NCT: NCT06508489

16.1.9 Statistical analysis plan

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STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1/Phase 2, randomized, open-label, multi-cohort, multi-center, study assessing the safety, tolerability and preliminary efficacy of SAR443579 a natural killer cell engager (NKCE) targeting CD123, administered with different agents in participants with CD123 expressing Hematological malignancies - Master protocol**
Protocol number:	**TCD17796 - Master**
Compound number (INN/Trademark):	**SAR443579** **Not applicable**
Study phase:	**Phase 1/Phase 2**
Short title:	**A study to investigate natural killer cell engager (SAR443579) with different agents in participants with hematological malignancies – Master protocol**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**13-Aug-2025**

Regulatory agency identifier number(s):

IND:	169765
EudraCT:	2023-509438-20
NCT:	Not applicable
WHO:	Not applicable

Total number of pages:27

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VERSION HISTORY

This statistical analysis plan (SAP) for study TCD17796 is based on the protocol amendment 01 (Master) dated 09-Apr-2024.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	13-Aug-2025	Not Applicable	Original version

1 INTRODUCTION

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

1.1 STUDY DESIGN

This is a parallel, Phase 1/Phase 2, randomized, open-label, multi-cohort, multi-center study assessing the safety, tolerability and preliminary efficacy of SAR443579 with different agents for treatment in adolescent and/or adult participants with CD123 expressing hematological malignancies.

Individual sub-studies will explore SAR443579 with combination partners, either approved or investigational, whose mechanism of action (MOA) is hypothesized to favor combined use with SAR443579 or for which nonclinical studies supports the putative safety and proof of concept (POC).

For the combination partners which are approved and marketed, the dose and schedule per the approved product information will be followed, Alternate schedules may be used as per local practices and evaluated when clinically indicated. For combinations proposed with investigational products, clinical and nonclinical data from the development program has been used to support the dose and schedule of each product.

Experimental sub-studies will be tested through 3 parts:

- Part 1: dose finding (such as dose escalation/safety run-in).
- Part 2: dose optimization (when applicable).
- Part 3: dose expansion.

In each sub-study, a dose escalation following the modified toxicity probability interval 2 (mTPI-2) design or other appropriate dose-finding designs will identify preliminary recommended dose for expansion (pRDE) of SAR443579 and its respective combination partner. At least 3-6 dose-limiting toxicity (DLT) evaluable participants will be treated at each dose level (DL) in the dose escalation or safety run-in, and safety data for these participants will be reviewed by the Study Board. The DLT-evaluable population and DLT observation period are defined in the individual sub-study.

Following the determination of the preliminary RDE, additional participants will be enrolled in the dose expansion part, or if dose optimization needs to be further evaluated, additional participants will be enrolled in the “dose optimization/expansion” part. Dose optimization and dose expansion part could involve randomization depending on the specific sub-study design. Participants who are enrolled in the dose escalation/safety run-in and treated at the RDE will be included in the total number of participants for that specific cohort, if the inclusion/exclusion criteria are identical. Please refer to the individual sub-study for the specific design option.

A backfilling may then be proposed based on the data obtained in dose escalation/safety run-in. Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment-emergent adverse event [TEAE] which occurred during and after completion of DLT observation period), pharmacodynamic (PDy), pharmacokinetic (PK), and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled.

Overall safety monitoring will be performed throughout the study.

Following the determination of the RDE, additional participants will be enrolled in the dose expansion part.

In May 2025, the company decided to prematurely terminate the clinical trial TCD17796 with SAR443579. The sub-study 01 was prematurely terminated.

1.2 OBJECTIVES AND ENDPOINTS

The common objectives and endpoints are summarized below.

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the RDE of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies.	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity.
Secondary	
• To assess overall safety and tolerability profile of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To characterize the PK profile of SAR443579 in combination with other drugs if relevant (all parts).	• PK parameters of SAR443579 (C_{trough}).
• To evaluate the potential immunogenicity of SAR443579 in combination with other drugs if relevant (all parts).	• Incidence of anti-drug anti body (ADA) against SAR443579.
• To assess other indicators of antitumor activity of SAR443579 in combination with other drugs if relevant.	• Please refer to individual sub-studies for details.
Tertiary	
• For Tertiary objectives and endpoints please refer to individual sub-studies.	

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Enrolled	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not.
Exposed/safety	All screened participants who have taken at least 1 dose of study intervention regardless of the amount of study intervention administered. Participants will be analyzed according to the intervention they actually received.
Efficacy population	See the sub-study SAP for definition.
DLT-evaluable	See the sub-study SAP for definition.
Pharmacokinetic (PK)	All participants from the exposed population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times.
Pharmacodynamics (PDy)	See the sub-study SAP for definition.
ADA	See the sub-study SAP for definition.

Abbreviations: ICF = informed consent form, DLT = dose-limiting toxicity, PK = pharmacokinetics, PDy = pharmacodynamics, ADA = anti-drug antibody

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

There is no formal statistical hypothesis to be tested.

Unless otherwise specified, analyses will be performed separately for the dose finding part, dose optimization part (if applicable) and dose expansion part.

In the dose finding part, analyses will be presented by dose level and overall.

In the dose optimization part (if applicable) and dose expansion part, all analyses will be presented by cohort, unless otherwise specified.

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) unless otherwise specified.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to the first IMP administration.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

Dose escalation/safety run-in

Please refer to the individual sub-study for the definition of primary endpoints.

Dose optimization (when applicable)

Please refer to the individual sub-study for the definition of primary endpoints.

Dose expansion

Please refer to the individual sub-study for the definition of primary endpoints.

3.2.2 Main analytical approach

Dose escalation/safety run-in

Please refer to the individual sub-study for detailed analytical approach of primary endpoints.

Dose optimization (when applicable)

Please refer to the individual sub-study for detailed analytical approach of primary endpoints.

Dose expansion

Please refer to the individual sub-study for detailed analytical approach of primary endpoints.

Unless otherwise specified, descriptive statistics will be used to summarize binary, categorical and continuous variables. The 90% two-sided confidence interval (CI) computed using Clopper-Pearson method will be provided. The Kaplan-Meier method will be used to summarize time-to-event variables.

3.2.3 Sensitivity analyses

If applicable, sensitivity analyses will be described in the individual sub-study.

3.2.4 Supplementary analyses

If applicable, supplementary analyses will be described in the individual sub-study.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

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

3.3.1 Key/Confirmatory secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

Please refer to the individual sub-study for the definition of secondary efficacy endpoints.

The secondary safety endpoints include treatment-emergent AEs/SAEs including those from clinically significant laboratory abnormalities during the on-treatment period, and severity, frequency and type of infections. Other secondary endpoints include PK and immunogenicity.

3.3.1.2 Main analytical approach

Please refer to the individual sub-study for detailed analytical approach of secondary efficacy endpoints.

Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3 (laboratory abnormalities), Section 3.7.1 (PK) and Section 3.7.2 (immunogenicity).

3.4 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

If applicable, tertiary endpoints analyses will be described in the individual sub-study.

