NCT03594955

STATISTICAL ANALYSIS PLAN

Protocol title:	**An open-label, first-in-human, dose escalation study of SAR440234 administered as single agent by intravenous infusion in patients with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL), or high risk myelodysplasia (HR-MDS)**
Protocol number:	**TED15138**
Compound number (INN/Trademark):	**SAR440234 (Not applicable)**
Study phase:	**Phase 1/2A**
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Statistician:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study TED15138 is the first version and is based on the amended protocol 03 dated 11 July 2019.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	Current version	Not Applicable	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is an open-label, nonrandomized, dose escalation and dose expansion, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) evaluation study of SAR440234 administered as a single agent IV infusion every week to patients ≥ 16 years of age with relapsed or refractory acute myeloid leukemia (R/R AML), high risk myelodysplastic syndrome (HR-MDS), or B-cell lymphoblastic leukemia (B-ALL).

After a screening period of up to 14 days, participants will receive treatment in one of the two The study duration for a patient will include a period for screening of up to 14 days starting from the time the patient signs the informed consent form. The cycle duration is 42 days with weekly IMP administration (except for Cycle 1 Week 1 in dose level (DL) ≥3 when 2 administrations will be given). Patients will continue study treatment as long as a clinical benefit is possible, or until disease progression, unacceptable adverse reaction, patient's decision to stop treatment, or any other reason, whichever comes first.

The study will be performed in two parts:

- Dose Escalation Part with SAR440234 as monotherapy
- Expansion Part with SAR440234 as monotherapy

Enrollment of patients in the Expansion Part will start after completion of Dose Escalation Part and indication of the MTD/RP2D.

Approximately 72 patients (67 to 77 patients) will be enrolled overall from up to 13 sites.

1.2 OBJECTIVE AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• **Dose Escalation Part**: To determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) of SAR440234 administered as a single agent in patients with R/R AML, HR-MDS, or B-ALL, and determine the recommended phase 2 dose (RP2D) for the subsequent Expansion Part. • **Expansion Part**: To assess the activity of single agent SAR440234	• **Dose Escalation Part:** Incidence of DLT observed during the first 42 days following the first administration of IMP in the first cycle of treatment. • **Dose Escalation Part:** Incidence of allergic reactions/hypersensitivity and CRS/acute infusion reactions. • **Expansion Part:** Preliminary anti-leukemia activity as defined by the IWG for MDS or AML: Overall response rate (ORR) including CR, CRi, and partial response, Duration of response, Event-free survival.

Objectives	Endpoints
at the RP2D in patients with R/R AML, or HR-MDS.	
Secondary	
• To characterize the safety profile of SAR440234 including cumulative adverse drug reactions. • To characterize the pharmacokinetic profile of SAR440234 when administered as a single agent. • To evaluate the potential immunogenicity of SAR440234. • To assess any preliminary evidence of hematologic response in the Dose Escalation Part.	• The safety profile of SAR440234 in terms of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and changes in laboratory parameters, vital signs, electrocardiograms (ECGs), and assessment of physical examination. • Pharmacokinetic parameters of SAR440234: Concentration observed at the end of IV infusion, maximum concentration observed (Cmax), time to reach Cmax, last concentration observed above the lower limit of quantification, time of the last concentration observed above the lower limit of quantification (ie, Clast), concentration observed just before treatment administration during repeated dosing, area under the plasma concentration versus time curve (area under the curve (AUC)) calculated using the trapezoidal method from time zero to Clast, AUC calculated using the trapezoidal method from time zero to infinity, AUC calculated using the trapezoidal method over the dosing interval (7 days). • Incidence rate of anti-drug antibody (ADA, ie, anti-SAR440234 antibody) development. • In the Dose Escalation Part, preliminary anti-leukemia activity as defined by IWG for MDS or AML, or NCCN for B-ALL.
Exploratory	

• To perform pharmacodynamic assessments on blood and bone marrow including:
  • To measure CD123 expression in malignant cells and kinetics of this expression under treatment.
  • To monitor CD123 expression on normal cells.
  • To assess minimal residual disease (MRD) in patients achieving a complete response (CR) or complete response with incomplete hematological recovery (CRi), and correlate MRD with clinical outcome.
  • To assess T-cell subpopulations (eg, CD4, CD8) and activation status.
	• Assessment of CD123 expression in cells in the peripheral blood and bone marrow aspirate. Percentage of CD123-expressing cells may be a pharmacodynamic biomarker for response to the IMP.
	• Monitoring of T-cell subpopulations (eg, CD4, CD8) and activation status in the peripheral blood and bone marrow aspirate.
	• Minimal residual disease by molecular biology assessment and/or flow cytometry will be assessed in bone marrow from patients achieving a CR or CRi and correlated with clinical outcome.
	• Assessment of plasma cytokine levels in blood at specific time points following treatment administration to evaluate potential associations of cytokine levels with safety and clinical outcomes.

