NCT03594955

AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: SAR440234

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)

STUDY NUMBER: TED15138

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OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, Version
Amended Protocol 03	All	29 August 2019, Version number: 2 (electronic 8.0)
Amended Protocol 03	All	11 July 2019, Version number: 1 (electronic 7.0)
Amended Protocol 02	All	15 February 2019, Version number: 1 (electronic 6.0)
Amended Protocol 01	All	29 May 2018, Version number: 1 (electronic 4.0)
Amendment 01	All	29 May 2018, Version number: 1 (electronic 4.0)
Original Protocol	All	22 November 2017, Version number: 1 (electronic 2.0)

Amended protocol 03 (29-Aug-2019)

This amended protocol (Amendment 3) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amended protocol is to replace the first 3 patients treated during the Dose Escalation Part because of uncertainties in the doses that they received and to restart the study at dose level 1 using a 3+3 design, following resolution of the full clinical hold.

In addition, minor editorial corrections (especially for consistency and clarity) have been made.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Tabular Summary "Statistical Considerations", Section 6.3, Section 11.2, and Section 13.1.1	The following sentence has been added: The first 3 patients treated during the Dose Escalation Part will be replaced. Another 3 patients will be enrolled in dose level 1 and the trial will proceed according to the 3+3 design.	Text was added to clarify that the first 3 patients treated during the Dose Escalation Part will be replaced because abnormalities were detected in their pharmacokinetic profiles. These findings suggest that these patients may have received unintentional overdoses of SAR440234 on some occasions. Data from these patients will be used as part of the safety database but will not be used for dose escalation decision.

Section # and Name	Description of Change	Brief Rationale
Section 6.2.1	The following text was modified: Within a dose level, subsequent patients will initiate treatment at least 1 week after the first patient in that dose level started treatment with SAR440234.	Clarification to be consistent with Clinical Trial Summary.
Tabular Summary, Sections 6.2.1, Section 6.2.2, and Table 3	The following text was modified: ~~Two~~ A 3+3 dose escalation scheme ~~(accelerated in DL1 and DL2), then 3 + 3 escalation (DL ≥3)~~ will be used, based on DLTs observed during the first 42 days following the first administration of IMP in the first cycle (the DLT observation period).The goal is to treat ~~1 patient~~ 3 patients per dose level ~~at DL1 and DL2 (accelerated part) unless any Grade 2 or higher AE occurs, in which case 3 patients will be included~~ in order to follow a 3 + 3 design~~.~~ ~~DL3 to DL8 will include 3 patients per dose level.~~	To improve the ability to detect safety signals accurately, the Dose Escalation Part will now follow a 3+3 trial design, rather than an accelerated design.
Section 13.3.2	The following sentence has been added: The first 3 patients treated will be excluded from the DLT-evaluable population.	[redacted]
Flow Chart Table 1.2.1, Table 1.2.2, Table 1.2.3, and Table 1.2.4	The following sentence has been added to the footnote concerning SAR440234 administration: Specific details about SAR440234 preparation and administration are provided in the Pharmacy Manual.	Text was added to draw attention to the importance of referring to the Pharmacy Manual regarding details of SAR440234 preparation and administration.
Throughout	Correction of formatting, typographical errors and standardization of wording.	To increase clarity

CLINICAL TRIAL SUMMARY

COMPOUND: SAR440234	STUDY No: TED15138
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)
INVESTIGATOR/TRIAL LOCATION	United States (US), European Union (EU), Asia
PHASE OF DEVELOPMENT	Phase 1/2A
STUDY OBJECTIVES	**Primary objectives:** • 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 at the RP2D in patients with R/R AML, or HR-MDS. **Secondary objectives:** • 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. **Exploratory objectives:** 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. • 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.

STUDY DESIGN	This Phase 1/2A study is an open-label, nonrandomized, dose escalation and dose expansion, safety, efficacy, pharmacokinetic, and pharmacodynamic evaluation study of SAR440234 administered as a single agent intravenous (IV) infusion every week to patients ≥16 years of age with R/R AML, HR-MDS, or B-ALL. ***Dose Escalation Part*** The administration of the investigational medicinal product (IMP) will begin at 1 ng/kg, representing the selected safe starting dose for a first-in-human (FIH) trial, based on the Minimal Anticipated Biological Effect Level (MABEL), and by integration of all available in vivo and in vitro data at the start of the study. A 3+3 dose escalation scheme will be used, based on dose-limiting toxicities (DLTs) observed during the first 42 days following the first administration of the first cycle of treatment. Adverse events (AEs) will be graded according to the National Cancer Institute (NCI) common terminology criteria (CTC) for AEs (NCI-CTCAE) v4.03, except for cytokine release syndrome (CRS), which will be graded according to the 2014 NCI Consensus Guidelines. In this FIH study, potential DLTs are defined as the following: • Any Grade ≥3 nonhematological AE, unless either caused by disease progression or obviously unrelated cause or caused by a laboratory abnormality without associated clinical consequences that resolves within 5 days (AE's related to cytopenias that were present prior to starting SAR440234 or to underlying leukemia will not be considered DLT's). • Grade 4 hematological toxicities, ie, new onset or worsening of life-threatening hematological abnormalities after administration of SAR440234. (AE's related to cytopenias that were present prior to starting SAR440234 or to underlying leukemia will not be considered DLT's.): - Grade 4 bone marrow hypocellularity, if not caused by disease progression and not improved to baseline value or Grade ≤1 within 14 days, - Grade 4 decreased neutrophils, if not present at baseline and not resolved to baseline value or Grade ≤1 within 14 days, - Grade 4 febrile neutropenia not resolved within 7 days, - Grade 4 decreased platelet count, if not present at baseline and not improved to baseline value or Grade ≤1 within 14 days, - Grade 4 anemia, if not improved to baseline value or Grade ≤1 within 14 days. • Grade 3 or Grade 4 CRS. • Grade 2 CRS if it persists for >48 hours or is present <48 hours before the time when the next planned dose of SAR440234 is due. • Any treatment-emergent adverse event (TEAE) that, in the opinion of the Principal Investigator and Sponsor, is of potential clinical significance such that further dose escalation would expose patients to unacceptable risk. • IMP-related adverse reaction (unless caused by disease progression or an obviously unrelated cause) lasting more than 2 weeks with failure to recover to baseline or improve to Grade ≤1. The occurrence of DLTs will inform the dose recommendation that will be used during the Expansion Part.