3.5 MULTIPLICITY ISSUES

Not applicable.

3.6 SAFETY ANALYSES

All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT. All other safety analyses will be performed on the safety population using descriptive statistics. No statistical testing is planned.

3.6.1 Extent of exposure

Please refer to the sub-study SAP.

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 4.

Table 4 - 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]

AE presentation	Sorting rules
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 permanent full intervention discontinuation
- Any TEAE leading to permanent partial intervention discontinuation

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for Grades ≥3.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
	PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT
Treatment-emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial intervention discontinuation	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT

Type of AE	MedDRA levels
AE leading to death[b]	Primary SOC and PT
- In context of disease progression[c]	
- In context other than disease progression[d]	
Pre-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment AE	Overview[a]
	Primary SOC and PT
TEAE leading to dose modification (including dose interruption and reduction) of any drugs, and of each drug separately	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 full intervention discontinuation
b Death as an outcome of the AE as reported by the Investigator in the AE page
c Death within 30 days from last IMP administration and the cause of death is disease progression
d 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

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

Analysis of deaths

In addition to the analyses of deaths included in Table 5 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 if collected in the death eCRF form
- 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 on-treatment 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 AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 6. 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 4.

Table 6 - Selections for AESIs and other AEs of interest

AESIs	Selection
Pregnancy	e-CRF specific pregnancy page
Symptomatic overdose (serious or nonserious) with IMP	e-CRF specific overdose page
Infusion-related reaction (IRR): Grade ≥3	e-CRF specific tick box on the AE page
CRS: Grade ≥2	CMQ00078
ICANS of any grade	CMQ40067
Tumor lysis syndrome (TLS)	CMQ00081

Listings of participants with reported overdose and reported pregnancy will be provided separately.

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 with at least one IRR
- Number (%) of participants with at least one serious IRR
- Number (%) of participants by worst grade
- 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 at 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 and conventional unit, if applicable.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, red blood cell count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), blasts
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: total protein and albumin
  - Electrolytes: sodium, potassium, phosphate and calcium corrected
  - Renal function: creatinine, blood urea nitrogen, urea.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, gamma glutamyl transferase (GGT).
  - Other: glucose, C-reactive protein (CRP), ferritin, magnesium, bicarbonate, uric acid, lactate dehydrogenase (LDH), amylase, lipase.
- Urinalysis
  - Specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
- Vital signs: heart rate, systolic and diastolic blood pressure, weight, Eastern Cooperative Oncology Group (ECOG) performance status (PS), temperature, respiratory rate
- 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 database 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 on the PK population as defined in Section 2.

3.7.1.1 Observed PK parameters

Please refer to the sub-study SAP.

3.7.1.2 Population PK analysis

Please refer to the sub-study SAP.

3.7.1.3 Analyses endpoints for PK/PD

Please refer to the sub-study SAP.

3.7.2 Immunogenicity analyses

[redacted]

3.7.3 Biomarkers analyses

[redacted]

3.8 INTERIM ANALYSES

3.8.1 Dose optimization (when applicable) and expansion stopping rule based on safety

Continuous evaluation of toxicity events will be performed throughout enrollment for each dose optimization (when applicable) and expansion cohort. Bayesian toxicity monitoring analysis (1) will be conducted to determine the stopping rule based on excessive toxicities, which are defined as deaths (other than death related to PD) within 30 days of last IMP administration or Grade 4 and above TEAEs.

The stopping boundary is the number of participants with excessive toxicities observed associated with a >80% posterior probability of true excessive toxicity rate >20% under the corresponding number of participants being evaluated.

If a stopping boundary is met, the patient enrollment will be paused. An appropriate evaluation of the cause of death and toxicity will be conducted by the Study Board, and a correction plan will be established and submitted to FDA for review prior to enrolling any new participants.

The stopping boundaries (Table 7) are determined based on the following assumptions:

- maximum probability of true excessive toxicities allowed = 0.2,
- prior distribution for excessive toxicity rate: Beta (1,1),
- minimum number of participants before early stopping rule applies = 6,
- posterior probability of excessive toxicity rate >0.2 is at least 80%.
- cohort size = 1.

Table 7 - [redacted]

[redacted]

3.8.2 Dose optimization (when applicable) and expansion stopping rule based on efficacy

No formal interim analyses (IAs) are planned. However, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the dose optimization part (when applicable) and dose expansion part of the study, eg, after 10 participants have been treated and completed the induction period or have discontinued the study intervention, whichever is earlier. Such continuous assessments will be performed for cohort(s) with clinical benefits until the planned sample size per cohort is reached. Early futility decisions by cohort may be made at any of the informal interim analysis based on the totality of data.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

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

4 SAMPLE SIZE DETERMINATION

Please refer to the individual sub-study SAP for corresponding sample size determination.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AESI:	adverse event of special interest
ASTCT:	American Society for Transplantation and Cellular Therapy
ATC:	anatomical therapeutic chemical
BUN:	blood urea nitrogen
CI:	confidence interval
CMQ:	customized MedDRA queries
CRS:	cytokine release syndrome
DL:	dose level
DLT:	dose-limiting toxicity
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
HLGT:	high-level group term
HLT:	high-level term
ICANS:	immune effector cell-associated neurotoxicity syndrome
IMP:	investigational medicinal product
IRR:	infusion-related reaction
LLN:	lower limit of normal
LLOQ:	lower limit of quantitation
LLT:	lower-level term
MedDRA:	medical dictionary for regulatory activities
MOA:	mechanism of action
mTPI-2:	modified toxicity probability interval 2
PCSA:	potentially clinically significant abnormalities
PDy:	pharmacodynamic
PK:	pharmacokinetic
POC:	proof of concept
PS:	performance status
PT:	preferred term
Q1:	Quartile 1
Q3:	Quartile 3
RDE:	recommended dose for expansion
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SMQ:	standardized MedDRA queries
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
TLS:	tumor lysis syndrome
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.

Regarding intervention discontinuation, the following definitions will be used:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of at least one of the study drugs but at least one is continued
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs

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

- Enrolled but not exposed participants
- Enrolled and exposed 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 full intervention discontinuation
- Participants who completed induction and moved in maintenance phase (if applicable)
- 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 full and/or partial intervention discontinuation will be provided.

Protocol deviations

If applicable, critical and major protocol deviations (automatic or manual) will be summarized in the exposed 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 the exposed 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 and surgical history will be coded using the MedDRA version currently in effect at Sanofi at the time of database lock.

Please refer to the individual sub-study for disease characteristics.

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 received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP from the first administration of IMP to the last IMP intake +30 days.
- Post-treatment medications are those the participant received 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 the exposed population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Infusion Reaction (IR) medications

As defined in Section 6.1.2 of the study protocol, participants will receive premedication to prevent or reduce the acute effect of IRRs.

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 8 and Table 9) are provided in tables below.

