, will be identified taking into account all available data. Separate RDEs may be identified for the adult and pediatric populations.

Arm	Age group	Phases
Adult arm	≥18 years old	Escalation phase Expansion/Optimization Cohort A1, A2, B, and C
Pediatric arm	1 (except in France ≥2) to <18 years old	Escalation Phase Expansion/Optimization Cohort D

- **Cohort A1 and A2 R/R AML** (adult arm; ≥18 years old)
- **Cohort B HR-MDS** (adult arm; ≥18 years old)
- **Cohort C R/R AML, B-ALL, HR-MDS** (adult arm; ≥18 years old): Japan specific
- **Cohort D R/R AML** (pediatric arm; 1 to <18 years old)

In May 2025, the company decided to prematurely terminate the clinical trial TCD17197 with SAR443579, after completion of the dose escalation phase and the dose expansion/optimization Cohort A1. The dose expansion/optimization Cohorts A2, B, C and D will not be initiated. Therefore, the current document will only introduce statistical analyses planned for the dose escalation and dose expansion/optimization Cohort A1.

1.2 OBJECTIVES AND ENDPOINTS

The objectives and endpoints from the protocol are presented below. Cohorts A represents Cohort A1 and Cohort A2 in the table below.

Since the study is prematurely terminated, not all the endpoints are applicable for analysis.

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Escalation part: - Adults Arm: To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and preliminary Recommended Dose(s) for Expansion (pRDEs) of SAR443579 administered as a single agent in participants with relapsed or refractory acute myeloid leukemia (R/R AML) and, high risk myelodysplastic syndrome (HR-MDS) - Pediatrics: To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and RDEs of SAR443579 administered as a single agent in participants with R/R AML, blastic plasmacytoid dendritic cell neoplasm (BPDCN), or B-ALL	• Incidence of dose-limiting toxicity (DLT), occurring during Cycle 1 (Day 1 to Day 28).
• Japan Cohort C: To confirm the tolerability of SAR443579 in Japanese participants	
• Expansion/Optimization part (Cohorts A1, A2, B & D): To assess the anti-cancer activity of SAR443579 administered as a single agent at the pRDEs and confirm the RDE in participants with R/R AML and MDS.	• AML: Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (CR with partial hematologic recovery) + CRi (CR with Incomplete Hematologic Recovery according to the modified AML IWG 2003 criteria. • MDS: overall response rate (CR+CR equivalent+PR+CR_L+CRh +HI) - IWG 2023 MDS response criteria

Objectives	Endpoints
Secondary (Adults and Pediatrics Arms)	
• To identify the preliminary RDEs (escalation part) and confirm the RDE (Expansion/Optimization part cohorts A, B and D).	• Overall safety & tolerability, pharmacokinetics (PK), pharmacodynamics (PDy), and preliminary anti-cancer activity.
• To characterize the overall safety and tolerability profile of SAR443579 (escalation & Expansion/Optimization parts)	• Type, frequency, severity, seriousness, and relationship to SAR443579 of adverse events or abnormalities of laboratory tests or investigations; drug discontinuation due to adverse events.
• To characterize the PK profile of SAR443579 when administered as a single agent.	• PK parameters of SAR443579 (at least C_{trough} at Cycle 1).
• To evaluate the potential immunogenicity of SAR443579.	• Percentage of participants with presence of anti-drug antibody (ADA) against SAR443579.
• To assess preliminary evidence of hematologic response (except BPDCN) (escalation part and Expansion/Optimization, and Japan Cohort C).	• AML: Rate of CR+CRh+CRi per AML 2003 modified International Working Group (IWG) response criteria • MDS: CR rate and ORR rate per IWG 2023 MDS response criteria for escalation part and ORR rate per IWG 2023 • B-ALL: Rate of CR+CRh+CRi as defined by NCCN.
• To assess additional parameters of SAR443579 anti-cancer activity in AML participants at the RDE (Expansion/Optimization part; cohorts A and D).	• Overall response rate defined as proportion of participants who have a CR or CRi or CRh or PR or MLFS (morphological leukemia-free state) according to the modified AML IWG response criteria. • Duration of CR+CRh+CRi (Duration of CRc) defined as the time interval from first documented evidence of CRc (CR, CRh or CRi) until disease relapse or death due to any cause, whichever comes first. • Duration of CR+CRi+CRh+PR+MLFS (Duration of overall response rate) defined as the time from the first documented evidence of CR or CRi or CRh or PR or MLFS until disease relapse or death due to any cause, whichever comes first. • Alternative CR rate defined as proportion of participants with CR+CRh (complete remission with partial hematological recovery). • Duration of CR+CRh (Duration of alternative CR) defined as the time from the first documented evidence of CR or CRh until disease relapse or death due to any cause, whichever comes first. • Event-free survival (EFS) defined as the time interval from the first day of treatment assignment to the date of earliest evidence of relapse, treatment failure, or death. • Overall survival defined as time interval from

Objectives	Endpoints
	the first day of treatment assignment to death from any cause. • Rate of hematopoietic stem cell transplantation (HSCT) procedures immediately following study treatment administration but prior to subsequent therapy for treatment of AML. • Time to treatment failure (TTF) defined as the time from first day of treatment assignment to discontinuation for any reason excluding remission, eg, relapsed disease, refractory disease, unacceptable AE, participant preference or death.
• To assess transfusion independence rate (TI) after treatment with SAR443579 at the RDE (Expansion/Optimization part, Cohorts A and D).	• The transfusion dependency (TD) at baseline is based on the receipt of any red blood cell or platelets transfusions within at least 28 days prior to the start of study treatment. For post baseline treatment, transfusion independency (TI) will be defined as the absence of transfusion during any 56 consecutive day period during treatment. The TI rate is defined differently for participants who were TD at baseline and participants who were TI at baseline. For subgroup of participants with TD at baseline, the TI rate is defined as the proportion of participants who convert from baseline TD to TI during on-treatment period; For subgroup of participants with TI at baseline, the TI rate is defined as the proportion of participants who remain TI during 56-day post-baseline period during treatment.
• To assess additional parameters of SAR443579 anti-cancer activity in MDS participants at the RDE (Expansion/Optimization part, Cohort B)	• Alternative CR rate defined as proportion of participants with CR, CR equivalent, CRuni, CRbi, and CRh. • Duration of ORR : Defined as the time interval from the first documented evidence of CR, CR equivalent, CR_L, CRh, PR or HI to PD or relapse from CR, CR equivalent, CR_L, CRh, PR or HI as per 2023 IWG recommendations or death due to any cause, whichever comes first. • Event-free survival (EFS): Measured from the first day of treatment assignment to the date of the first of the following events: - PD. - Failure to achieve CR (or CR equivalent), PR, CR_L, CRh, or HI within 6 months of study entry. - Relapse from CR (or CR equivalent), PR, CR_L CRh, or HI.