Response assessment will be performed according to the International Working Group (IWG) 2003 recommendations for AML, the revised 2000 criteria for HR-MDS and the 2016 National Comprehensive Cancer Network (NCCN) Guidelines for ALL.

If at the end of a cycle the patient exhibits clinical benefit by symptoms or response criteria and does not meet study treatment discontinuation criteria, the patient may continue therapy until an unacceptable AE, disease progression, patient's decision to stop the treatment, or any other reason.

To minimize the risk of severe CRS, an intra-patient dose escalation in Cycle 1 is proposed, as shown in Table 1. Lead-in doses include the first 2 doses in Dose Level (DL) 1 and DL2 (ie, Week 1 and Week 2 administered doses), the first 3 doses in DL3 to DL5, and the first 4 doses in DL6 to DL8. After the lead-in doses, each patient will receive a fixed dose until the end of treatment, unless the dose needs to be decreased for safety reasons. DL1 to DL8 will achieve a range of lead-in doses from [redacted] and a range of final doses from [redacted]. During Cycle 1 and Cycle 2, pharmacokinetic and pharmacodynamic data will be collected that will be used, together with acute safety monitoring, to inform the choice of subsequent dose levels for both the Dose Escalation Part and the Expansion Part.

Table 1

Dose Level	Cycle 1 (doses in ng/kg)						
	W1		W2	W3	W4	W5	W6
	D1	D4	D8	D15	D22	D29	D36
DL1	[redacted]						
DL2							
DL3							
DL4							
DL5							
DL6							
DL7							
DL8							

D=Day, W=Week

For subsequent cycles, patients will maintain the maximum weekly dose that they achieved in Cycle 1, as shown in Table 2.

Table 2

Dose Level	Cycle ≥2 (doses in ng/kg)					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
DL1	[redacted]					
DL2						
DL3						
DL4						
DL5						
DL6						
DL7						
DL8						

	Dose-limiting toxicity The DLT observation period is 42 days from the first administration of IMP in the first cycle, with administration on Day 1, Day 4 (DL ≥3), Day 8, and weekly thereafter. A new dose level may begin after the DLT observation period of the previous dose level is finished. The goal is to treat 3 patients per dose level in order to follow a 3 + 3 design. DL3 to DL8 will include 3 patients per dose level. In the event of a DLT, the dose level will be expanded to a total of 6 patients, who will be treated at the same dose level that the DLT occurred (3 + 3 design). If 1 of the 6 patients experience an IMP-related DLT at the dose level, the dose escalation will proceed with 3 patients per dose level. If ≥2 of 6 patients experience an IMP-related DLT, the MAD has been reached and the dose escalation will be stopped. **Inclusion of B-ALL patients** At any DL ≥3, patients with B-ALL (see inclusion criterion I 01) may also be recruited in the Dose Escalation Part. **Study continuation** The duration of each cycle of treatment is 42 days, with weekly administration of IMP (except for Cycle 1 Week 1 in DL ≥3 when 2 administrations will be given). In the Dose Escalation Part, at the end of Cycle 1, 43 days after the first SAR440234 infusion, a patient may begin Cycle 2 provided he or she did not experience a DLT. The dose given in the second or subsequent cycles will be the last dose given in the previous cycle. If severe toxicity occurs, dose reduction, omission, treatment delay, and/or treatment discontinuation are planned (details are provided in Section 6.5). A Study Committee, including the main Investigators, Sponsor clinical team, and ad hoc experts, when appropriate, will regularly review the safety data, and will make recommendations as appropriate. Additional (optional) cohort(s) beyond DL8, or intermediate dose levels, may be evaluated; the decision to proceed with these optional cohort(s), however, will be discussed with the Study Committee and based on the available safety, exploratory, and pharmacokinetic data. **Maximum tolerated dose** The MTD will be defined as the highest dose level at which no more than 1 patient of a maximum of 6 patients experienced an IMP-related DLT. ***Expansion Part*** The Study Committee will decide the RP2D, including the recommended lead-in dose and schedule, for the Expansion Part in R/R AML and HR-MDS patients. The expected total enrollment for the Expansion Part is 37 patients, all treated at the RP2D, to evaluate further the safety, pharmacokinetics, and possible disease response.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Confirmed diagnosis of primary or secondary AML (any subtype except acute promyelocytic leukemia) according to World Health Organization (WHO) classification, or myelodysplastic syndrome (MDS) with a revised International Prognostic Scoring System (R-IPSS) risk category of intermediate or higher. Patients must have exhausted available treatment options and must not be eligible for any treatment known to provide clinical benefit.

	I 02. Patients with AML must have relapsed or refractory disease that has been resistant to available therapies, as defined by any 1 of the following criteria: - Leukemia refractory to ≥2 intensive remission induction attempts, - Leukemia in first relapse within 1 year following allogeneic stem cell transplant, - Leukemia in second or higher relapse, - Not eligible for intensive remission induction therapy and have persistent leukemia despite ≥2 cycles of therapy, including any of the following: hypomethylating agent (eg, decitabine or 5-azacitidine), chemotherapy, or targeted agents (eg, gemtuzumab ozogamicin or enasidenib). I 03. During the Dose Escalation Part, patients with B-ALL without extramedullary lesions, in second or subsequent relapse, may also be recruited at any DL ≥3 during the 3 + 3 escalation period. B-ALL patients should have completed previously ≥1 cycle of a salvage regimen, including any of the following: chemotherapy, blinatumomab, tyrosine kinase inhibitors, cellular therapy (eg, tisagenlecleucel), or targeted agents (eg, inotuzumab ozogamicin). Patients must have exhausted available treatment options and must not be eligible for any treatment known to provide clinical benefit. I 04. Patients with HR-MDS must have >10% blasts in the bone marrow at the time of enrollment and fit one of the following categories: - Not eligible for induction therapy and having completed ≥2 cycles of therapy, including any of the following: hypomethylating agent (eg, 5-azacitidine or decitabine), chemotherapy, or targeted agents. - Not eligible for allogeneic stem cell transplant and having completed ≥1 course of induction therapy. I 05. Signed written informed consent. **Exclusion criteria:** E 01. Age <16 years old. E 02. Eastern Cooperative Oncology Group (ECOG) performance status >2. E 03. Abnormal laboratory parameters, including the following: - Total bilirubin >1.5 x upper limit of normal (ULN), unless Gilbert's syndrome is present, - Alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase >2.5 x ULN, - Serum creatinine >2 x ULN and/or creatinine clearance <30 mL/min, - Grade 4 hematological toxicity: febrile neutropenia, bone marrow hypocellularity, symptomatic disseminated intravascular coagulation, life-threatening anemia, or life-threatening thrombotic thrombocytopenic purpura, - White blood cell count > 30,000/mm^3. - If the white blood count exceeds 30,000/mm^3, hydroxyurea may be used to reduce the white blood cell count to < 30,000/ mm^3 at start of treatment.