Objectives	Endpoints
• To investigate the relationship between CD123 expression, disease molecular subtype (as defined by marker expression, cytogenetics, and/or genomics) and parameters of clinical response. • To assess levels of cytokines following treatment administration, and their relationship with safety profile and clinical outcome. To explore other indicators of antitumor activity.	

2 SAMPLE SIZE DETERMINATION

It is anticipated that approximately 72 patients (67 to 77 patients) will be enrolled in this study (Dose Escalation and Expansion Parts).

Dose Escalation Part

It is anticipated that approximately 30 to 40 DLT-evaluable patients will be entered in the Dose Escalation Part. The actual sample size will vary depending on DLTs observed and number of dose levels actually explored.

Any patient who is not evaluable for DLT, ie, who discontinues the study treatment before the end of Cycle 1 for any reason other than DLT, or who did not receive treatment as planned, will be replaced.

Expansion Part

It is hypothesized that SAR440234 would induce a response rate of 40% and that the null hypothesis for ORR is 20%. Under these hypotheses and using a Simon 2-stage design (optimal), with a 1-sided 10% significance level and a power of 90%, it is planned to enroll 37 patients in the Expansion Part of the study. Eleven (11) responses out of 37 patients will be necessary to reject the null hypothesis (H0 response rate = 20%).

An interim analysis of the ORR will be done after treatment of the first 17 patients through 2 cycles. If 3 or fewer responses (CR, CRi, or PR) are observed, the Expansion Part will be stopped due to futility.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who have given their informed consent.
All-treated	All participants from the screened population and exposed to the investigational drug, regardless of the amount of treatment administered.
Efficacy	All participants from the all-treated population with at least one post-baseline evaluable disease assessment allowing status evaluation.
DLT-evaluable	All participants in the dose escalation part, who have received at least 5 out of 6, weekly IV administrations of SAR440234 in DL1 and DL2, or at least 6 out of 7 IV administrations of SAR440234 in DL≥3. Patients who discontinue the IMP before completion of Cycle 1 because of a DLT will also be included in the DLT-evaluable population. Patient who discontinues the study treatment before the end of Cycle 1 for another reason than DLT will be replaced.
Pharmacokinetic (PK)	All participants from the all-treated population with at least one drug concentration post-baseline (whatever the cycle and even if dosing is incomplete).
ADA	All participants from the all-treated population with at least 1 available ADA result (positive, negative or inconclusive) post-baseline.
Biomarker	All participants from exposed population with at least one valid assessment for: • CRP or ferritin, or • Cytokines, or • Disease molecular subtype, or • immunophenotyping by flow cytometry, or • MRD.

For any participant enrolled and treated more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation, median, 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 administration of SAR440234. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Unless otherwise specified, analyses will be performed by part, by dose level (if applicable) and overall (if applicable).

All efficacy analyses will be performed on the efficacy population. Objective response rate, as well as all other efficacy variables will be derived using the Investigator's assessment.

All safety analyses will be performed on the all-treated population.

Analysis period

The analysis period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period from when the participants give informed consent up to first administration of IMP.
- 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, ie, 31 days after the last administration of IMP.

4.2 PARTICIPANT DISPOSITIONS

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

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

Permanent intervention discontinuation is defined as the discontinuation of SAR440234.

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

- Exposed participants
- Participants who did not complete the study period and main reason for study discontinuation.

In addition, the number (%) of participants screened, screened-failed, enrolled, with permanent intervention discontinuation will be provided by country and site.

Protocol deviations

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

4.3 PRIMARY ENDPOINT(S) ANALYSIS

No primary efficacy endpoint will be analyzed due to early termination of the clinical trial. Primary safety endpoints analyses are defined in Section 4.7.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

No secondary efficacy endpoint will be analyzed due to early termination of the clinical trial. Other secondary endpoints analyses are defined in Section 4.7 (safety), Section 4.8.1 (PK) and Section 4.8.2 (immunogenicity).

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Tertiary endpoints analyses are defined in Section 4.8.3 (biomarkers).

4.6 MULTIPLICITY ISSUES

No formal testing will be performed. Therefore, no multiplicity issues need to be addressed.