Objectives	Endpoints
	- Death from any cause. Patients not known to have any of these events are censored on the last date they were known not to have any of these events. • Overall survival defined as time interval from the first day of treatment assignment to death from any cause. • Rate of hematopoietic stem cell transplantation (HSCT) procedures immediately following study treatment administration but prior to subsequent therapy. • Time to treatment failure (TTF) defined as the time interval from first day of treatment assignment to discontinuation for any reason excluding remission, eg, relapsed disease, disease progression, unacceptable AE, participant preference or death. • Duration of alternative CR (CR+CR equivalent + CR_L+ CRh): the time interval from first documented evidence of CR, CR equivalent, CR_L or CRh until PD or relapse from CR, CR equivalent, CR_L or CRh as per 2023 IWG recommendations or death due to any cause, whichever comes first. • Progression free survival (PFS): defined as the time interval from the first day of treatment assignment to the date of PD, relapse from CR (or CR equivalent), PR, CR_L, CRh, or HI, death due to any cause, whichever comes first.
Tertiary/exploratory • **Pediatric arm only:** To assess preliminary evidence of hematologic response (escalation part) • **Adults and Pediatric Arms**: [redacted] • **Adults and Pediatric Arms:** To assess minimal residual disease (MRD) in participants achieving a CR, CRh, or CRi, and correlate MRD with clinical outcome (AML expansion/optimization only, Cohort A2, C, D). • **Adults and Pediatric Arms:** [redacted]	• Anti-cancer activity as defined by International Harmonization Project (IHP) lymphoma criteria for BPDCN (modified) participants (eg, ORR, clinical CR rate) • [redacted] • Minimal residual disease by molecular biology assessment and/or flow cytometry will be assessed in bone marrow and/or blood from participants achieving a CR, CRh, or CRi and correlated with clinical outcome. • [redacted]

Objectives	Endpoints
• **Adults and Pediatric Arms:** To investigate the relationship between CD123 expression, disease molecular subtype (as defined by marker expression, cytogenetics and/or genomics/transcriptomics) baseline IgG, different AML subpopulations (ie, PIF/ER vs LR) and parameters of clinical response.	• Assessment of potential correlation between specific disease characteristics at baseline (CD123 expression, molecular subtypes, PIF/ER vs LR, cytogenetics and/or genomics/transcriptomics), baseline IgG, and clinical outcomes.
• **Adults and Pediatric Arms:** To determine % reduction in CD123+ blasts in the dose escalation and expansion/optimization.	• Assessment of the kinetics of treatment-induced reduction in the % of CD123+ blasts as a pharmacodynamic marker for response to the IMP.
• To assess levels of cytokines following treatment administration, and their relationship with safety profile and clinical outcomes.	• Assessment of plasma cytokine levels in blood at specific time points following treatment administration to evaluate potential associations of cytokine levels with safety and clinical outcomes.
• To assess the participant health-related quality of life (HRQL), disease and treatment related symptoms and impacts of symptoms (Expansion/Optimization part Cohort A	• Assessment of the Quality of Life in Acute Myeloid Leukemia (AML-QOL) participant reported outcome instrument. • Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scales will be utilized as anchors to estimate/confirm established clinically meaningful change scores for AML-QOL/domain scores.
• To assess qualitatively patient experience with treatment (Expansion/Optimization part Cohorts A.)	• Results from the Patient's Qualitative Assessment of Treatment version 2 (PQAT-v2) will be used to assess participant-perceived advantages and disadvantages of treatment.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Population for analyses

Population	Description
Screened	All participants who signed the informed consent form (ICF).
Enrolled	All participants from screened population who meet study entry criteria and are registered in the study Interactive Response Technology (IRT) to receive SAR443579, regardless of whether the SAR443579 was administered or not.
All treated	For both dose escalation and dose expansion/optimization phases of the study, all treated population will include all participants who have given their informed consent and received at least any dose (even incomplete) of study intervention (SAR443579). This population is the primary population for the analyses of efficacy and safety parameters. All analyses using this population will be based on the dose level actually received in the first cycle.
DLT evaluable	The DLT evaluable population is defined as all participants who receiving at least 75% of the planned SAR443579 doses for twice-weekly or weekly schedule during the first 28 days of the treatment (DLT observation period) and completed the DLT observation period after the first IMP administration. Any participant who experienced a DLT during that period will also be DLT-evaluable. The dose recommended for dose expansion/optimization part will be determined based on the DLT evaluable population.
Pharmacokinetic (PK)	PK population includes all participants from all treated population with at least one post-baseline PK sample result with adequate documentation of dosing and sampling dates and times.
Immunogenicity	The immunogenicity population includes all participants from all treated population with at least one ADA result (positive, negative or inconclusive) post-baseline.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

There is no formal statistical hypothesis to be tested for the dose escalation and dose expansion/optimization parts.

Unless otherwise specified, analyses will be performed separately for the dose escalation and dose expansion/optimization parts.

In the dose escalation part, analyses will be performed separately for adult and pediatric arms. In addition, analyses will be presented by dose level and overall.

In the dose expansion part, analyses will be presented by cohort.

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of the investigational medicinal product (IMP).

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to the first administration of the IMP to the participant.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period that the participant receives the first administration of IMP up to 30 days after the participant receives his or her last administration of IMP.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

3.2 PRIMARY ENDPOINTS ANALYSIS

3.2.1 Definition of endpoints

Dose escalation

The primary endpoint for dose escalation is the incidence of dose-limiting toxicity (DLT) during the DLT evaluation period.

The DLT evaluation period is the first 28-days of treatment. DLTs will be defined using NCI-CTCAE Version 5.0 or ASTCT criteria for CRS or ICANS (see Section 4.3.2 of the protocol). A list of DLTs to be considered in the study is defined in the protocol (see Section 8.3.9 of the

protocol). For analysis purposes, DLTs will be identified based on the AEs reported on the e-CRF DLT page during the DLT evaluation period.

The incidence of DLT will be used to determine the maximum tolerated dose (MTD). MTD is defined as the highest dose level with the highest probability of IMP-related DLT rate within the target range (15% to 25%) among dose levels with less than 0.40 probability of DLT rate above target (>25%). Dose escalation will stop once the MTD is determined or until the planned maximum administered dose (MAD) has been declared safe.

Dose expansion/optimization

The primary efficacy analysis will be conducted for all treated population in the expansion/optimization part.