	- Hydroxyurea may be administered at the investigator's discretion during Cycle 1, but must be stopped ≥1 day prior to Cycle 2, Day 1.
	E 04. Graft-versus-host disease following allogeneic stem cell transplantation requiring treatment with more than 10 mg of oral prednisone or equivalent daily. The stem cell transplant and/or donor lymphocyte infusion should have been performed more than 3 months before study treatment start.
	E 05. History of an active or chronic autoimmune condition that has required or requires therapy.
	E 06. Prior treatment with an anti-CD123-directed agent.
	E 07. Second primary malignancy that requires active therapy. Adjuvant hormonal therapy is allowed.
	E 08. Previous treatment with chemotherapy, radiotherapy, or immunotherapeutic agents in the 4 weeks prior to IMP administration (Cycle 1 Day 1), except for hydroxyurea.
	E 09. Previous treatment with any other investigational agent in the 4 weeks prior to IMP administration (Cycle 1 Day 1).
	E 10. Receiving at the time of first IMP administration concurrent steroids >10 mg/day of oral prednisone or the equivalent for $\geq$3 months, except steroid inhaler, nasal spray or ophthalmic solution.
	E 11. Requirement for tocilizumab for any other diagnosis within $\leq$14 days before the first administration of SAR440234.
	E 12. Known contraindication to any of the noninvestigational medicinal products (NIMPs) (dexamethasone and tocilizumab), acetaminophen, diphenhydramine, ranitidine, montelukast or similar agents.
	E 13. Evidence of active central nervous system leukemia at the time of enrollment.
	E 14. Known acquired immunodeficiency syndrome (AIDS-related illnesses) or HIV disease requiring antiretroviral treatment, or having active hepatitis A, B or C infection, or tuberculosis.
	E 15. Pregnant and breast-feeding women, female patients of childbearing potential, and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2 barrier method or 1 barrier method with a spermicide, intrauterine device, or hormonal contraception with inhibition of ovulation, for 2 weeks prior to the first dose of SAR440234, during treatment, and 12 weeks after the last dose of study treatment). A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile.
	E 16. Any country-related specific regulation that would prevent the patient from entering the study.
	E 17. Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results.
	E 18. Patients weighing <60 kg (DL1, DL2, and DL3 only).

Total expected number of patients	It is expected that a total of 67 to 77 patients will be enrolled. It is anticipated that 30 to 40 patients will be enrolled in the Dose Escalation Part, and up to 37 patients will be enrolled in the Expansion Part.
Expected number of sites	Up to 4 sites in the Dose Escalation Part, in France and the United States. Up to 14 sites in the Expansion Part in Europe, the United States, and Asia.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation:**	**SAR440234** The drug product is presented as a lyophilisate powder for solution for IV injection at [redacted] The concentration [redacted] after reconstitution with water for injection.
Route of administration:	IV
Dose regimen:	SAR440234 will be administered IV every 7 days (except for Cycle 1 Week 1 in DL ≥3 when 2 administrations will be given) for a 42-day cycle. Cycles run consecutively so that Day 1 of each cycle is normally 7 days after the start of the last infusion in the previous cycle. The dosing regimen will be weight-based; however, if a patient weighs >140 kg, the patient's weight will be capped at 140 kg for dose calculations. The patient may continue to receive therapy provided he or she continues to have clinical benefit and does not meet the stopping criteria. The dose is defined by dose level rule during the Dose Escalation Part and by the selected dose in the Expansion Part. During the Dose Escalation Part, escalation to the next dose level cohort will occur after the last patient has completed the DLT observation period for the previous dose level. Within a dose level, subsequent patients will initiate treatment at least one week after the first patient in that dose level started treatment with SAR440234.
Noninvestigational medicinal products **Formulation:**	**Dexamethasone:** 4 mg/mL for IV injection. **Tocilizumab:** 200 mg/10 mL vial Montelukast: 10 mg tablets
Routes of administration:	IV (dexamethasone), IV (tocilizumab), oral (montelukast)
Dose regimen:	Dexamethasone 20 mg IV will be instituted as systematic premedication 4 hours and 1 hour prior to each IMP administration. Montelukast 10 mg oral (PO) will be given once, 4 hours before the start of SAR440234 infusion. Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. This rule will be applied for the same patient who experienced a CRS event for subsequent infusions and for all patients subsequently enrolled at that dose level or higher. For each patient treated, the clinical site must have at least 2 full doses of tocilizumab in the clinical pharmacy ready for immediate administration in case of CRS Grade 2 or above. For patients with Grade 2 CRS, tocilizumab will be administered at 8 mg/kg infused over 1 hour for patients weighing ≥30 kg (maximum dose 800 mg) or 12 mg/kg infused over 1 hour for patients weighing <30 kg. If there is insufficient improvement in CRS within 12 hours, tocilizumab may be repeated at the same dose every 12 hours for a total of 3 doses.