4.7 SAFETY ANALYSES

The analysis of the safety variables will be essentially descriptive, and no testing is planned.

4.7.1 Extent of exposure

4.7.1.1 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 any study interventions is administered.
- Duration of IMP exposure (in weeks) is defined as (Last day of exposure – first day of exposure +1)/7.
  - The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (SAR440234).
  - The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the last administration date + 7 days for SAR440234.

Overall study treatment exposure will be presented in a listing along with the overall number of cycles started.

4.7.1.2 SAR444245 exposure

The dose information will be assessed by the following:

- Cumulative dose for SAR440234 (ng/kg): the cumulative dose is the sum of all doses from cycle 1 day 1 up to treatment discontinuation
- Actual dose intensity (ng/kg/week) for SAR440234:

  ADI = Cumulative dose (ng/kg) / Overall duration of exposure in weeks
- Planned dose intensity (ng/kg/week) for SAR440234:

  PDI = Total planned dose (ng/kg) / Overall duration of exposure in weeks

  The total planned dose for SAR440234 will be calculated by the sum of the theoretical planned dose (ie, the intended dose as per CRF) over the duration of treatment.
- The relative dose intensity (RDI, in %) for SAR440234 is defined as

$$\text{Relative Dose Intensity} = \left(\frac{\textit{Actual Dose Intensity}}{\textit{Planned Dose Intensity}}\right) \times 100$$

  It is an indicator of the feasibility of the chosen schedule of administration.

A listing will be provided for cumulative dose, actual dose intensity and relative dose intensity.

Dose or cycle modifications

- Cycle delay: A cycle is deemed to have been delayed if start date of the current cycle – start date of previous cycle >42 days.
- Dose delay: A dose is deemed to have been delayed if the infusion is made >1 day later than the scheduled administration.
- Dose omission: A dose is considered to be omitted if the dose is not administered at the scheduled visit and 1 or more doses are given afterwards.
- Dose interruption: An infusion is considered to be interrupted if the administration is stopped before the infusion is completed, regardless of whether or not the infusion is restarted.
- Dose reduction: a dose is deemed to have been reduced if the dose taken by a patient is lower than 80% of the intended dose.
- Reason for dose reduction.

Dose information variables will be provided in a listing:

- Cycle/day of occurrence
- Dose reduction Y/N
- Dose omission Y/N
- Dose interruption Y/N
- Cycle delay Y/N

4.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be 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.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs reported 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 focus of AE reporting 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. If the grade is missing for 1 of the treatment-emergent occurrences of an AE, the grade will be imputed with the maximal severity of the other occurrences. If the grade is missing for all the occurrences, the 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, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the AE incidence.
b The table of all TEAEs presented by 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 TEAEs with the details below will be generated:

- Any TEAE
- Any grade ≥3 TEAE
- Any treatment emergent SAE
- Treatment related TEAEs (overall and for each individual drug)
- Treatment related TEAEs of Grade ≥ 3 (overall and for each individual drug)
- Serious treatment related TEAEs (overall and for each individual drug)
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period)
- Any TEAE leading to permanent partial intervention discontinuation (for each individual drug)

- Any TEAE leading to permanent full 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, HLT and PT Primary SOC and PT
TEAE related to IMP (overall and for each drug) as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP (overall and for each drug) 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 (for each individual drug)	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pre-treatment AE	Primary SOC and PT
Post-treatment AE	Primary SOC and PT
TEAE leading to dose interruption	Primary SOC and PT
TEAE leading to dose modification (including dose reduction, dose omission and cycle delay, excluding dose interruption)	Primary SOC and PT

Analysis of deaths

Deaths will be analyzed through a listing with following information:

- Death date
- Study period
- Reason of death
- For AE with fatal outcome: PT, date of onset, relationship

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. Listings with PT and grade will be provided.

Table 6 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
DLT during cycle 1	e-CRF specific DLT page
Pregnancy of a female participant as well as pregnancy occurring in a female partner of a male participant	e-CRF specific pregnancy page
Symptomatic overdose with IMP/NIMP	e-CRF specific tick box in overdose page
CRS	e-CRF specific category in AE page

Further analyses of Cytokine release syndrome (CRS) with a listing providing a more detailed description of CRS by patient:

- Action taken
- Relationship to IMP according to Investigator's opinion
- Number of episodes
- Onset of first occurrence CRS (at the first infusion and subsequent infusions)
- Day of onset from infusion (by category 1 day/ 2 to 3 days/ More than 3 days when applicable)
- Duration (in days) (by category 1 day/ 2 to 3 days/ More than 3 days)