The primary endpoint for Cohort A1 is the composite complete remission (CRc) rate per modified AML International Working Group (IWG) 2003 response criteria.

CRc rate is defined as the proportion of participants who have a response of complete remission (CR), CR with partial hematologic recovery (CRh) or CR with incomplete hematologic recovery (CRi) according to modified AML IWG 2003 criteria (see Section 10.11.4.1 of the protocol).

3.2.2 Main analytical approach

Dose escalation

DLTs will be summarized by dose level and overall. Details of DLTs will be provided by the participant for DLT evaluable population.

To determine the MTD, the following statistics will be provided:

- The posterior probability of DLT rate within the target range (15% to 25%)
- The posterior probability of DLT rate above the target range (>25%)
- Median and 95% credible interval of DLT rate posterior distribution

The following Bayesian logistic regression model (BLRM) (1) will be used to derive these statistics:

$$\text{logit}(p_i) = \log[a] + \exp(\log[b]) \log(d_i/d_{ref})$$

where p_i is the probability of DLT for a participant at dose level d_i, a and b are parameters that are random variables, and d_{ref} is the reference dose (ie, here the highest planned target dose).

The bivariate normal prior for (log(a), log(b)) is defined with the following 5 parameters: $\ln(\alpha)\_\mu = -1.457$, $\ln(\alpha)\_\sigma = 1.508$, $\ln(\beta)\_\mu = 0.876$, $\ln(\beta)\_\sigma = 1.009$, $\rho = 0.554$.

MTD will be determined by the Study Board, along with the recommendation from BLRM. In case the MTD is not reached, the recommended dose for expansion phase will be decided by the Study Board, based on DLT (if established) and other relevant data such as safety, anti-tumor activity, PK, and PDy information.

Dose escalation will be stopped as soon as the MTD is determined. If a MTD is not determined, dose escalation will continue until the MAD is achieved.

Dose expansion/optimization

For Cohort A1, CRc rate (for R/R AML) will be summarized with descriptive statistics. The 90% two-sided confidence interval (CI) will be computed using Clopper-Pearson method.

3.2.3 Sensitivity analysis

Not applicable.

3.2.4 Supplementary analyses

Not applicable.

3.3 SECONDARY ENDPOINTS ANALYSIS

3.3.1 Key/Confirmatory secondary endpoint(s)

No key/confirmatory secondary endpoints are selected for this study, the definitions and main analytical approaches of all secondary endpoints are described below.

3.3.1.1 Definition of endpoint(s)

Dose escalation and dose expansion/optimization parts

The secondary endpoint for R/R AML is the CRc rate per modified AML IWG 2003 response criteria.

The secondary endpoints for HR-MDS are the CR rate and overall response rate (ORR) per IWG 2023 MDS response criteria.

ORR is defined as the proportion of participants who have a response of CR, CR equivalent, partial remission (PR), CR with limited count recovery (CR_L), CRh or hematologic improvement (HI) according to IWG 2023 MDS response criteria (see Section 10.11.4.4 of the protocol).

CR rate is defined as the proportion of participants who have a response of CR or CR equivalent according to IWG 2023 MDS response criteria.

Dose expansion/optimization part: Cohort A1

Overall response rate

ORR is defined as the proportion of participants who have a response of CR or CRi or CRh or PR or morphological leukemia-free state (MLFS) according to modified AML IWG 2003 criteria.

Alternative CR rate

Alternative CR rate is defined as the proportion of participants who have a response of CR or CRh according to modified AML IWG 2003 criteria.

Duration of CRc (Duration of CR+CRh+CRi)

Duration of CRc is defined as the time interval from first documented evidence of CRc (CR, CRh or CRi) until disease relapse (DR) or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of CRc will only be calculated for participants who have a CR or CRh or CRi.

Duration of overall response rate (Duration of CR+CRi+CRh+PR+MLFS)

Duration of overall response rate is defined as the time from the first documented evidence of CR or CRi or CRh or PR or MLFS until DR or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of overall response rate will only be calculated for participants who have a CR or CRi or CRh or PR or MLFS.

Duration of alternative CR (Duration of CR+CRh)

Duration of alternative CR is defined as the time from the first documented evidence of CR or CRh until DR or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of alternative CR will only be calculated for participants who have a CR or CRh.

Event-free survival (EFS)

EFS is defined as the time interval from the first day of treatment assignment to the date of earliest evidence of relapse, treatment failure, or death. Treatment failure was defined as failure to achieve CR or CRh or CRi by 16 weeks. Subjects who do not achieve CR or CRh or CRi by Week 16 will be considered to have had an event at Day 1 of treatment assignment. For the remaining CR or CRh or CRi responders, the event time will be the time of either disease relapse or death, whichever occurs first. Event-free survival will be censored upon initiation of a new

anticancer therapy should a new therapy be initiated prior to any EFS event. Table 4 summarizes the event or censoring time rules for EFS endpoint in more details.

Table 4 - Summary of event or censoring time rules for EFS

Situation	Date of progression or censoring	Outcome
Achieve CR/CRh/CRi by 16 weeks, experience relapse afterward	Date of relapse	Event (relapse)
Achieve CR/CRh/CRi by 16 weeks, do not experience relapse, die afterward	Date of death	Event (death)
Achieve CR/CRh/CRi by 16 weeks, no relapse or death and no new anti-cancer therapy	Date of last assessment	Censored
Achieve CR/CRh/CRi by 16 weeks, no relapse or death while on a new anti-cancer therapy (excluding HSCT)	Date of last assessment before initiation of new therapy	Censored
No CR/CRh/CRi achieved, >=16 weeks since the first treatment	Day 1 of treatment assignment	Event (treatment failure)
No CR/CRh/CRi achieved, <16 weeks and discontinued	Day 1 of treatment assignment	Event (treatment failure)
No CR/CRh/CRi achieved, <16 weeks while active in the study	Date of last assessment	Censored

Overall survival (OS)

Overall survival is defined as time interval from the first day of treatment assignment to death from any cause. If death is not observed before the analysis cut-off date, data on OS will be censored at the last date participant is known to be alive or at the analysis cut-off date, whichever occurs first.

Hematopoietic stem cell transplantation (HSCT) rate

A participant who achieves an adequate response to treatment with SAR443579 and meets other criteria required to undergo HSCT may proceed to HSCT after discontinuation of SAR443579. HSCT rate is defined as the proportion of such participants who undergo HSCT immediately following study treatment administration but prior to subsequent therapy for treatment of AML.