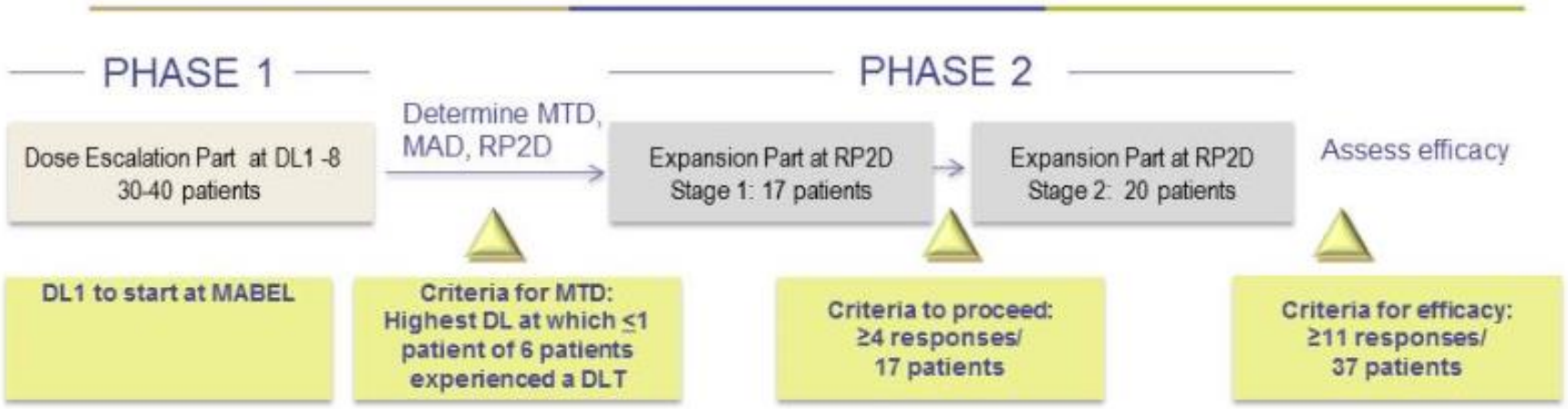
	Tocilizumab must not be used for prophylaxis of CRS. Patients with Grade 3 or Grade 4 CRS should be treated with tocilizumab as for patients with Grade 2 CRS. For patients with Grade 3 or Grade 4 CRS who do not respond to tocilizumab within 24 hours, dexamethasone 10 mg IV should be given every 6 hours.
ENDPOINTS	**Primary endpoints:** With an objective of defining the RP2D and dose schedule, the safety of SAR440234 will be evaluated using the following assessments during the Dose Escalation Part: • Incidence of DLT observed during the first 42 days following the first administration of IMP in the first cycle of treatment. • Incidence of allergic reactions/hypersensitivity and CRS/acute infusion reactions. In the Expansion Part, disease response for R/R AML and HR-MDS will be an additional primary endpoint: • 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. **Secondary endpoints:** • The safety profile of SAR440234 in terms of 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 (C_{max}), time to reach C_{max}, last concentration observed above the lower limit of quantification, time of the last concentration observed above the lower limit of quantification (ie, C_{last}), concentration observed just before treatment administration during repeated dosing, area under the plasma concentration versus time curve (AUC) calculated using the trapezoidal method from time zero to C_{last}, 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 endpoints:** • 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.

ASSESSMENT SCHEDULE	See Section 1.2
STATISTICAL CONSIDERATIONS	**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. The first 3 patients treated during the Dose Escalation Part of TED15138 will be replaced. Another 3 patients will be enrolled in DL1 and the trial will proceed according to the 3+3 design. *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. **Analysis population:** The DLT-evaluable population in the Dose Escalation Part will include all patients who have received at least 5 out of 6, weekly IV administrations of SAR440234 in DL1 and DL2, patients who have received at least 6 out of 7 IV administrations of SAR440234 in DL ≥3, and patients who discontinue the IMP before completion of Cycle 1 because of a DLT. The all-treated/safety population for both Dose Escalation and Expansion Parts of the study will include all patients who have given their informed consent and who have received at least 1 dose (even incomplete) of SAR440234. Response evaluable patients are defined as patients from the all-treated/safety population with at least 1 post-baseline evaluable disease assessment allowing status evaluation. The ADA (ie, anti-SAR440234 antibody) population will include all patients from the all-treated/safety population with at least 1 available ADA result after IMP administration. The pharmacokinetic population will include patients from the all-treated/safety population with at least 1 evaluable drug concentration after IMP administration (whatever the cycle and even if incomplete). **Safety and dose escalation primary analysis:** DLTs occurring during the DLT observation period will be analyzed in the DLT-evaluable population. Adverse events meeting DLT criteria occurring at any additional cycle will be assessed and analyzed in the all-treated/safety population. Pharmacokinetic parameters will be summarized with descriptive statistics. Dose proportionality and accumulation will also be assessed on relevant parameters in the pharmacokinetic population. The safety profile will be summarized for all the treated patients, as well as separately, in the Dose Escalation Part and Expansion Part.

	Efficacy analyses in the expansion cohort The ORR and other efficacy will be summarized using descriptive statistics. A 95% 2-sided confidence interval will be computed for ORR using the Clopper-Pearson method.
DURATION OF STUDY PERIOD (per patient)	The duration of the study for a patient will include a period for screening of up to 14 days. The cycle duration is 42 days. After study treatment discontinuation, patients will return to the study site 30 days after the last IMP administration for end of treatment assessments. Patients may continue treatment with the IMP as long as clinical benefit is possible, or until disease progression, unacceptable adverse reaction, patient's decision to stop treatment, or other reason for discontinuation. During the follow-up period, IMP-related AEs and all SAEs (regardless of relationship to study treatment) present at the time of study treatment discontinuation will be followed every month until resolution or stabilization, or until initiation of another antineoplastic therapy. Patients without documented disease progression at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with monthly follow-up visits until initiation of another anti-cancer therapy, disease progression, study cut-off date, or death, whichever comes first. The first cut-off date will be at the end of the first cycle of the last patient treated in the Dose Escalation Part in order to have at least the first cycle evaluable for all patients for determination of the MTD and for the RP2D. The second cut-off date will be when the last patient in the Expansion Part will have been treated for 2 cycles (approximately 3 months), or has early progression, whichever occurs first, in order to assess tumor response. After the second cut-off date, ongoing patients will receive study treatment until disease progression or occurrence of an AE leading to treatment discontinuation, whichever is earlier, and they will only be followed for study treatment administration, SAEs, study treatment-related AEs, and reason for end of treatment.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



H_0=overall response rate ≤20%
H_1=overall response rate ≥40%
Abbreviations: DL (dose level), MABEL (minimum anticipated biological effect level), MTD (maximum tolerated dose), MAD (maximum administered dose), RP2D (recommended phase 2 dose), DLT (dose limiting toxicity), ORR (overall response rate).