Table 8 - 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 9 - 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. Bayesian Toxicity Monitoring [Internet]. [cited 2023 Dec 14]. Available from: URL:https://trialdesign.org/one-page-shell.html#BTOX

Signature Page for VV-CLIN-0704674 v1.0
tcd17796-16-1-9-sap-master

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1/Phase 2, open-label, multi-center study, assessing the safety, tolerability and the preliminary efficacy of SAR443579 administered in combination with azacitidine + venetoclax in adult participants with CD123 expressing newly diagnosed Acute Myeloid Leukemia (ND-AML) that are ineligible for intensive chemotherapy - Substudy 01**
Protocol number:	**TCD17796-01**
Compound number (INN/Trademark):	**SAR443579** **Not applicable**
Study phase:	**Phase 1/Phase 2**
Short title:	**A study to investigate natural killer cell engager (SAR443579) in combination with azacitidine + venetoclax in adult participants with newly diagnosed acute myeloid leukemia - Substudy 01**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**13-Aug-2025**

Regulatory agency identifier number(s):

IND:	169765
EudraCT:	2023-509438-20
NCT:	Not applicable
WHO:	Not applicable

Total number of pages:27

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VERSION HISTORY

This statistical analysis plan (SAP) for study TCD17796 is based on the protocol amendment 02 (Sub-study01) dated 17-May-2024. This SAP is approved before database lock.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	13-Aug-2025	Not Applicable	Original version

1 INTRODUCTION

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

1.1 STUDY DESIGN

This is a parallel, Phase 1/2, 2-arms, open-label, controlled, dose-escalation and expansion study to determine the safety, pharmacokinetic (PK), pharmacodynamic (PDy) and preliminary efficacy of SAR443579 administered IV combined to venetoclax and azacitidine treatment in adult participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).

Study treatment consists of 3 cycles of 28 days in the Induction period, followed by up to 21 cycles of 28 days in the Maintenance/continued therapy period.

Dose-escalation part: During the dose-escalation, it is planned for approximately 3 dose levels to be tested. Participants with adverse risk cytogenetics per European Leukemia Net (ELN) 2022 criteria (1) will be enrolled in dose escalation. Escalation will start at a dose of 0.6 mg/kg SAR443579 in combination with venetoclax and azacitidine and will escalate to 1 mg/kg and 1.5 mg/kg according to the incidence of dose-limiting toxicities (DLTs) occurring within the DLT observation period using a modified toxicity probability interval 2 (mTPI-2) approach (2). Lower dose levels (DLs) may be investigated in case of excessive toxicity. The final decision will be determined by the Study Board based on evaluation of available safety data (including DLTs, adverse events [AEs] and serious adverse events [SAEs]), clinical PK and PDy. SAR443579 will be administered IV once-weekly during induction period from Cycle 1 to Cycle 3 (Days 1, 8, 15, and 22) that may be extended up to 6 cycles in case the patient didn't reach complete remission (CR)/CR with incomplete hematologic recovery (CRi)/CR with partial hematologic recovery (CRh) within the first 3 induction cycles after discussion and agreement between the Investigator and the Sponsor. Participants achieving a CR, CRi or CRh will then be transition to SAR443579 administration every 4 weeks during maintenance/continued therapy period combined with venetoclax and azacitidine up to 21 maintenance/continued therapy cycles. When supported by PK data, alternative schedules may be tested. The DLT observation period is from the first administration of study treatment until the end of the 28th day. A participant in the escalation will be considered evaluable for DLT assessment if he/she completes the DLT observation period and receive at least 75% of the planned dose of SAR443579 and 75% of the adjusted dose of venetoclax and azacitidine during that period, or if a DLT occurs during the DLT observation period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment.

A minimum of 3 DLT-evaluable participants will be treated per each DL for escalation-part. De-escalation to DL(-1) occurs if excessive toxicity is observed at DL1. Recommendations for the dose level at which the next cohort of participants may be treated will be provided by mTPI-2. However, the final decision whether to move to the next DL, or stay at the current DL, or to evaluate an alternative lower dose level will be determined by the Study Board based on evaluation of available safety data (including DLTs, AEs and SAEs), PK and PDy. If an alternative DL is chosen, a minimum of 3 participants will be enrolled in the chosen DL. Within the escalation part there will be at least 7 days between dosing of the first participant and all

subsequent participants in each dose level. [redacted] Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment-emergent adverse events [TEAE] which occurred during and after completion of DLT observation period), PDy, PK, and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled in escalation part.

At the end of escalation, a preliminary Recommended Dose(s) for Expansion (RDE) will be based on all available data including PK, PDy, preliminary efficacy, safety and tolerability of SAR443579 when combined with venetoclax and azacitidine.

Enrollment will be paused upon completion of Part 1: Dose Escalation. The available data including but not limited to safety, PK, PDy, and preliminary efficacy will be reviewed and the recommended doses and schedule for optimization will be selected by the study board.

The sub-study 01 was prematurely terminated during the dose escalation part and the dose optimization and dose expansion parts will not be initiated. Therefore, the current document will only introduce statistical analyses planned for the dose escalation part.

1.2 OBJECTIVES AND ENDPOINTS

The objectives and endpoints from the protocol are presented 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: To determine the preliminary recommended dose(s) for optimization of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Incidence of dose limiting toxicities (DLTs).
• Optimization part: To determine the RDE of SAR443579 with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity.
• Expansion part: To assess the anti-tumor activity of SAR443579 at the identified RDE combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Complete Remission (CR) rate: proportion of participants who have a CR (Complete Remission) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML.

Objectives	Endpoints
Secondary	
• To assess overall safety and tolerability profile of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for IC (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinically significant laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To assess minimal residual disease (MRD) in participants achieving a CR, CRh or CRi (expansion part).	• Percentage of participants with Minimal residual disease as defined by 2022 ELN recommendations for AML.
• To characterize the PK of SAR443579, venetoclax and azacitidine (all parts).	• PK parameters of SAR443579 (C_{trough}), venetoclax and azacitidine (C_{max} and AUC).
• To evaluate the potential immunogenicity of SAR443579 (all parts).	• Incidence of anti-drug antibody (ADA) against SAR443579.
• To assess additional parameters of antitumor activity of SAR443579 at the RDE in combination with venetoclax and azacitidine (expansion part).	• Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. (CRc = CR + CRh + CRi).
	• Overall response rate: Proportion of participants who have a CR or CRi or CRh or PR or MLFS (morphological leukemia-free state) according to the 2022 ELN criteria.
	• Duration of CR defined as the time interval from the first documented evidence of CR until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.
	• 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 as per 2022 ELN recommendations 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 as per 2022 ELN recommendations or death due to any cause, whichever comes first.