Time to treatment failure (TTF)

TTF is defined as the time from first day of treatment assignment to discontinuation for any reason excluding remission, eg, relapsed disease, refractory disease, unacceptable AE, participant preference or death. In the absence of specified events (discontinuation for any reason excluding remission), participant will be censored at the date of the last valid disease assessment performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. In the situation of no post-baseline disease assessment, participants will be censored at the date of the first day of treatment assignment.

Transfusion independence (TI) rate

The transfusion dependency (TD) at baseline is based on the receipt of any red blood cell or platelets transfusions within at least 28 days prior to the start of study treatment. For post baseline treatment, transfusion independency (TI) will be defined as the absence of transfusion during any 56 consecutive day period during treatment. The TI rate is defined differently for participants who were TD at baseline and participants who were TI at baseline. For subgroup of participants with TD at baseline, the TI rate is defined as the proportion of participants who convert from baseline TD to TI during on treatment period; For subgroup of participants with TI at baseline, the TI rate is defined as the proportion of participants who remain TI during 56-day post baseline period during treatment.

3.3.1.2 Main analytical approach

The secondary efficacy analysis will be conducted for trial participants with R/R AML enrolled in the expansion part.

The CRc rate for R/R AML will be summarized with descriptive statistics. The CR rate and ORR for HR-MDS will be summarized with descriptive statistics. If applicable, the 90% two-sided CI will be computed using Clopper-Pearson method.

The alternative CR rate, ORR, HSCT rate and TI rate will be summarized with descriptive statistics. If applicable, the 90% two-sided confidence interval (CI) will be computed using Clopper-Pearson method.

For duration of CRc, duration of overall response rate, duration of alternative CR, EFS, OS and TTF, the following descriptive analyses will be performed (if applicable):

- Number of participants who have events or have been censored will be summarized for each time-to-event endpoint.
- The Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associated 90% confidence intervals will be provided for each time-to-event endpoint.
- Number (%) of participants at risk as well as the probabilities of being event-free at different time points with 90% CIs using the Kaplan-Meier method.

A listing of participants who achieve a CR or CRh or CRi will be provided for R/R AML participants. A listing of response data will be provided for all treated population.

3.4 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

The tertiary endpoints analyses are defined in Section 3.7.3 (biomarker).

3.5 MULTIPLICITY ISSUES

Not applicable.

3.6 SAFETY ANALYSES

All safety analyses will be performed on all treated population as defined in Section 2, unless otherwise specified. The analysis of the safety variables will be essentially descriptive, and no testing is planned.

3.6.1 Extent of exposure

The extent of IMP exposure will be summarized within all treated population. The variables below will be summarized by descriptive statistics.

The SAR443579 dose information will be assessed by the following:

- Total number of cycles started by induction and maintenance period
- Number of cycles started per participant by induction and maintenance period
- Duration of SAR443579 exposure (in weeks) defined depending on the SAR443579 administration schedule as follows:
  - For participants (dose escalation) who discontinued in induction period during Cycle 1:
  - If date of last dose at D1 or D8 (ie, the first dose for twice-weekly dosing) for DL1/DL2: [(date of last dose +3) - date of first dose]/7
  - If date of last dose at D4 or D11 (ie, the second dose for twice-weekly dosing) for DL1/DL2: [(date of last dose +4) - date of first dose]/7
  - If date of last dose at D1 (ie, the first dose for twice-weekly dosing) for DL3: [(date of last dose +3) - date of first dose]/7
  - If date of last dose at D4 (ie, the second dose for twice-weekly dosing) for DL3: [(date of last dose +4) - date of first dose]/7
  - If date of last dose in weekly-dosing schedule: [(date of last dose +7) - date of first dose]/7
- For participants (dose escalation of Cycle 2 and beyond or dose expansion/optimization) whose last dose is in induction period: [(date of last dose +7) - date of first dose]/7
- For participants whose last dose is in maintenance period: [(date of last dose +28) - date of first dose]/7
- Actual dose (in µg/kg): for each administration, the actual dose in µg/kg corresponds to the actual dose in µg administered divided by the last available body weight up to the administration day.
- Cumulative dose (in µg/kg): the cumulative dose is the sum of all actual doses of SAR443579, given from the first to last administration
- Actual dose intensity (ADI, in µg/kg/week), defined as the cumulative dose divided by the duration of SAR443579 exposure (in weeks)

- Planned dose intensity (PDI, in µg/kg/week): corresponds to the sum of the planned doses in each cycle started and divided by the theoretical cycle duration expressed in weeks.
- Overall relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (µg/kg/week)}}{\text{PDI (µg/kg/week)}}$
- Relative dose intensity in Cycle 1 (in %):$100 \times \frac{\text{ADI only for Cycle 1}}{\text{PDI only for Cycle 1}}$

The total number of cycles started, and the number of cycles started by participants will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc.). Duration of SAR443579 exposure, cumulative dose, ADI, and RDI will be summarized quantitatively.

The following variables will be derived to describe dose delays and dose modifications:

- Cycle delay:
  - A cycle is deemed as delayed in the maintenance phase if the start date of the current cycle - 56 days - start date of the previous cycle is >=6 days.
- Dose delay:
  - A dose is deemed as delayed if administered ≥2 days beyond the theoretical treatment day for the once-weekly schedule in Induction Phase.
  - A dose is deemed as delayed if administered ≥2 day beyond the theoretical treatment day for the twice-weekly schedule in Induction Phase.
- Dose omission: a dose is omitted if not administered before the next planned dose in an induction cycle. Dose omission will not be considered for maintenance phase.
- Dose interruption: a dose will be considered as interrupted if SAR443579 administration is stopped during an infusion regardless of whether it is restarted or not. Dose interruption information from the exposure infusion eCRF page will be used.

Dose delay/modifications will be analyzed by participant, cycle and dose as follows:

- **Participant** (number of participants treated will be used as the denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose delayed
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with at least 1 dose interruption
- **Cycle** (number of cycles started will be used as denominator)
  - Number (%) of cycles with at least 1 dose modification
    - Number (%) of cycles with at least 1 dose delayed
    - Number (%) of cycles with at least 1 dose omission
  - Number (%) of cycles with at least 1 dose interruption

- **Dose** (number of doses started will be used as denominator)
  - Number (%) of dose interruptions

3.6.2 Adverse events

General common rules for adverse events

All AEs will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE Version 5.0) and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock. Cytokine Release Syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) will be graded using ASTCT consensus grading.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing grade will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase, using the maximum (worst) grade by treatment phase. Summaries will be provided for all grades combined and for Grade ≥3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the "all grades" in All group.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any TEAE related to IMP
- Any Grade ≥3 TEAE
- Any Grade ≥3 TEAE related to IMP
- Any treatment-emergent SAE
- Any treatment-emergent SAE related to IMP
- Any treatment-emergent AESI
- Any treatment-emergent AESI related to IMP
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Grade 5 TEAE related to IMP
- Any TEAE leading to dose modification of SAR443579 (including dose interruption and reduction)
- Any TEAE leading to permanent discontinuation of SAR443579

The AE summaries of Table 6 will be generated with the number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for Grade ≥3.