1.2 STUDY FLOW CHARTS

1.2.1 Dose Escalation Part: Screening and Treatment Cycle 1

Evaluation [a]	Screening	Treatment Cycle 1																			
		Week 1				Week 2				Week 3			Week 4			Week 5			Week 6			
	D-14 to D-1	D1[b]	D2, D3	D4	D5, D6, D7	D8	D9	D10, D11	D12, D13, D14	D15	D16, D17, D18	D19, D20, D21	D22	D23, D24, D25	D26, D27, D28	D29	D30, D31, D32	D33, D34, D35	D36	D37, D38, D39	D40, D41	D42
Inclusion/Exclusion criteria	X																				
Demographics and Medical/ Disease History	X																				
Disease assessment																					
Bone marrow aspiration/biopsy[c,d]	X																				X
Blood hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunophenotyping (blood and bone marrow)[f]	X																				X
Extramedullary leukemic localizations[g]	X	X																			X[v]
Minimal residual disease[h]	X																				X
Other clinical assessments																					
ECOG PS, Body Weight, Height (only baseline)	X	X				X				X			X			X			X			X[v]
Physical examination[i]	X	X				X				X			X			X			X			X[v]
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other laboratory tests																					
Coagulation[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[l]	X	X	X	X	X[m]	X	X	X		X	X		X	X		X	X		X	X		X[v]
Serum or urine pregnancy test[n]	X																					

Evaluation [a]	Screening	Treatment Cycle 1																				
		Week 1				Week 2				Week 3			Week 4			Week 5			Week 6			
	D-14 to D-1	D1[b]	D2, D3	D4	D5, D6, D7	D8	D9	D10, D11	D12, D13, D14	D15	D16, D17, D18	D19, D20, D21	D22	D23, D24, D25	D26, D27, D28	D29	D30, D31, D32	D33, D34, D35	D36	D37, D38, D39	D40, D41	D42
Urinalysis[o]	X																					
12-lead ECG	X																					
Cytogenetic/FISH	X																					
Pharmacokinetics	See Pharmacokinetics/Pharmacodynamics Flow-Charts																					
Anti-drug antibodies	See Pharmacokinetics/Pharmacodynamics Flow-Charts																					
Cytokines[p]	See Pharmacokinetics/Pharmacodynamics Flow-Charts																					
CRP/ferritin[q]	See Pharmacokinetics/Pharmacodynamics Flow-Charts																					
SAR440234 administration[r]		D1[b]		D4[m]		D8				D15			D22			D29			D36			
Hospitalization[s]		X	X	X	X[m]	X	X	X		X	X		X	X		X	X		X	X		
AE assessment[t]	X	Continuous																				
Prior/concomitant medication[u]	X	Continuous																				
Disease status																						X

a **Evaluation:** Any specific procedures should be performed after informed consent is signed. The informed consent can be signed >14 days prior to the first administration of SAR440234. Assessments should be performed prior to administration of SAR440234 unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose.

b **Day 1*: Cycle 1 Day 1*** refers to the day the patient receives the initial dose of SAR440234.

c **Bone marrow biopsy** must be performed at baseline.

d **Bone marrow aspiration** will be performed at baseline for morphology (% of blasts) and immunophenotyping, and on Day 42 (±2 days) for evaluation of disease status (morphology, immunophenotyping). Additional bone marrow aspirate shall be performed as clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, or anemia Grade 4 occurs with onset in >14 days before or after Day 42.

e **Blood hematology:** Must be performed daily during Cycle 1. Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count.

f **Immunophenotyping** of the peripheral blood and bone marrow is required at baseline and on Day 42 (±2 days) (to assess CD123- expression and to monitor T-cell subpopulations and activation status).

g **Extramedullary leukemic localizations at physical examination:** Evaluation for hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, as clinically indicated, and any other examinations as clinically indicated to be performed to assess disease status at baseline.

h **MRD assessment:** The modalities of MRD evaluation should be identified and a baseline level of disease involvement should be determined from the Screening bone marrow aspirate. MRD evaluation will be performed on the bone marrow if the patient enters CR or CRi. If MRD is positive, the MRD assessment will be repeated on subsequent bone marrow evaluations, or as clinically indicated.

i **Physical examination**: Examination of major body systems, including cardiovascular, respiratory, neurologic, and digestive.

j **Vital signs:** Temperature, blood pressure, heart rate, respiration rate, and oxygen saturation 5 minutes before starting infusion, 0.5 hours after the start of infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then daily. During infusion, vital signs must be monitored as follows: temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate every 30 minutes. For each patient treated, the hospital must have an available bed in the ICU in case the patient develops hemodynamic or respiratory compromise. The ICU should be staffed by a critical care physician who has experience in treating cytokine release syndrome. In addition, the ICU must have the necessary equipment to commence immediate treatment and monitoring of a patient with CRS Grade ≥2 before he/she is admitted to ICU. Vital signs monitoring shall be made continuously if CRS Grade ≥2 develops. Specific guidance on monitoring of vital signs during CRS are provided in Section 6.7.

k **Coagulation:** Must be performed daily during Cycle 1. PT/INR, aPTT, fibrinogen (and D-dimer at Screening).

l **Blood chemistry:** *Liver tests*: SGOT (AST), SGPT (ALT), GGT, total bilirubin, direct bilirubin, AP. *Renal function tests and electrolytes*: Sodium, potassium, calcium, magnesium, phosphorus, bicarbonate, BUN, creatinine, and estimated creatinine clearance (Cockcroft-Gault formula), uric acid. Others: LDH, albumin, and total protein. *Serology at screening*: testing for active hepatitis B virus, and hepatitis C virus infection. Patients should be monitored every 8 hours after the start of drug administration and for at least 72 hours after the end of infusion for signs and symptoms of tumor lysis: serum creatinine, potassium, calcium, magnesium, phosphorus, and uric acid. Blood chemistry will also be rechecked 8 hours or less prior to each administration of SAR440234.