Objectives	Endpoints
	• 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 as per 2022 ELN recommendations 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. 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 (OS) defined as time interval from the 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 in combination with venetoclax and azacitidine (all parts).	• Rate of conversion from transfusion dependence to transfusion independence and rate of participants who are transfusion independent at baseline and remain independent during 56-day post-baseline period.
Exploratory/Tertiary	
• To assess levels of cytokines following treatment administration, and their relationship with safety profile and clinical outcomes.	• Assessment of blood cytokine levels at specific time points following treatment administration to evaluate potential associations of cytokine levels with safety and clinical outcomes.
• To [redacted]	• [redacted]
• [redacted]	• [redacted]

Objectives	Endpoints
• [redacted] • To determine % reduction CD123 blasts.	• [redacted] • Assessment of the kinetics of treatment-induced reduction in the % of CD123+ blasts as a pharmacodynamic marker for response to the study treatment.
• To assess the participant health-related quality of life (HRQL), disease and treatment related symptoms and impacts of symptoms (Expansion part).	• 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 participant experience with treatment (Expansion part).	• 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 - Populations for analyses

Population	Description
DLT-evaluable (escalation only)	All participants who complete the DLT observation period and receive at least 75% of the planned dose of SAR443579, and 75% of the adjusted dose of venetoclax and azacitidine during that period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment. Any participant who experiences any DLT in the DLT observation period will also be DLT evaluable.
Efficacy	All participants from the exposed population.
Pharmacodynamics (PDy)	All participants from the exposed population with at least one post-baseline PDy parameter assessed after the first dose of study intervention.
ADA	All participants from the exposed population treated with IMP with at least one post-baseline ADA result (positive, negative or inconclusive). This is also called the "immunogenicity" population.

Abbreviations: DLT = dose-limiting toxicity, PDy = Pharmacodynamics, ADA = anti-drug antibody

For additional details please refer to master SAP.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

Please refer to master SAP.

3.2 PRIMARY ENDPOINTS ANALYSIS

3.2.1 Definition of endpoints

Dose escalation

The primary endpoint is the incidence of DLTs during the DLT observation period.

The DLT observation period is from the first administration of study treatment until the end of the 28th day. A list of DLTs to be considered in the study is defined in the protocol (see Section 8.3.6 of the protocol). For analysis purposes, DLTs will be identified based on the AEs reported on the electronic case report form (eCRF) DLT page during the DLT observation period.

3.2.2 Main analytical approach

Dose escalation

All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT. Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall. Details of DLTs will be provided by the participant for DLT-evaluable population.

3.2.3 Sensitivity analyses

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 definition and main analytical approach of all secondary endpoints are described below.

3.3.1.1 Definition of endpoint(s)

Overall response rate (ORR)

The overall response rate is defined as the proportion of participants who have a response of CR, CRh, CRi, PR, or MLFS as BOR as assessed by the Investigator according to the 2022 ELN criteria.

Composite complete remission (CRc) rate

The CRc rate is defined as the proportion of participants who have a response of CR, CRh or CRi as BOR as assessed by the Investigator according to the 2022 ELN criteria.

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 ORR, CRc 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.

3.4 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

[redacted]

3.5 MULTIPLICITY ISSUES

Not applicable.

3.6 SAFETY ANALYSES

3.6.1 Extent of exposure

The extent of exposure will be summarized by descriptive statistics and summarized within the exposed population.

3.6.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of study treatment is administered.
- Duration of overall exposure (in weeks) is defined as (date of last administration - date of first administration)/7.

The date of first administration is defined by the earliest of SAR443579, venetoclax and azacitidine administration date. The date of last administration is defined as the last day of study treatment administration plus appropriate carryover days as described in subsequent sections for each treatment.

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc.). The duration of overall exposure will be summarized quantitatively.

3.6.1.2 SAR443579 exposure

The SAR443579 dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of SAR443579 exposure (in weeks) is defined depending on the SAR443579 administration schedule as follows:
  - If last dose is in induction period: [min (date of last dose +7, date of death +1) - date of first dose]/7
  - If last dose is in maintenance/continued therapy period: [min (date of last dose +28, date of death +1) - date of first dose]/7
- Actual dose (in mg/kg): for each administration, the actual dose in mg/kg corresponds to the actual dose in mg administered divided by the last available body weight up to the administration day
- Cumulative dose (in mg/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 mg/kg/week), defined as the cumulative dose divided by the duration of SAR443579 exposure (in weeks)
- Planned dose intensity (PDI, in mg/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 %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{PDI (mg/kg/week)}}$

- 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 if the start date of the current cycle - 28 days - start date of the previous cycle is ≥4 days.
- Dose delay:
  - A dose is deemed as delayed if administered >1 days beyond the theoretical treatment day in the induction period (weekly dosing).
  - A dose is deemed as delayed if administered >3 day beyond the theoretical treatment day in the maintenance/continued therapy period (monthly dosing).
  - Dose delay does not apply to the first administration of each cycle. However, it will be considered as cycle delay.
- Dose omission: a dose is omitted if not administered within the cycle as per protocol-defined window.
- 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

3.6.1.3 Venetoclax exposure

The venetoclax dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of venetoclax exposure (in weeks) is defined by [min(date of last dose +1, date of death +1) - date of first dose]/7
- Cumulative dose (in mg): the cumulative dose is the sum of all actual doses of venetoclax, given from the first to last administration
- Actual dose intensity (ADI, in mg/week): defined as the cumulative dose divided by the duration of venetoclax exposure (in weeks)
- Planned dose intensity (PDI, in mg/week): corresponds to the sum of the planned doses in each cycle started and divided by the theoretical cycle duration expressed in weeks
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

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 venetoclax exposure, cumulative dose, ADI, and RDI will be summarized quantitatively.

An individual data listing with venetoclax administration results will be provided.

3.6.1.4 Azacitidine exposure

The azacitidine dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of azacitidine exposure (in weeks) is defined depending on the azacitidine administration schedule as follows:
  - If last dose is on D7: [min (date of last dose +21, date of death +1) - date of first dose]/7
- Cumulative dose (in mg/m^2): the cumulative dose is the sum of all actual doses of azacitidine, given from the first to last administration
- Actual dose intensity (ADI, in mg/m^2/week), defined as the cumulative dose divided by the duration of azacitidine exposure (in weeks)
- Planned dose intensity (PDI, in mg/m^2/week): corresponds to the sum of the planned doses in each cycle started and divided by the theoretical cycle duration expressed in weeks

- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

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 azacitidine exposure, cumulative dose, ADI, and RDI will be summarized quantitatively.

An individual data listing with azacitidine administration results will be provided.

3.6.2 Adverse events

Please refer to master SAP.

3.6.3 Additional safety assessments

Please refer to master SAP.

3.7 OTHER ANALYSES

3.7.1 PK analyses

PK analyses will be performed on the PK population.

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

Not applicable.

3.7.1.3 Analyses endpoints for PK/PD

Not applicable.

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.

[redacted]

[redacted]



[redacted]

3.7.3.3 Relationship between CD123 expression, molecular subtype, and clinical response

The CD123 expression in several cell populations at baseline will be reported and plotted according to the clinical response group. Also, the frequency of CR/CRi/CRh will be reported according to the molecular subtype, if data will allow.

3.7.3.4 CD123+ evolution under treatment

The evolution of the absolute count and % of parent population of CD123+ cell subpopulations will be plotted along time, both in terms of the absolute value and the of relative change from baseline.