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
	PT
Common TEAE (≥5% overall)	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT

Type of AE	MedDRA levels
Treatment-emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent discontinuation of SAR443579	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT
TEAE leading to death related to IMP as per Investigator's judgment[b]	Primary SOC and PT
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
TEAE leading to dose modification of SAR443579 (including dose interruption and reduction)	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation.
b Death as an outcome of the AE as reported by the Investigator in the AE page

Listings of treatment-emergent SAEs and TEAEs leading to permanent discontinuation of SAR443579 will be provided.

Analysis of deaths

In addition to the analyses of deaths included in Table 6 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by main reason for death
- Summary of AEs leading to death, by primary SOC and PT:
  - In context of disease progression (death within 30 days from last IMP administration and the cause of death is disease progression).
  - In context other than disease progression (death within 30 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last IMP administration and the cause of death is AE.
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment)
  - Fatal TEAE (regardless of date of death/period)
    - Grade 5 TEAE with a fatal outcome during the treatment-emergent period
    - Any Grade TEAE with a fatal outcome during the post-treatment period
  - Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period)

A listing of all deaths will be provided.

Analysis of adverse events of special interest (AESIs) and other groupings of events

The following AESIs will be selected using the specific eCRF page or specific tick box from the AE page:

- Pregnancy
- Symptomatic overdose
- Infusion-related reactions (IRRs)

In addition, the following groupings of events are defined:

- Cytokine release syndrome (CRS) selected using CMQ00078
- Immune effector cell-associated neurotoxicity syndrome (ICANS) related TEAE selected using CMQ40067

Number (%) of participants experiencing at least one event will be provided for each event of interest, by PT if applicable. Tables will be sorted as indicated in Table 5.

Listings of participants with reported overdose and reported pregnancy will be provided separately. Number of participants with symptoms of CRS presented by primary SOC and PT will be summarized for Grade ≥2 and overall (it uses the grades of the IRR symptoms). Number of participants with symptoms of IRRs (excluding symptoms of CRS) presented by primary SOC and PT will be summarized for Grade ≥2 and overall (it uses the grades of the IRR symptoms).

For adult participants in dose escalation phase who experience IRR in Cycle 1, mean grade of IRR with the corresponding standard error in each IMP infusion day will be plotted by different lead-in dose (LID) schedule (1-Step LID corresponds to DL4, DL5; 2-Step LID corresponds to DL1, DL2 and DL3; and full dose corresponds to DL 0.75mg, DL 0.8mg, DL 1mg, DL 1.5mg, DL 2mg, DL6 and DL7).

In addition, for IRRs, the following analyses will be provided:

Analysis by participants

IRRs presented by primary SOC and PT will be summarized by grades and overall. Besides, the following will be provided：

- Number (%) of participants by worst grade
- Number (%) of participants with serious IRR
- Number (%) of participants by action taken
- Number (%) of participants by corrective treatment (Yes/No)
- Number (%) of participants with 1, ≥2, ≥3, ≥4, and ≥5 episodes
- Number (%) of participants with first occurrence of IRR at each infusion in Cycle 1 and at subsequent infusions

- Number (%) of participants with at least two episodes of IRRs during the same infusion

Analysis by episodes

The following summary will be provided:

- Number of episodes
- Grade of IRR
- Day of onset of IRR
- Duration of IRR (days)

A listing of IRRs will be provided.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Platelet count, Red blood cell (RBC) count, Hemoglobin, Hematocrit, Percentage of blasts
  - RBC indices: MCV, MCH, %Reticulocytes
  - White blood cell (WBC) count with differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
- Clinical chemistry:
  - Metabolism: total protein and albumin.
  - Electrolytes: sodium, potassium, phosphate and corrected calcium.
  - Renal function: creatinine, blood urea nitrogen, urea nitrogen.
  - Liver function: alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT), aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), total and direct bilirubin, gamma-glutamyl transferase (GGT).
  - Other: Glucose, CRP, Ferritin, Magnesium, Bicarbonate, Uric Acid, LDH, Amylase, Lipase.
  - Other test: Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only), Coagulation (PT/INR, aPTT, fibrogen and D-dimer).
  - Serology (anti-HIV antibody [only when requested by local authorities], hepatitis B surface antigen [HBsAg], and anti-hepatitis C virus antibody).

- Urinalysis
  - Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
  - Microscopic examination (if blood or protein is abnormal)
- Vital signs: heart rate, systolic and diastolic blood pressure, weight, ECOG Performance Status (PS), body temperature, respiratory rate, and oxygen saturation
- ECG variables: heart rate, PR, QRS, QT, and QTc (according to Fridericia). ECG assessments will be described as normal or abnormal.

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Section 5.5). For other biochemistry parameters, grading will be derived using local laboratory normal ranges.

Analyses according to potentially clinically significant abnormalities (PCSA) and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE Version 5.0. In addition, for laboratory variables for which NCI-CTCAE scale is not applicable, vital signs and ECG variables, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the data base lock.

Analyses according to PCSA and NCI grading will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables graded by NCI-CTCAE,

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade and with Grade 3-4 abnormalities will be provided.

For laboratory variables and vital signs, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

3.7 OTHER ANALYSES

3.7.1 PK analyses

PK analyses will be performed using population PK approaches on the PK population as defined in Section 2.

3.7.1.1 Observed PK parameters

The description of concentrations observed over time will be summarized for each time-point by standard descriptive statistics from SAR443579 concentrations.

Exclusion rules from standard descriptive statistics:

- For predose concentrations (C_{trough}), samples collected after starting infusion.
- For end of infusion concentration (C_{eoi}), samples collected before and after 10 minutes of the actual end of infusion time.
- No other exclusion rule based on collection time window will be applicable for other timepoints.

Individual concentrations will be summarized by dose and dose level (if applicable) using descriptive statistics (such as the number of observations, arithmetic and geometric means, median, standard deviation, standard error [SE], coefficient of variation [CV], minimum, and maximum). For C_{trough} value observed below the Lower Limit of quantification, will be replaced by the value of LLOQ for descriptive statics calculation. Individual and mean C_{eoi} and C_{trough} profiles over time will be plotted by dose level.