m **Additional assessments/Administration of SAR440234/Hospitalization**: Only for patients treated in Dose Level ≥3.

n **Serum or urine pregnancy test:** Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to the initial dose of study treatment.

o **Urinalysis:** Dipstick for pH, protein, glucose, at baseline, then as clinically indicated and at EOT.

p **Plasma cytokines (including interleukin-6 and interferon-γ):** will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional sample will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.

q **CRP/ferritin:** will be collected at the same time points as cytokines.

r **SAR440234 administration:** Systematic prophylactic premedication with dexamethasone 20 mg IV 4 and 1 hour prior to infusion of SAR440234 and montelukast 10 mg oral (PO) 4 hours prior to infusion are required. Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. Specific instructions for the preparation and administration of SAR440234 are provided in the Pharmacy Manual.

s **Hospitalization:** Patients will be hospitalized for the duration of the SAR440234 infusion (1 to 19 hours), and for 72 hours after completion of each subsequent infusion. For DL ≥3, patients will be hospitalized continuously from Day 1 of Week 1 until 72 hours after completion of the third infusion, ie, for 11 days.

t **Adverse event assessment:** The period of observation for collection of adverse events extends from the signature of the ICF until 30 days after the last administration of the SAR440234. Serious adverse events, AESIs, pregnancy, and overdose reports should be assessed and reported as described in the protocol. SAEs and ongoing treatment-related AEs should be followed beyond EOT until resolution or stabilization.

u **Concomitant medication assessment:** The period of collection of concomitant medications extends from the signature of the ICF until EOT, and post EOT if associated with ongoing SAEs or ongoing treatment-related AEs.

v **The investigations and test scheduled for Day 42** may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion. If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment.

Abbreviations: AE=adverse event, AESI=adverse events of special interest, ALT=alanine aminotransferase, AML=acute myeloid leukemia, ANC=absolute neutrophil count, AP=alkaline phosphatase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CD123=cluster of differentiation 123, CR=complete response, CRi=complete response with incomplete count recovery, CRP=C-reactive protein, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, FISH=fluorescent in situ hybridization, GGT=gamma glutamyl transferase, ICF=informed consent form, ICU=intensive care unit, INR=international normalized ratio, LDH=lactate dehydrogenase, MRD=minimal residual disease, PO=oral, PT=prothrombin time, SAE=serious adverse event, SGOT=serum glutamate-oxalate transferase, SGPT=serum glutamate-pyruvate transferase.

1.2.2 Dose Escalation Part: Treatment Cycle 2 and Subsequent, End of Treatment, and Follow-up

Evaluation [a]	Treatment Cycle 2 and Subsequent													EOT[b]	FU[c]
	Week 1			Week 2		Week 3		Week 4		Week 5		Week 6			
	D1[d]	D2, D3, D4	D5, D6, D7	D8	D9, D10, D11	D15	D16, D17, D18	D22	D23, D24, D25	D29	D30, D31, D32	D36	D37, D38, D39	D42		
Disease assessment																
Bone marrow aspiration[e]														X[f]		
Blood hematology[g]	X	X[f]	X[f]	X		X		X		X		X		X[w]	X	
Immunophenotyping (blood and bone marrow)[h]														X	X	
Extramedullary leukemic localizations[i]	X													X[w]	X	
Minimal residual disease[j]														X		
Other clinical assessments																
ECOG PS, Body Weight	X			X		X		X		X		X		X[w]	X	
Physical examination[k]	X			X		X		X		X		X		X[w]	X	
Vital signs[l]	X	X		X	X	X	X	X	X	X	X	X	X	X[w]	X	
Other laboratory tests																
Coagulation[m]	X			X		X		X		X		X		X[w]	X	
Blood chemistry[n]	X	X[f]		X	X[f]	X		X		X		X		X[w]	X	
Serum or urine pregnancy test[o]															X	
Urinalysis[p]															X	
12-lead ECG															X	
Pharmacokinetics	See Pharmacokinetics/Pharmacodynamics Flow-Charts															
Anti-drug antibodies	See Pharmacokinetics/Pharmacodynamics Flow-Charts															

Evaluation [a]	Treatment Cycle 2 and Subsequent														EOT[b]	FU[c]
	Week 1			Week 2		Week 3		Week 4		Week 5		Week 6				
	D1[d]	D2, D3, D4	D5, D6, D7	D8	D9, D10, D11	D15	D16, D17, D18	D22	D23, D24, D25	D29	D30, D31, D32	D36	D37, D38, D39	D42		
Cytokines[q]	See Pharmacokinetics/Pharmacodynamics Flow-Charts															
CRP/ferritin[r]	See Pharmacokinetics/Pharmacodynamics Flow-Charts															
SAR440234 administration[s]	D1			D8		D15		D22		D29		D36				
Hospitalization[t]	X	X[f]		X	X[f]	X		X		X		X				
AE assessment[u]	Continuous														X	
Concomitant medication[v]	Continuous															
Disease status[w]														X	X	X

a **Evaluation:** Assessments should be performed prior to administration of SAR440234 (end of the previous cycle) unless otherwise indicated, at the end of the patient's participation in the trial, and at follow-up. Results should be reviewed by the Investigator prior to the administration of the next dose.

b **End of treatment (within 30 days after the last administration of SAR440234):** Obtain end of treatment assessments. If the patient does not plan to return for an EOT visit, the EOT evaluation must be performed on the day that the decision is made that the patient will discontinue SAR440234.

c **Post-study follow-up** for disease status, IMP-related AEs, and SAEs: Patients without documented disease progression at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with monthly follow-up visits until initiation of another anti-cancer therapy, disease progression, study cut-off date, or death. If the patient is unable to attend monthly study visits, the investigator must obtain study follow up information via telephone call and record review from the patient's treating physicians.

d **Day 1:** Cycles run consecutively so that Day 1 of each cycle is normally 7 days after the start of the last infusion in the previous cycle.

e **Bone marrow aspiration** will be performed for morphology (% of blasts) on Day 42 (±2 days) of Cycle 2 for evaluation of disease status. Subsequent bone marrow aspirates will be performed when clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, anemia Grade 4 occurs with onset in >14 days before or after Day 42.