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

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

- Hematology
  - **Hemoglobin and coagulation**: hemoglobin, prothrombin time (PT), activated partial thromboplastin time, fibrogen, D-dimer and international normalized ratio (INR)
  - **Platelet count**
  - **White blood cells**: white blood cells (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, leukocytes
  - **Hematocrit**
  - **Blasts**
- Biochemistry
  - **Electrolytes**: sodium, potassium, calcium, phosphate, bicarbonate/carbon dioxide, albumin, protein, magnesium
  - **Renal function**: serum creatinine, estimated creatinine clearance by Cockcroft-Gault formula, blood urea nitrogen (BUN), uric acid

  - **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT), total and direct bilirubin

- Urinalysis
  - **Qualitative urinalysis**: protein, glucose, pH
- Pregnancy: urine, serum
- Serology: hepatitis B virus surface antigen, hepatitis C virus antibody
- Pro-inflammatory cytokines, CRP, and ferritin
- Cytogenetic/FISH data collection
- Vital signs: heart rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, weight, body surface area (BSA), temperature and ECOG PS (0, 1, 2, 3, 4).
- ECG

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 (ULOQ) will be replaced by ULOQ value.

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

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

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version specified in the protocol.

Analyses according to NCI CTCAE 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).

In addition, for basophils, eosinophils, monocytes, creatinine clearance, eGFR, hematocrit, uric acid, PH, uric acid, blood urea nitrogen, potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

For laboratory variables above, vital signs and ECG variables, 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 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.

4.8 OTHER ANALYSES

4.8.1 PK analyses

Pharmacokinetic parameters of SAR440234 will be analyzed under the responsibility of Sanofi, Pharmacokinetics, Dynamics and Metabolism (PKDM) department. Pharmacokinetic parameters will be determined by non-compartmental analysis using PKDMS V3.1 (running Phoenix software).

The PK parameters will include, but may not be limited to the following:

Parameters	Definition/calculation
C_{eoi}	Concentration observed at the end of intravenous infusion
C_{max}	Maximum concentration observed
t_{max}	Time to reach C_{max}
C_{last}	Last concentration observed above the lower limit of quantification
t_{last}	Time of the last concentration observed above the lower limit of quantification (ie, C_{last})
C_{trough}	Concentration observed just before treatment administration during repeated dosing
AUC_{last}	Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to time of the last concentration observed above the lower limit of quantification (ie, C_{last})
AUC	Area under the concentration versus time curve calculated using the trapezoidal method from time zero to time infinity according to: $AUC = AUC_{last} + C_{last}/\lambda z$ where λz is the slope of the regression line of the observed terminal phase of the concentration versus time curve, in semi-logarithmic scale
AUC_{0-T}	Area under the concentration versus time curve calculated using the trapezoidal method during a dosing interval (T)

Descriptive statistics (arithmetic mean, standard deviation, geometric mean, coefficient of variation (%), median, minimum and maximum) for concentrations and PK parameters of SAR440234 as well as associated plots will be provided by Sanofi, PKDM.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics.

4.8.2 Immunogenicity analysis

The immunogenicity of SAR440234 will be presented for all patients through an individual listing of immunogenicity sample results (positive, negative or inconclusive) together with the associated titer, C_{trough} value, the immunogenicity status of the patient and associated characterization of the immune response (transient, persistent, indeterminate) for positive ones.

The impact of positive immune response will be evaluated on pharmacokinetic, and safety endpoints when relevant.

Participant's ADA status

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA sample.
  - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
  - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample during the TE period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

Kinetics of ADA response

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

- **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.

- **Duration of ADA response** is defined as the 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 summarized only for participants with persistent ADA response.
  - A positive sample (boosted positive sample for participants with pre-existing ADA) occurring after the TE period will be considered as treatment-induced/boosted ADA if a previous treatment-induced/boosted ADA occurred during the TE period and less than 16 weeks before this sample.
- **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample is not treatment-induced/boosted.
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

ADA response variable:

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.

4.8.3 Biomarker analyses

Plasma levels of pro-inflammatory cytokines, including interleukin-6 and interferon-γ, as well as blood levels of 2 acute phase proteins, C-reactive protein (CRP) and ferritin, will be assessed during the trial.

Several immune populations and sub-populations will be assessed through immunophenotyping performed on blood and bone marrow samples. Different panels will be investigated such as the blasts, the plasmacytoid dendritic cells and basophils, the T cells, and the NK cells, granzyme B and interferon-γ, as well as analysis of T cell functional status including frequency of Tregs (CD4+CD25+CD127-) and expression of activation markers such as PD-1 and CD25.