In addition, individual and mean concentration profiles over Cycle 1 will be plotted by dose level (if applicable).

3.7.1.2 Population PK analysis

The population PK analyses will be described in the PK Population analysis plan (PAP). The results of the population PK analysis will be presented in a separate document.

3.7.1.3 Analyses endpoints for PK/PD

If applicable, a separate PK/PD analysis report will be reported in a separate stand-alone report or included in the population PK stand-alone report.

3.7.2 Immunogenicity analyses

A summary table with number (%) of participants with pre-existing ADA, number (%) of participants with treatment-boosted ADA, number (%) of ADA-negative participants at baseline, number (%) of participants with treatment-induced ADA (either transient, persistent or indeterminate) (see definitions below) along with descriptive statistics of titer will be reported by dose level (if applicable) and overall on the ADA population (as defined in Section 2). Number (%) of ADA-positive participants and ADA incidence will also be presented.

For ADA treatment-emergent participants, descriptive statistics on time to onset and duration of ADA response will be provided using a summary table.

An individual data listing will be provided for participants having at least one positive or inconclusive ADA sample with study period (cycle), ADA sample study day, corresponding SAR443579 C_{trough} value, ADA samples result (positive, negative or inconclusive), ADA samples titer (if applicable), ADA participant response (kinetic of the immune response: indeterminate, transient or inconclusive).

The summary statistics of C_{trough} will be provided by dose and dose level for non-treatment emergent participants for comparison to individual profile of ADA treatment-emergent participants.

Note that treatment-boosted ADA are excluded from the analyses of ADA kinetics because this type of immune response differs mechanistically.

The impact on PK, safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ADA incidence.

Immunogenicity impact on PK of SAR443579 will be explored, depending on the ADA incidence:

- Descriptive statistics of C_{trough} will be provided at each cycle in the subset of non-treatment emergent participants by dose and dose level (if applicable).
- The impact of immunogenicity on PK will be assessed graphically by plotting individual C_{trough} profiles of treatment-emergent participants along with mean (+/- SD) C_{trough} profile of ADA-negative participants by dose level, if applicable. In this plot, concentrations obtained at the time of an ADA-positive result will be highlighted.

ADA endpoint

Anti-therapeutic antibodies are biologic drug-reactive antibody, including pre-existing host antibodies that are cross-reactive with the administered biotherapeutic (baseline ADA).

ADA attributes

Pre-existing ADA is defined as ADA reactive with the biotherapeutic present in participants before first administration of intervention (or before initiation of the clinical study).

Treatment-emergent ADA:

- **Treatment-boosted ADA** is defined as pre-existing ADA that was boosted to a higher-level following administration of biotherapeutic (ie, any time after the initial drug administration) the ADA titer is significantly higher than the baseline titer. A low serial dilution schema (2-fold or 3-fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.
- **Treatment-induced ADA** is defined as ADAs developed de novo (seroconversion) following administration of the biotherapeutic (ie, formation of ADAs any time after the initial drug administration in a participant without pre-existing ADAs). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ADA assessment.

Participant status

Among evaluable population for immunogenicity (described in Section 2), following participant status will be defined:

- **ADA treatment-emergent** participant: A participant with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period.
- **ADA non-treatment emergent** participant: Participant without any treatment-induced, treatment-boosted ADA-positive or ADA-inconclusive sample during the treatment or follow-up observation period.
- **ADA-inconclusive** participant: A participant who cannot irrefutably be classified as ADA negative (eg, all post baseline samples inconclusive).
- **Unclassified ADA** participant**:** participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (ie, a positive ADA sample during the TE period in a participant with pre-existing ADA but with missing titer at this sample or at baseline).

- ***Overview of the ADA response***
  - The term **ADA incidence** only defines the proportion of subjects found to either have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response during the study. Only evaluable subjects (described in Section 2) are considered for computing ADA incidence.

Kinetics of the immune response

- **Time to onset of ADA response:** time period between the first IMP administration and the first treatment-induced/boosted ADA. The use of real-elapsed days should be used for the calculations. The "median time to ADA development" and the quartiles Q1 and Q3 should be reported.
- **Duration of ADA response:** time between the first treatment-induced/boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between; ADA duration will be calculated only for participants with at least two ADA-positive samples. Median duration of an induced ADA response and the quartiles Q1 and Q3 should be reported.
- **Transient ADA response** is defined by:
  - Treatment-induced/boosted ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point), OR
  - Treatment-induced/boosted ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the participant's last sampling time point is ADA negative.
- **Persistent ADA response** is defined by:
  - Treatment-induced/boosted ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples are separated by at least 16 weeks (irrespective of any negative samples in between).
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

3.7.3 [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
    - [redacted]
    - [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.7.3.1 [redacted]

[redacted]

3.7.3.2 [redacted]

[redacted]

3.7.3.3 [redacted]

[redacted]

3.7.3.4 [redacted]

[redacted]

3.7.3.5 [redacted]

[redacted]

3.8 INTERIM ANALYSES

No formal interim analyses are planned. However, at the end of the dose escalation, the occurrence of DLT and other safety data will be reviewed by Study Board (SB) to determine preliminary RDEs. Informal interim analyses will be performed in the dose expansion/optimization phase.

As a general rule, continuous safety and efficacy monitoring will be performed for all cohorts using Bayesian methods during the conduct of the expansion/optimization and could trigger early decisions to stop or expand the specific cohorts/dose levels.

Stopping rules:

[redacted] (2) is used to determine the stopping boundaries based on the following assumptions: maximum probability of excessive toxicities allowed = [redacted] prior distribution for excessive toxicity rate: [redacted] minimum number of participants before early stopping rule applies = [redacted], cohort size = 1, and posterior probability of excessive toxicity rate [redacted] Table 7 shows the number of participants with excessive toxicities observed before enrollment in the trial will be paused until an appropriate evaluation of the cause of death and toxicity is conducted by the Study Board and a correction plan is established. The safety stopping rules will be applied to different cohorts separately.

Table 7 - [redacted]

[redacted]

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

There are no major statistical changes in the protocol amendment(s).

4 SAMPLE SIZE DETERMINATION

A total of approximately 116 DLT-evaluable adult participants and 24 DLT-evaluable pediatric participants will be enrolled when SAR443579 is administered as a single agent, depending on the investigated DLs during the escalation phase. The Cohort A1 will enroll up to 20 participants.

The study was prematurely terminated, a total of 101 participants were enrolled and treated with SAR443579.