3.7.3.5 [redacted]

[redacted]

3.8 INTERIM ANALYSES

Stopping rules are defined in the master SAP.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

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

4 SAMPLE SIZE DETERMINATION

Escalation part: There is no formal sample size calculation in the escalation part. SAR443579 combined with venetoclax and azacitidine will be administered to participants with CD123 expressing ND-AML ineligible for IC. It is anticipated that approximately 3-6 DLT-evaluable participants per each DL may be enrolled in the escalation part with expected assessment of about 3 main DLs while intermediate DLs may be investigated in case of dose or schedule modifications. Approximately 9-18 participants will be enrolled in dose escalation part. The actual sample size will vary depending on dose limiting toxicities (DLTs) observed, number of DLs actually explored and the number of participants enrolled that are not DLT-evaluable.

Since the study is prematurely terminated during the dose escalation part, 7 participants were enrolled finally.

Dose escalation will proceed using the mTPI-2 design (2). Detailed operating characteristics is described in Section 5.5.

A minimum of three DLT evaluable participants will be included in the dose escalation cohort. The target toxicity rate for the candidate dose is 0.20, with the acceptable toxicity probability interval of (0.15,0.25). The decision by the study board for dose escalation/de-escalation/stay will be performed after the completion of the DLT evaluation period of the last DLT evaluable participant at each dose level. The mTPI-2 decision rules are based on calculating the unit probability mass (UPM) of intervals as following: (0, 0.05), (0, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45), (0.45, 0.55) …… (0.85, 0.95), (0.95, 1). The interval with the largest UPM will be the winning interval and implies the corresponding dose escalation decision. The winning interval with an upper limit lower than 0.15 indicates dose escalation; the winning interval being the equivalence interval (0.15,0.25) indicates staying at the current dose level; and the winning interval with a lower limit higher than 0.25 indicates dose de-escalation. The detailed mTPI-2 rules calculated with prior Beta (1/3, 1/3) are displayed in Table 4. When using Table 4, note the following:

- If the next dose level is considered to have unacceptable high toxicity, ie, the probability that the DLT rate is larger than 0.20 at the next dose is more than 0.80, then the next enrolled cohort should be kept into the last current dose and the higher dose will never be used (Decision “DU” in Table 4).
- If the current dose is the lowest dose and the rule indicates dose de-escalation, the Study Board and Sponsor will discuss if another 3 participants may be tested at this dose level.
- If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose, until at least 6 participants had been treated at the highest dose, when the determination of candidate dose(s) will be made.
- The dose-escalation will proceed in a sequential manner, starting from a minimal of 3 DLT-evaluable participants at the lower dose level, and continuing by the mTPI-2 model recommendation.

Table 4 - Dose escalation rule of the modified toxicity probability interval-2 method

Number of participants treated at current dose					
# of participants with DLT	3	4	5	6	7
0	E	E	E	E	E
1	S	E	E	E	E
2	DU	DU	DU	D	S
3	DU	DU	DU	DU	DU
4		DU	DU	DU	DU
5			DU	DU	DU
6				DU	DU
7					DU

E = Escalate to the next higher dose level.
S = Add additional participants at this dose level.
D = De-escalate to a lower dose level.
DU = Unacceptable toxicity at this dose level and no further evaluation will be made at this dose level.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA: anti-drug antibodies
ADI: actual dose intensity
AE: adverse event
CI: confidence interval
CR: complete remission
CRc: composite complete remission
CRh: complete remission with partial hematological recovery
CRi: complete remission with incomplete hematological recovery
CSR: clinical study report
CV: coefficient of variation
DL: dose level
DLT: dose-limiting toxicity
eCRF: electronic case report form
IC: intensive chemotherapy
IV: intravenous
MLFS: morphologic leukemia-free state
MTD: maximum tolerated dose
mTPI-2: modified toxicity probability interval 2
ORR: overall response rate
PDy: pharmacodynamic
PK: pharmacokinetic
PR: partial remission
RDE: recommended dose for expansion
RDI: relative dose intensity
SAE: serious adverse event
SAP: statistical analysis plan
SE: standard error

5.2 APPENDIX 2 PARTICIPANTS DISPOSITIONS

Please refer to master SAP.

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

5.3.1 Demographics, baseline characteristics, medical surgical history

For demographics and baseline characteristics, medical and surgical history, please refer to master SAP.

Disease characteristics

The following disease characteristics at study entry will be described:

- Time from initial diagnosis to first dose of study treatment (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),
- Prior-cancer medications will also be summarized by anatomic and therapeutic levels.

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

Please refer to master SAP.

5.3.3 Post anticancer therapies

Please refer to master SAP.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Please refer to master SAP.

5.5 APPENDIX 5 OPERATING CHARACTERISTICS OF THE MTPI-2 DESIGN

The escalation part will test approximately 3 main dose levels of SAR443579 in combination with azacitidine and venetoclax, starting by 0.6 mg/kg and will proceed to test 1 mg/kg and 1.5 mg/kg according to the incidence of DLTs, using a mTPI-2 approach. Specifications of the mTPI-2 are within Section 4.

The operating characteristics of the proposed mTPI-2 design were assessed via simulation using the Dose Escalation Execution Platform (DEEP) R shiny app hosted by Sanofi. As shown in Table 5, five scenarios were created representing a wide range of possible dose-toxicity situations, from "the safest" case (scenario 1) that maximum tolerated dose (MTD) is at the highest DL, to "safe" case (scenario 2), "moderate" case (scenario 3), "toxic" case (scenario 4), and "very toxic" case (scenario 5) that even the lowest DL exceed the MTD.

Table 5 - Scenarios corresponding to different dose-toxicity curves

Dose Levels	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
DL1 – 0.6 mg/kg	5%	10%	10%	**20%**	30%
DL2 – 1.0 mg/kg	10%	**15%**	**20%**	30%	40%
DL3 – 1.5 mg/kg	**15%**	**25%**	30%	40%	50%

DLT rates between 15% and 25% are in **bold**, corresponding to true MTD(s)

Based on 1000 simulations for each scenario, the probability of identifying MTD correctly and the probabilities of over-MTD and under-MTD are summarized in Table 6. Overall, this mTPI-2 design can identify MTD with good accuracy while avoiding exposing participants to excessive toxicity.