All biomarkers will be summarized by dose level at baseline and over time by using descriptive statistics. For cytokines, the number of values below the LLOQ will be provided and for the computation of summary statistics, LLOQ/2 will be used to impute the test results with below LLOQ (BLOQ, ie, value<LLOQ).

4.9 INTERIM ANALYSES

Not applicable due to early termination of the clinical trial.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1: LIST OF ABBREVIATIONS

ADA: anti-drug antibody
ADI: actual dose intensity
AE: adverse event
AESIs: adverse events of special interest
ALT: alanine aminotransferase
AST: aspartate aminotransferase
AUC: area under the curve
B-ALL: B-cell acute lymphoblastic leukemia
BUN: blood urea nitrogen
CR: confirmed response
CRF: case report form
CRi: complete response with incomplete hematologic recovery
CRS: cytokine release syndrome
DL: dose level
DLT: dose limiting toxicity
ECG: electrocardiogram
eCRF: Electronic case report form
FISH: fluorescence in situ hybridization, Eastern Cooperative Oncology Group
GGT: gamma glutamyl transpeptidase
HLT: high level term
HR-MDS: high risk myelodysplastic syndrome
IMP: investigational medicinal product
INR: international normalized ratio
IV: intravenous
IWG: International Working Group
LDH: lactate dehydrogenase
LLT: lower-level term
MAD: maximum administered dose
MDS: myelodysplastic syndrome
MedDRA: medical dictionary for regulatory activities
MRD: minimal residual disease
MTD: maximum tolerated dose
NCCN: National Comprehensive Cancer Network
NIMP: non-investigational medicinal product
ORR: overall response rate
PD: pharmacodynamic
PDI: planned dose intensity
PK: pharmacokinetic
PR: partial response
PT: preferred term

R/R AML:	relapsed or refractory acute myeloid leukemia
RDI:	relative
RP2D:	recommended phase 2 dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
WBC:	white blood cells
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2: CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

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

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 (([16-18],[19-24],[25-40],[41-60],[61-75], ≥78)
- gender (Male, Female)
- race:
  - White
  - Black
  - Asian
  - Native Hawaiian or Other Pacific Islander
  - American Indian or Alaska Native
  - Not reported
  - Unknown
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)
- weight (kg)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) at baseline

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes relevant history of previous pathologies and smoking status. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Specific disease characteristics at diagnosis includes:

- Time from initial diagnosis of disease (AML, Leukemia/Myelodysplasia or B-ALL) to first study treatment administration (in years),
- Diagnosis type,
- Among patients with AML diagnosis:
  - Staging
  - Risk Group
  - FLT3-ITD mutation (Yes, No, Unknown)
  - NPM1 mutation (Yes, No, Unknown)
  - IDH2 mutation (Yes, No, Unknown)
- Among patients with B-ALL diagnosis:
  - Staging
  - Risk Group

Concomitant medications

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.

- Concomitant medications are any interventions received by the participant 14 days prior to registration of the study, or at any time during the study in addition to the IMP.

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

Anticancer therapies

- Prior anti-cancer therapies

  Prior anti-cancer treatments are collected by regimen in the eCRF. The following variables will be collected/derived and presented in a listing:

  - Intent of prior anti-cancer therapy as collected in eCRF
  - If conditioning therapy, transplant (Yes, No)

- If yes, type of transplant (allogeneic or autologous)

- Number of prior lines of treatment in advanced setting.
- Reason for discontinuation of the last regimen
- Best response to the last regimen
- Time from last progression date to first study drug administration (months)
- Time from start of last prior anti-cancer therapy (last regimen start date) up to last progression (months)
- Duration of last prior anti-cancer therapy (last regimen end date - last regimen start date) (months)

- Prior surgery: listing providing information on any prior surgery related to cancer, type of procedure (Preferred Term) and time from the last surgery to the first study treatment administration (months)
- Prior radiotherapy: listing providing information on any prior radiotherapy related to cancer, intent, intent of last prior radiotherapy, time from the last radiotherapy to the first study treatment administration (months) overall and by intent (curative and palliative) and location of prior radiation therapy by intent

5.4 APPENDIX 4: DATA HANDLING CONVENTIONS

Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, ECG and ADA will be used for computation of baseline, the worst on-treatment value, analysis according to PCSAs/NCI grade, and the shift summaries for safety.

6 REFERENCES

Not applicable

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