4.1 DOSE ESCALATION PART

There is no formal sample size calculation in the dose escalation phase. SAR443579 will be administered to participants with R/R AML, HR-MDS, B-ALL, or BPDCN. It is anticipated that approximately 116 participants will be enrolled in the adult arm dose escalation part with expected assessment of about 11 main DLs while intermediate DLs may be investigated in case of dose or schedule modifications. Approximately 24 participants will be enrolled in the dose escalation part for pediatric with expected assessment of about 2 main DLs while intermediate DLs may be investigated in case of dose or schedule modifications. The actual sample size will vary depending on DLTs observed and number of DLs actually explored and the number of participants enrolled but not DLT-evaluable.

The dose escalation decision is described in Section 4.3.2 of the protocol. The preliminary RDEs (pRDE) identified during the dose escalation part may be further evaluated during the expansion/optimization part among the first 10 to 20 participants enrolled in the Cohort A1.

The adult arm dose escalation part ended up with enrolling and treating 69 participants. The pediatric arm dose escalation part ended up with enrolling and treating 12 participants.

4.2 DOSE EXPANSION/OPTIMIZATION PART

In the expansion/optimization part of SAR443579 as a single agent, up to 20 participants with R/R AML are expected to be treated in Cohort A1. The sample size for the dose expansion/optimization part is not based upon a power calculation but is intended to provide preliminary information on the activity of SAR443579 as a single agent in the R/R AML adult, HR-MDS adult and pediatric R/R AML populations.

Table 8 lists estimated CRc rate and the corresponding 90% exact confidence intervals (CIs) by number of responders.

Table 8 - Estimated composite complete remission (CRc) rate and 90% CI for dose expansion

Number of Responders (N=20)	CRc rate	90% CI for CRc rate (Clopper-Pearson)
3	15.0%	(4.2%, 34.4%)
4	20.0%	(7.1%, 40.1%)
5	25.0%	(10.4%, 45.6%)
7	35.0%	(17.7%, 55.8%)
9	45.0%	(25.9%, 65.3%)
12	60.0%	(39.4%, 78.3%)

The overall efficacy and safety profile will be assessed based on mature CRc rate data available at the interim and final analyses of the dose expansion/optimization cohort to determine if further development of SAR443579 will be initiated.

With a sample size of 20 study participants at the confirmed safe dose in the dose expansion/optimization phase, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 18.2%, 33.2%, or 64.2%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

Cohort A1 ended up with enrolling and treating 20 participants.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibodies
ADI:	actual dose intensity
AML:	acute myeloid leukemia
ATC:	anatomical therapeutic chemical
B-ALL:	B-cell acute lymphoblastic leukemia
BLRM:	Bayesian logistic regression model
BPDCN:	blastic plasmacytoid dendritic cell neoplasm
BUN:	blood urea nitrogen
CI:	confidence interval
CMQ:	customized MedDRA queries
CR:	complete remission
CRc:	composite complete remission
CRh:	complete remission with partial hematologic recovery
CRi:	complete remission with incomplete hematologic recovery
CRS:	cytokine release syndrome
CV:	coefficient of variation
DLT:	dose-limiting toxicity
DR:	disease relapse
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
HLGT:	high-level group term
HLT:	high-level term
HR-MDS:	high risk-myelodysplasia
IRR:	infusion related reaction
IWG:	International Working Group
LID:	lead-in dose
LLN:	lower limit of normal
LLOQ:	lower limit of quantitation
LLT:	lower-level term
MAD:	maximum administered dose
MedDRA:	medical dictionary for regulatory activities
MLFS:	morphological leukemia-free state
MTD:	maximum tolerated dose
ORR:	overall response rate
PCSA:	potentially clinically significant abnormalities
PDI:	planned dose intensity
PR:	partial remission
PS:	performance status
PT:	preferred term
Q1:	Quartile 1

Q3:	Quartile 3
R/R AML:	relapsed or refractory acute myeloid leukemia
RDE:	recommended dose for expansion
RDI:	relative dose intensity
SAP:	statistical analysis plan
SD:	standard deviation
SE:	standard error
SMQ:	standardized MedDRA queries
SOC:	system organ class
ULN:	upper limit of normal
ULOQ:	upper limit of quantitation
WHO-DD:	World Health Organization-Drug Dictionary

5.2 APPENDIX 2 PARTICIPANTS DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

The number (%) of participants in the following categories will be provided:

- Enrolled but not treated participants
- Enrolled and treated participants
- Participants still on study intervention
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed induction and move in maintenance phase
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation
- Status at last contact (alive, death)

A listing of participants with permanent discontinuation of SAR443579 will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in all treated population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

5.3.1 Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history, and disease characteristics at baseline will be summarized using descriptive statistics in all treated population.

Demographic and baseline characteristics:

- Age in years as quantitative variable and in categories (<65, 65 to <75, ≥75)
- Gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- ECOG PS (0, 1)
- Baseline weight in kg as quantitative variable

Medical or surgical history includes the relevant history of previous pathologies and surgeries other than AML (for R/R AML patients), ALL (for B-ALL patients), or myelodysplasia (for HR-MDS patients). Medical and surgical history will be coded using the MedDRA version currently in effect at Sanofi at the time of database lock.

<u>Disease characteristics related to AML:</u>

The following disease characteristics at study entry will be described:

- Planned Population (Early Relapse, Late Relapse, Primary Induction Failure)
- Diagnosis (B-Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, High Risk Myelodysplasia for adult arm and B-Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Blastic Plasmacytoid Dendritic Cell Neoplasm for pediatric arm)
- Time from initial diagnosis to first dose of IMP (in years) (quantitative and by category: <2 and ≥2)
- Bone Marrow Biopsy
  - Fibrosis (Yes/No)
  - Auer Rods Detected (Yes/No)
- Bone Marrow Aspiration
  - Fibrosis (Yes/No)
  - Auer Rods Detected (Yes/No)

- Blasts/Total Cells (%) at baseline (quantitative and by category: <30%, [30%-50%], >50%)
- White Blood Cell counts at baseline (quantitative and by category: Normal, Abnormal and by category: 0 to <5, 5 to <10, 10 to <20, 20 to <50, ≥50)
- Extramedullary Leukemic (Yes/No)

Prior anti-cancer therapies:

Prior anti-cancer treatments are collected by regimen in the eCRF. The following variables will be summarized:

- Number of prior regimens (quantitative and by category: 1, 2, …7 and ≥8),
- Number of prior lines (quantitative and by category: 1, 2, …7 and ≥8),

  Derivation of prior lines

  Regimens that share the same relapse/progression date will be considered as the same line of therapy. In other cases, the next regimen is a new line of therapy.
- Prior-cancer medications will also be summarized by anatomic and therapeutic levels.