Table 6 - Summary of mTPI-2 simulation results

Scenario	Correct MTD	Over-MTD	Under-MTD	No MTD
Scenario 1	**74.0%**	0%	24.8%	1.2%
Scenario 2	**80.5%**	0%	14.4%	5.1%
Scenario 3	**39.8%**	28.8%	26.2%	5.2%
Scenario 4	**37.8%**	36.0%	0%	26.2%
Scenario 5	0%	42.3%	0%	**57.7%**

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tcd17796-16-1-9-sap-substudy01

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

STATISTICAL ANALYSIS PLAN

Protocol title:	**A Phase 1/Phase 2, open-label, multi-center study, assessing the safety, tolerability and the preliminary efficacy of SAR443579 administered in combination with azacitidine + venetoclax in adult participants with CD123 expressing newly diagnosed Acute Myeloid Leukemia (ND-AML) that are ineligible for intensive chemotherapy - Substudy 01**
Protocol number:	**TCD17796-01**
Compound number (INN/Trademark):	**SAR443579** **Not applicable**
Study phase:	**Phase 1/Phase 2**
Short title:	**A study to investigate natural killer cell engager (SAR443579) in combination with azacitidine + venetoclax in adult participants with newly diagnosed acute myeloid leukemia - Substudy 01**
Statistician:	[redacted]
Statistical project leader:	[redacted]
Date of issue:	**13-Aug-2025**

Regulatory agency identifier number(s):

IND:	169765
EudraCT:	2023-509438-20
NCT:	Not applicable
WHO:	Not applicable

Total number of pages:27

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VERSION HISTORY

This statistical analysis plan (SAP) for study TCD17796 is based on the protocol amendment 02 (Sub-study01) dated 17-May-2024. This SAP is approved before database lock.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	13-Aug-2025	Not Applicable	Original version

1 INTRODUCTION

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

1.1 STUDY DESIGN

This is a parallel, Phase 1/2, 2-arms, open-label, controlled, dose-escalation and expansion study to determine the safety, pharmacokinetic (PK), pharmacodynamic (PDy) and preliminary efficacy of SAR443579 administered IV combined to venetoclax and azacitidine treatment in adult participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).

Study treatment consists of 3 cycles of 28 days in the Induction period, followed by up to 21 cycles of 28 days in the Maintenance/continued therapy period.

Dose-escalation part: During the dose-escalation, it is planned for approximately 3 dose levels to be tested. Participants with adverse risk cytogenetics per European Leukemia Net (ELN) 2022 criteria (1) will be enrolled in dose escalation. Escalation will start at a dose of 0.6 mg/kg SAR443579 in combination with venetoclax and azacitidine and will escalate to 1 mg/kg and 1.5 mg/kg according to the incidence of dose-limiting toxicities (DLTs) occurring within the DLT observation period using a modified toxicity probability interval 2 (mTPI-2) approach (2). Lower dose levels (DLs) may be investigated in case of excessive toxicity. The final decision will be determined by the Study Board based on evaluation of available safety data (including DLTs, adverse events [AEs] and serious adverse events [SAEs]), clinical PK and PDy. SAR443579 will be administered IV once-weekly during induction period from Cycle 1 to Cycle 3 (Days 1, 8, 15, and 22) that may be extended up to 6 cycles in case the patient didn't reach complete remission (CR)/CR with incomplete hematologic recovery (CRi)/CR with partial hematologic recovery (CRh) within the first 3 induction cycles after discussion and agreement between the Investigator and the Sponsor. Participants achieving a CR, CRi or CRh will then be transition to SAR443579 administration every 4 weeks during maintenance/continued therapy period combined with venetoclax and azacitidine up to 21 maintenance/continued therapy cycles. When supported by PK data, alternative schedules may be tested. The DLT observation period is from the first administration of study treatment until the end of the 28th day. A participant in the escalation will be considered evaluable for DLT assessment if he/she completes the DLT observation period and receive at least 75% of the planned dose of SAR443579 and 75% of the adjusted dose of venetoclax and azacitidine during that period, or if a DLT occurs during the DLT observation period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment.

A minimum of 3 DLT-evaluable participants will be treated per each DL for escalation-part. De-escalation to DL(-1) occurs if excessive toxicity is observed at DL1. Recommendations for the dose level at which the next cohort of participants may be treated will be provided by mTPI-2. However, the final decision whether to move to the next DL, or stay at the current DL, or to evaluate an alternative lower dose level will be determined by the Study Board based on evaluation of available safety data (including DLTs, AEs and SAEs), PK and PDy. If an alternative DL is chosen, a minimum of 3 participants will be enrolled in the chosen DL. Within the escalation part there will be at least 7 days between dosing of the first participant and all

subsequent participants in each dose level. [redacted]. Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment-emergent adverse events [TEAE] which occurred during and after completion of DLT observation period), PDy, PK, and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled in escalation part.

At the end of escalation, a preliminary Recommended Dose(s) for Expansion (RDE) will be based on all available data including PK, PDy, preliminary efficacy, safety and tolerability of SAR443579 when combined with venetoclax and azacitidine.

Enrollment will be paused upon completion of Part 1: Dose Escalation. The available data including but not limited to safety, PK, PDy, and preliminary efficacy will be reviewed and the recommended doses and schedule for optimization will be selected by the study board.

The sub-study 01 was prematurely terminated during the dose escalation part and the dose optimization and dose expansion parts will not be initiated. Therefore, the current document will only introduce statistical analyses planned for the dose escalation part.

1.2 OBJECTIVES AND ENDPOINTS

The objectives and endpoints from the protocol are presented 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: To determine the preliminary recommended dose(s) for optimization of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Incidence of dose limiting toxicities (DLTs).
• Optimization part: To determine the RDE of SAR443579 with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity.
• Expansion part: To assess the anti-tumor activity of SAR443579 at the identified RDE combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Complete Remission (CR) rate: proportion of participants who have a CR (Complete Remission) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML.

Objectives	Endpoints
Secondary	
• To assess overall safety and tolerability profile of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for IC (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinically significant laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To assess minimal residual disease (MRD) in participants achieving a CR, CRh or CRi (expansion part).	• Percentage of participants with Minimal residual disease as defined by 2022 ELN recommendations for AML.
• To characterize the PK of SAR443579, venetoclax and azacitidine (all parts).	• PK parameters of SAR443579 (C_{trough}), venetoclax and azacitidine (C_{max} and AUC).
• To evaluate the potential immunogenicity of SAR443579 (all parts).	• Incidence of anti-drug antibody (ADA) against SAR443579.
• To assess additional parameters of antitumor activity of SAR443579 at the RDE in combination with venetoclax and azacitidine (expansion part).	• Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. (CRc = CR + CRh + CRi).
	• Overall response rate: Proportion of participants who have a CR or CRi or CRh or PR or MLFS (morphological leukemia-free state) according to the 2022 ELN criteria.
	• Duration of CR defined as the time interval from the first documented evidence of CR until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.
	• 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 as per 2022 ELN recommendations 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 as per 2022 ELN recommendations or death due to any cause, whichever comes first.