f **Cycle 2 assessments**: Not required during Cycle 3 and subsequent cycles, unless clinically indicated. If the patient discontinues SAR440234 prior to the end of cycle 2, the day 42 assessments must be performed on the day that the decision is made that the patient will not continue SAR440234.

g **Blood hematology:** Daily during Week 1 of Cycle 2, then weekly thereafter (on IMP administration days and on Day 42). Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count. If the patient discontinues SAR440234 prior to the end of cycle 2, the day 42 assessments must be performed on the day that the decision is made that the patient will not continue SAR440234.

h **Immunophenotyping** of the peripheral blood and bone marrow is required on Day 42 (±2 days) of Cycle 2 (to assess CD123- expression and to monitor T-cell subpopulations and activation status). Bone marrow aspiration is not required for immunophenotyping at the end of subsequent cycles and at EOT unless clinically indicated; the test will be done using blood.

i **Extramedullary leukemic localizations at physical examination:** Evaluation for hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, as clinically indicated.

j **MRD assessment:** MRD evaluation will be performed on the bone marrow if the patient enters CR or CRi. If MRD is positive, the MRD assessment will be repeated on subsequent bone marrow evaluations, or as clinically indicated.

k **Physical examination**: Examination of major body systems, including cardiovascular, respiratory, neurologic, and digestive.

l **Vital signs**: Temperature, blood pressure, heart rate, respiration rate, and oxygen saturation 5 minutes before starting infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then as clinically indicated at least until 72 hours from the start of the infusion. During infusion, vital signs must be monitored as follows: temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate every 30 minutes. Specific guidance on monitoring of vital signs during CRS are provided in Section 6.7.

m **Coagulation:** PT/INR, aPTT, fibrinogen.

n **Blood chemistry:** *Liver tests*: SGOT (AST), SGPT (ALT), GGT, total bilirubin, direct bilirubin, AP. *Renal function tests and electrolytes*: Sodium, potassium, calcium, magnesium, phosphorus, bicarbonate, BUN, creatinine, and estimated creatinine clearance (Cockcroft-Gault formula), uric acid. Others: LDH, albumin, and total protein. Patients should be monitored every 8 hours after the start of drug administration and for at least 72 hours after the end of the Week 1 and Week 2 infusions of Cycle 2 only, for signs and symptoms of tumor lysis: serum creatinine, potassium, calcium, magnesium, phosphorus, and uric acid. Blood chemistry will also be rechecked 8 hours or less prior to each administration of SAR440234.

o **Serum or urine pregnancy test:** Women of childbearing potential must have a negative serum or urine pregnancy test result at the end of study evaluation (Day 30 of the last cycle).

p **Urinalysis:** Dipstick for pH, protein, glucose, at baseline, then as clinically indicated and at EOT.

q **Plasma cytokines (including interleukin-6 and interferon-γ)** will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional sample will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.

r **CRP/ferritin:** will be collected at the same time points as cytokines.

s **SAR440234 administration:** Systematic prophylactic premedication with dexamethasone 20 mg IV 4 and 1 hour prior to infusion of SAR440234 and montelukast 10 mg oral (PO) 4 hours prior to infusion are required. Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. Specific instructions for the preparation and administration of SAR440234 are provided in the Pharmacy Manual.

t **Hospitalization:** During Cycle 2, patients will be hospitalized for the duration of each of the first 2 SAR440234 infusions (1 to 19 hours), and for 72 hours after completion. If the patient has tolerated the first 2 infusions during Cycle 2, the patient will be hospitalized only for the duration of each subsequent infusion (1 to 19 hours). During subsequent cycles, patients must be hospitalized only for the duration of infusion.

u **Adverse event assessment:** The period of observation for collection of adverse events extends from the signature of the ICF until 30 days after the last administration of SAR440234. Serious adverse events, AESIs, pregnancy, and overdose reports should be assessed and reported as described in the protocol. SAEs and ongoing treatment-related AEs should be followed beyond EOT until resolution or stabilization.

v **Concomitant medication assessment:** The period of collection of concomitant medications extends from the signature of the ICF until EOT, and post EOT if associated with ongoing SAEs or ongoing treatment-related AEs.

w **Disease status:** The treating physician will collect monthly the patient's disease status (CR, CRi, stable disease, relapse, or progressive disease) until the patient dies or starts new anti-neoplastic therapy, to collect either the date of progressive disease or the initiation of further antitumor therapy.

w **The investigations and test scheduled for Day 42** may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion. If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment.

Abbreviations: AE=adverse event, AESI=adverse events of special interest, ALT=alanine aminotransferase, AML=acute myeloid leukemia, ANC=absolute neutrophil count, AP=alkaline phosphatase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, B-ALL=B-cell acute lymphoblastic leukemia, BUN=blood urea nitrogen, CD123=cluster of differentiation 123, CR=complete response, CRi=complete response with incomplete count recovery, CRP=C-reactive protein, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, EOT=end of treatment, FU=follow-up, GGT=gamma glutamyl transferase, ICF=informed consent form, INR=international normalized ratio, LDH=lactate dehydrogenase, MRD=minimal residual disease, PO=oral, PT=prothrombin time, SAE=serious adverse event, SGOT=serum glutamate-oxalate transferase, SGPT=serum glutamate-pyruvate transferase.