Prior treatment on venetoclax:

- Last dose of venetoclax to first dose of IMP
- Reason for venetoclax discontinuation (if venetoclax was taken more than once, the reason for the last discontinuation will be presented)
- BOR among all regimens that include venetoclax
- BOR for the last regimen that includes venetoclax

Prior transplant and radiotherapy related to AML will be summarized:

- Prior transplant: number (%) of participants with at least one transplant, type of transplant (autologous, allogenic), number of transplants by participant, and time from last transplant to first IMP administration (months)
- Prior radiotherapy: number (%) of participants with any prior radiotherapy related to AML, intent, and time from last radiotherapy to first IMP administration (months)

5.3.2 Prior or concomitant medications (other than anti-cancer therapies)

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.

- Concomitant medications are any interventions received by the participant concomitantly to any IMP from the first administration of IMP to the last IMP intake +30 days. Any anti-leukemic treatment administered after the date of the last study treatment administration will not be considered as a concomitant medication and will be regarded as post anti-cancer therapy.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized on all treated population, by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on overall incidence. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Red blood cells (RBC) and platelets transfusion will be summarized on all treated population. Number (%) of participants with prior/concomitant red blood cells transfusions, with prior/concomitant platelets transfusions will be described.

Hydroxyurea administration is reported on a specific e-CRF page. Number (%) of participants with hydroxyurea administration will be summarized on all treated population by cycle.

Infusion Reaction (IR) medications are reported on a specific e-CRF page. Number (%) of participants with any IR medication will be provided. IR medications will be analyzed separately by prophylactic and curative intent.

5.3.3 Post anticancer therapies

Post anti-cancer treatments are collected by regimen in the eCRF. Number of regimens, as well as the medications, will be summarized.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

5.4.1 Missing data

The analyses of continuous and categorical variables will be based on observed data only. Percentages will be calculated using the number of participants with non-missing observation in the considered population as the denominator.

In case of incomplete or missing dates, the following rules will be applied:

Handling of missing/partial dates for disease characteristics

- If the day is missing, it will be imputed by the 1st of the month
- If the month is missing, it will be imputed by January (only for medical history variables)
- If the year is missing, no imputation will be made

Handling of missing/partial dates for medications

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Imputation of incomplete start dates for post anti-cancer treatment

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date +1
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start day will be set equal to the treatment end day +1
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date +1

Imputation of incomplete end date for prior anti-cancer treatment

For prior anti-cancer therapy, if the medication end date is missing, it will be imputed as follows:

- If the medication end day and month are missing and the medication year is before the year of first treatment dose, the medication end day/month will be set equal to 31 Dec.

- If the medication end day and month are missing and the medication year is the same as the year of first treatment dose, the medication end day/month will be set to first treatment dose - 1.
- If the medication end day is missing, the medication month is not missing and the medication year is before the year of first treatment dose, then the medication day will be set to last day of the medication month.
- If the medication end day is missing, the medication month is before the month of first treatment dose, and the medication year is the same as the year of first treatment dose, the medication day will be set to last day of the medication month.
- If the medication end day is missing, the medication month and year is the same as the month and year of first treatment dose, then medication day will be set to last day of the medication month.

Handling of adverse events with missing or partial date of onset

No imputation will be made. An AE with incomplete or missing date (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

Handling of missing ***or partial date of death***

The imputation for missing or partial death date will proceed as follows:

- If the day of the death date is missing, it will be imputed as the first day of the month, except if the date of the participant's last contact is in the same month as the death date. In this case, the death date will be imputed as the date of last contact +1 day.
- If the day and month of the death date is missing, the date of death will be imputed to the first of January of the year, except if the date of the participant's last contact is in the same year as the death date. In this case, the death date will be imputed as the date of last contact +1 day.
- If the death date is missing, it will be imputed to the last contact date.

Handling of missing assessment of relationship of adverse events to IMP

If the assessment of the relationship to the IMPs missing, the adverse event will be considered as related to the IMP in the analyses. No imputation will be done for relationship to NIMP.

Handling of parameters expressed as inequality or approximation

For safety and efficacy parameters (such as laboratory parameters), if the value is expressed as "<xx", "≤xx", the numeric value will be used (See example below).

Rule of imputation	Example of imputation		
	Character Result/Finding in Std Format (LBSTRESC)	Lower Limit of Quantitation (LBLLOQ)	Analysis Value (AVAL)
Character results including ">" are imputed by the numeric value after ">"	>3		3
Character results equal to "BELOW LOWER LIMIT" are imputed by the numeric value contained in LBLLOQ	BELOW LOWER LIMITS	0	0
Character results including "<" are imputed by the numeric value after "<"	<3		3

The rules for handling of PK and biomarker parameters are specified in Section 3.7.1 and Section 3.7.3 respectively.

Handling of missing date in duration of infusion calculation

Missing date will not be imputed, and data will be excluded from the analysis of duration of infusion.

Handling of other partial or missing dates

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month
- If day and month of the cancer diagnosis are missing, no imputation will be done

5.5 APPENDIX 5 SANOFI SPONSOR GENERIC RANGES FOR HEMATOLOGICAL AND BIOCHEMISTRY PARAMETERS

The current list of generic ranges (for adults) for hematological and biochemistry parameters (Table 9 and Table 10) are provided in tables below.

Table 9 - Generic ranges for hematological parameters

Parameter	Gender	Unit	LLN
Basophils		10^9/L	0
Eosinophils		10^9/L	0
Hematocrit	M	%	0.41
Hematocrit	F	%	0.36
Hemoglobin	F	g/L	120
Hemoglobin	M	g/L	135
Prothrombin time		INR	0.8
Platelets count		10^9/L	150
Lymphocytes		10^9/L	1
Monocytes		10^9/L	0.18
Neutrophils		10^9/L	1.8
White blood cells		10^9/L	4.5

Table 10 - Generic ranges for biochemistry parameters

Parameter	Unit	LLN	ULN
Albumin	g/L	35	55
Blood Urea Nitrogen (BUN)	mmol/L	3.6	7.1
Calcium	mmol/L	2.2	2.6
Corrected calcium	mmol/L	2.2	2.6
Glucose	mmol/L	3.9	7
Chloride	mmol/L	80	115
Potassium	mmol/L	3.5	5
Sodium	mmol/L	-136	145
Phosphate	mmol/L	1	1.4
Protein	g/L	55	80
Urea	mmol/L	3.6	7.1

6 REFERENCES

1. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27(13):2420-39.

2. Trial Design [Internet]. [cited 2021 Oct 4]. Available from: https://trialdesign.org/one-page-shell.html#BTOX

Signature Page for VV-CLIN-0645250 v2.0
tcd17197-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]