Objectives	Endpoints
	• 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 as per 2022 ELN recommendations 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. 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 (OS) defined as time interval from the 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 in combination with venetoclax and azacitidine (all parts).	• Rate of conversion from transfusion dependence to transfusion independence and rate of participants who are transfusion independent at baseline and remain independent during 56-day post-baseline period.
Exploratory/Tertiary	
• To assess levels of cytokines following treatment administration, and their relationship with safety profile and clinical outcomes.	• Assessment of blood cytokine levels at specific time points following treatment administration to evaluate potential associations of cytokine levels with safety and clinical outcomes.
• To [redacted]	• [redacted]
• [redacted]	[redacted]

Objectives	Endpoints
• [redacted] • To determine % reduction CD123 blasts.	[redacted] • Assessment of the kinetics of treatment-induced reduction in the % of CD123+ blasts as a pharmacodynamic marker for response to the study treatment.
• To assess the participant health-related quality of life (HRQL), disease and treatment related symptoms and impacts of symptoms (Expansion part).	• 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 participant experience with treatment (Expansion part).	• 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 - Populations for analyses

Population	Description
DLT-evaluable (escalation only)	All participants who complete the DLT observation period and receive at least 75% of the planned dose of SAR443579, and 75% of the adjusted dose of venetoclax and azacitidine during that period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment. Any participant who experiences any DLT in the DLT observation period will also be DLT evaluable.
Efficacy	All participants from the exposed population.
Pharmacodynamics (PDy)	All participants from the exposed population with at least one post-baseline PDy parameter assessed after the first dose of study intervention.
ADA	All participants from the exposed population treated with IMP with at least one post-baseline ADA result (positive, negative or inconclusive). This is also called the "immunogenicity" population.

Abbreviations: DLT = dose-limiting toxicity, PDy = Pharmacodynamics, ADA = anti-drug antibody

For additional details please refer to master SAP.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

Please refer to master SAP.

3.2 PRIMARY ENDPOINTS ANALYSIS

3.2.1 Definition of endpoints

Dose escalation

The primary endpoint is the incidence of DLTs during the DLT observation period.

The DLT observation period is from the first administration of study treatment until the end of the 28th day. A list of DLTs to be considered in the study is defined in the protocol (see Section 8.3.6 of the protocol). For analysis purposes, DLTs will be identified based on the AEs reported on the electronic case report form (eCRF) DLT page during the DLT observation period.

3.2.2 Main analytical approach

Dose escalation

All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT. Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall. Details of DLTs will be provided by the participant for DLT-evaluable population.

3.2.3 Sensitivity analyses

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 definition and main analytical approach of all secondary endpoints are described below.

3.3.1.1 Definition of endpoint(s)

Overall response rate (ORR)

The overall response rate is defined as the proportion of participants who have a response of CR, CRh, CRi, PR, or MLFS as BOR as assessed by the Investigator according to the 2022 ELN criteria.

Composite complete remission (CRc) rate

The CRc rate is defined as the proportion of participants who have a response of CR, CRh or CRi as BOR as assessed by the Investigator according to the 2022 ELN criteria.

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 ORR, CRc 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.

3.4 TERTIARY/EXPLORATORY ENDPOINTS ANALYSIS

[redacted]

3.5 MULTIPLICITY ISSUES

Not applicable.

3.6 SAFETY ANALYSES

3.6.1 Extent of exposure

The extent of exposure will be summarized by descriptive statistics and summarized within the exposed population.

3.6.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of study treatment is administered.
- Duration of overall exposure (in weeks) is defined as (date of last administration - date of first administration)/7.

The date of first administration is defined by the earliest of SAR443579, venetoclax and azacitidine administration date. The date of last administration is defined as the last day of study treatment administration plus appropriate carryover days as described in subsequent sections for each treatment.

The total number of cycles started, and the number of cycles started by participant will be summarized as a quantitative variable and by category (number [%] of participants receiving at least 1 cycle, at least 2 cycles, etc.). The duration of overall exposure will be summarized quantitatively.

3.6.1.2 SAR443579 exposure

The SAR443579 dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of SAR443579 exposure (in weeks) is defined depending on the SAR443579 administration schedule as follows:
  - If last dose is in induction period: [min (date of last dose +7, date of death +1) - date of first dose]/7
  - If last dose is in maintenance/continued therapy period: [min (date of last dose +28, date of death +1) - date of first dose]/7
- Actual dose (in mg/kg): for each administration, the actual dose in mg/kg corresponds to the actual dose in mg administered divided by the last available body weight up to the administration day
- Cumulative dose (in mg/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 mg/kg/week), defined as the cumulative dose divided by the duration of SAR443579 exposure (in weeks)
- Planned dose intensity (PDI, in mg/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 %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{PDI (mg/kg/week)}}$

- 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 if the start date of the current cycle - 28 days - start date of the previous cycle is ≥4 days.
- Dose delay:
  - A dose is deemed as delayed if administered >1 days beyond the theoretical treatment day in the induction period (weekly dosing).
  - A dose is deemed as delayed if administered >3 day beyond the theoretical treatment day in the maintenance/continued therapy period (monthly dosing).
  - Dose delay does not apply to the first administration of each cycle. However, it will be considered as cycle delay.
- Dose omission: a dose is omitted if not administered within the cycle as per protocol-defined window.
- 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

3.6.1.3 Venetoclax exposure

The venetoclax dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of venetoclax exposure (in weeks) is defined by [min(date of last dose +1, date of death +1) - date of first dose]/7
- Cumulative dose (in mg): the cumulative dose is the sum of all actual doses of venetoclax, given from the first to last administration
- Actual dose intensity (ADI, in mg/week): defined as the cumulative dose divided by the duration of venetoclax exposure (in weeks)
- Planned dose intensity (PDI, in mg/week): corresponds to the sum of the planned doses in each cycle started and divided by the theoretical cycle duration expressed in weeks
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

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 venetoclax exposure, cumulative dose, ADI, and RDI will be summarized quantitatively.

An individual data listing with venetoclax administration results will be provided.

3.6.1.4 Azacitidine exposure

The azacitidine dose information will be assessed by the following variables:

- Total number of cycles started by induction and maintenance/continued therapy period
- Number of cycles started per participant by induction and maintenance/continued therapy period
- Duration of azacitidine exposure (in weeks) is defined depending on the azacitidine administration schedule as follows:
  - If last dose is on D7: [min (date of last dose +21, date of death +1) - date of first dose]/7
- Cumulative dose (in mg/m^2): the cumulative dose is the sum of all actual doses of azacitidine, given from the first to last administration
- Actual dose intensity (ADI, in mg/m^2/week), defined as the cumulative dose divided by the duration of azacitidine exposure (in weeks)
- Planned dose intensity (PDI, in mg/m^2/week): corresponds to the sum of the planned doses in each cycle started and divided by the theoretical cycle duration expressed in weeks

- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/m}^2\text{/week)}}{\text{PDI (mg/m}^2\text{/week)}}$

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 azacitidine exposure, cumulative dose, ADI, and RDI will be summarized quantitatively.

An individual data listing with azacitidine administration results will be provided.

3.6.2 Adverse events

Please refer to master SAP.

3.6.3 Additional safety assessments

Please refer to master SAP.

3.7 OTHER ANALYSES

3.7.1 PK analyses

PK analyses will be performed on the PK population.

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

Not applicable.

3.7.1.3 Analyses endpoints for PK/PD

Not applicable.

3.7.2 [redacted]

[redacted]

[redacted]

[redacted]

3.7.3 Biomarkers analyses

[redacted]

[redacted]

[redacted]

[redacted]

3.7.3.3 Relationship between CD123 expression, molecular subtype, and clinical response

[redacted]

3.7.3.4 CD123+ evolution under treatment

[redacted]

3.7.3.5 [redacted]

[redacted]

3.8 INTERIM ANALYSES

Stopping rules are defined in the master SAP.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

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

4 SAMPLE SIZE DETERMINATION

Escalation part: There is no formal sample size calculation in the escalation part. SAR443579 combined with venetoclax and azacitidine will be administered to participants with CD123 expressing ND-AML ineligible for IC. It is anticipated that approximately 3-6 DLT-evaluable participants per each DL may be enrolled in the escalation part with expected assessment of about 3 main DLs while intermediate DLs may be investigated in case of dose or schedule modifications. Approximately 9-18 participants will be enrolled in dose escalation part. The actual sample size will vary depending on dose limiting toxicities (DLTs) observed, number of DLs actually explored and the number of participants enrolled that are not DLT-evaluable.

Since the study is prematurely terminated during the dose escalation part, 7 participants were enrolled finally.

Dose escalation will proceed using the mTPI-2 design (2). Detailed operating characteristics is described in Section 5.5.

A minimum of three DLT evaluable participants will be included in the dose escalation cohort. The target toxicity rate for the candidate dose is 0.20, with the acceptable toxicity probability interval of (0.15,0.25). The decision by the study board for dose escalation/de-escalation/stay will be performed after the completion of the DLT evaluation period of the last DLT evaluable participant at each dose level. The mTPI-2 decision rules are based on calculating the unit probability mass (UPM) of intervals as following: (0, 0.05), (0, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45), (0.45, 0.55) …… (0.85, 0.95), (0.95, 1). The interval with the largest UPM will be the winning interval and implies the corresponding dose escalation decision. The winning interval with an upper limit lower than 0.15 indicates dose escalation; the winning interval being the equivalence interval (0.15,0.25) indicates staying at the current dose level; and the winning interval with a lower limit higher than 0.25 indicates dose de-escalation. The detailed mTPI-2 rules calculated with prior Beta (1/3, 1/3) are displayed in Table 4. When using Table 4, note the following:

- If the next dose level is considered to have unacceptable high toxicity, ie, the probability that the DLT rate is larger than 0.20 at the next dose is more than 0.80, then the next enrolled cohort should be kept into the last current dose and the higher dose will never be used (Decision “DU” in Table 4).
- If the current dose is the lowest dose and the rule indicates dose de-escalation, the Study Board and Sponsor will discuss if another 3 participants may be tested at this dose level.
- If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose, until at least 6 participants had been treated at the highest dose, when the determination of candidate dose(s) will be made.
- The dose-escalation will proceed in a sequential manner, starting from a minimal of 3 DLT-evaluable participants at the lower dose level, and continuing by the mTPI-2 model recommendation.

Table 4 - Dose escalation rule of the modified toxicity probability interval-2 method

Number of participants treated at current dose					
# of participants with DLT	3	4	5	6	7
0	E	E	E	E	E
1	S	E	E	E	E
2	DU	DU	DU	D	S
3	DU	DU	DU	DU	DU
4		DU	DU	DU	DU
5			DU	DU	DU
6				DU	DU
7					DU

E = Escalate to the next higher dose level.
S = Add additional participants at this dose level.
D = De-escalate to a lower dose level.
DU = Unacceptable toxicity at this dose level and no further evaluation will be made at this dose level.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibodies
ADI:	actual dose intensity
AE:	adverse event
CI:	confidence interval
CR:	complete remission
CRc:	composite complete remission
CRh:	complete remission with partial hematological recovery
CRi:	complete remission with incomplete hematological recovery
CSR:	clinical study report
CV:	coefficient of variation
DL:	dose level
DLT:	dose-limiting toxicity
eCRF:	electronic case report form
IC:	intensive chemotherapy
IV:	intravenous
MLFS:	morphologic leukemia-free state
MTD:	maximum tolerated dose
mTPI-2:	modified toxicity probability interval 2
ORR:	overall response rate
PDy:	pharmacodynamic
PK:	pharmacokinetic
PR:	partial remission
RDE:	recommended dose for expansion
RDI:	relative dose intensity
SAE:	serious adverse event
SAP:	statistical analysis plan
SE:	standard error

5.2 APPENDIX 2 PARTICIPANTS DISPOSITIONS

Please refer to master SAP.

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

5.3.1 Demographics, baseline characteristics, medical surgical history

For demographics and baseline characteristics, medical and surgical history, please refer to master SAP.

Disease characteristics

The following disease characteristics at study entry will be described:

- Time from initial diagnosis to first dose of study treatment (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),
- Prior-cancer medications will also be summarized by anatomic and therapeutic levels.

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

Please refer to master SAP.

5.3.3 Post anticancer therapies

Please refer to master SAP.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Please refer to master SAP.

5.5 APPENDIX 5 OPERATING CHARACTERISTICS OF THE MTPI-2 DESIGN

The escalation part will test approximately 3 main dose levels of SAR443579 in combination with azacitidine and venetoclax, starting by 0.6 mg/kg and will proceed to test 1 mg/kg and 1.5 mg/kg according to the incidence of DLTs, using a mTPI-2 approach. Specifications of the mTPI-2 are within Section 4.

The operating characteristics of the proposed mTPI-2 design were assessed via simulation using the Dose Escalation Execution Platform (DEEP) R shiny app hosted by Sanofi. As shown in Table 5, five scenarios were created representing a wide range of possible dose-toxicity situations, from "the safest" case (scenario 1) that maximum tolerated dose (MTD) is at the highest DL, to "safe" case (scenario 2), "moderate" case (scenario 3), "toxic" case (scenario 4), and "very toxic" case (scenario 5) that even the lowest DL exceed the MTD.

Table 5 - Scenarios corresponding to different dose-toxicity curves

Dose Levels	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
DL1 – 0.6 mg/kg	5%	10%	10%	**20%**	30%
DL2 – 1.0 mg/kg	10%	**15%**	**20%**	30%	40%
DL3 – 1.5 mg/kg	**15%**	**25%**	30%	40%	50%

DLT rates between 15% and 25% are in **bold**, corresponding to true MTD(s)

Based on 1000 simulations for each scenario, the probability of identifying MTD correctly and the probabilities of over-MTD and under-MTD are summarized in Table 6. Overall, this mTPI-2 design can identify MTD with good accuracy while avoiding exposing participants to excessive toxicity.

Table 6 - Summary of mTPI-2 simulation results

Scenario	Correct MTD	Over-MTD	Under-MTD	No MTD
Scenario 1	**74.0%**	0%	24.8%	1.2%
Scenario 2	**80.5%**	0%	14.4%	5.1%
Scenario 3	**39.8%**	28.8%	26.2%	5.2%
Scenario 4	**37.8%**	36.0%	0%	26.2%
Scenario 5	0%	42.3%	0%	**57.7%**

6 REFERENCES

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