1.2.3 Expansion Part: Screening and Treatment Cycle 1

Evaluation[a]	Screen-ing	Treatment Cycle 1																			
		Week 1				Week 2			Week 3			Week 4			Week 5			Week 6			
	D-14 to D-1	D1[b]	D2, D3	D4	D5, D6, D7	D8	D9, D10, D11	D12, D13, D14	D15	D16, D17, D18	D19, D20, D21	D22	D23, D24, D25	D26, D27, D28	D29	D30, D31, D32	D33, D34, D35	D36	D37, D38, D39	D40, D41	D42
Inclusion/Exclusion criteria	X																				
Demographics and Medical/ Disease History	X																				
Disease assessment																					
Bone marrow aspiration/biopsy[c]	X																				X
Blood hematology[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunophenotyping (blood and bone marrow)[e]	X																				X
Extramedullary leukemic localizations[f]	X	X																			X[x]
Minimal residual disease[g]	X																				X
Other clinical assessments																					
ECOG PS, Body Weight, Height (only baseline)	X	X				X			X			X			X			X			X[x]
Physical examination[h]	X	X				X			X			X			X			X			X[x]
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other laboratory tests																					
Coagulation[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry[k]	X	X	X	X	X[l]	X	X		X	X		X	X		X	X		X	X		X[x]
Serum or urine pregnancy test[m]	X																				

Evaluation[a]	**Screen-ing**	**Treatment Cycle 1**																			
		Week 1				Week 2			Week 3			Week 4			Week 5			Week 6			
	D-14 to D-1	D1[b]	D2, D3	D4	D5, D6, D7	D8	D9, D10, D11	D12, D13, D14	D15	D16, D17, D18	D19, D20, D21	D22	D23, D24, D25	D26, D27, D28	D29	D30, D31, D32	D33, D34, D35	D36	D37, D38, D39	D40, D41	D42
Urinalysis[n]	X																				
12-lead ECG	X																				
Cytogenetic/FISH	X																				
Pharmacokinetics	See Pharmacokinetics/Pharmacodynamics Flow-Charts																				
Anti-drug antibodies	See Pharmacokinetics/Pharmacodynamics Flow-Charts																				
Cytokines[o]	See Pharmacokinetics/Pharmacodynamics Flow-Charts																				
CRP/ferritin[p]	See Pharmacokinetics/Pharmacodynamics Flow-Charts																				
SAR440234 administration[q]		D1[a]		D4[l]		D8			D15			D22			D29			D36			
Hospitalization[r]		X	X	X	X[l]	X	X		X	X		X	X		X	X		X	X		
AE assessment[s]	X	Continuous																			
Prior/concomitant medication[t]	X	Continuous																			
Disease status																					X

a **Evaluation:** Any specific procedures should be performed after informed consent is signed. The informed consent can be signed >14 days prior to the first administration of SAR440234. Assessments should be performed prior to administration of SAR440234 unless otherwise indicated. Results should be reviewed by the Investigator prior to the administration of the next dose.

b **Day 1*: Cycle 1 Day 1*** refers to the day the patient receives the initial dose of SAR440234.

c **Bone marrow aspiration** will be performed at baseline for morphology (% of blasts) and immunophenotyping, and on Day 42 (±2 days). Additional bone marrow aspirate shall be performed as clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, anemia Grade 4 occurs with onset in >14 days before or after Day 42.

d **Blood hematology:** Must be performed daily during Cycle 1. Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count.

e **Immunophenotyping** of the peripheral blood and bone marrow is required at baseline and on Day 42 (±2 days) (to assess CD123- expression and to monitor T-cell subpopulations and activation status).

f **Extramedullary leukemic localizations at physical examination:** Evaluation for hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, as clinically indicated, and any other examinations as clinically indicated to be performed to assess disease status at baseline.

g **MRD assessment:** The modalities of MRD evaluation should be identified and a baseline level of disease involvement should be determined from the Screening bone marrow aspirate. MRD evaluation will be performed on the bone marrow if the patient enters CR or CRi. If MRD is positive, the MRD assessment will be repeated on subsequent bone marrow evaluations, or as clinically indicated.

h **Physical examination**: Examination of major body systems, including cardiovascular, respiratory, neurologic, and digestive.

i **Vital signs:** Temperature, blood pressure, heart rate, respiration rate, and oxygen saturation 5 minutes before starting infusion, 0.5 hours after the start of infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then daily. During infusion, vital signs must be monitored as follows: temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate every 30 minutes. For each patient treated, the hospital must have an available bed in the ICU in case the patient develops hemodynamic or respiratory compromise. The ICU should be staffed by a critical care physician who has experience in treating cytokine release syndrome. In addition, the ICU must have the necessary equipment to commence immediate treatment and monitoring of a patient with CRS Grade ≥2 before he/she is admitted to ICU. Vital signs monitoring shall be made continuously if CRS Grade ≥2 develops. Specific guidance on monitoring of vital signs during CRS are provided in Section 6.7.

j **Coagulation:** Must be performed daily during Cycle 1. PT/INR, aPTT, fibrinogen (and D-dimer at Screening).

k **Blood chemistry:** *Liver tests*: SGOT (AST), SGPT (ALT), GGT, total bilirubin, direct bilirubin, AP. *Renal function tests and electrolytes*: Sodium, potassium, calcium, magnesium, phosphorus, bicarbonate, BUN, creatinine, and estimated creatinine clearance (Cockcroft-Gault formula), uric acid. Others: LDH, albumin, and total protein. *Serology at screening*: testing for active hepatitis B virus, and hepatitis C virus infection. Patients should be monitored every 8 hours after the start of drug administration and for at least 72 hours after the end of infusion for signs and symptoms of tumor lysis: serum creatinine, potassium, calcium, magnesium, phosphorus, and uric acid. Blood chemistry will also be rechecked 8 hours or less prior to each administration of SAR440234.

l **Additional assessments/Administration of SAR440234/Hospitalization**: Only if Dose Level ≥3 is selected for administration in the Expansion Part.

m **Serum or urine pregnancy test:** Women of childbearing potential must have a negative serum or urine pregnancy test result within 14 days prior to the initial dose of study treatment.

n **Urinalysis:** Dipstick for pH, protein, glucose, at baseline, then as clinically indicated.

o **Plasma cytokines (including interleukin-6 and interferon-γ):** will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional sample will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.

p **CRP/ferritin:** will be collected at the same time points as cytokines.

q **SAR440234 administration:** Systematic prophylactic premedication with dexamethasone 20 mg IV 4 and 1 hour prior to infusion of SAR440234 and montelukast 10 mg oral (PO) 4 hours prior to infusion are required. Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. Specific instructions for the preparation and administration of SAR440234 are provided in the Pharmacy Manual.

r **Hospitalization:** Patients will be hospitalized for the duration of the SAR440234 infusion (1 to 19 hours), and for 72 hours after completion of each infusion. If the RP2D is DL ≥3, patients will be hospitalized continuously from Day 1 of Week 1 until 72 hours after completion of the third infusion, ie, for 11 days.

s **Adverse event assessment:** The period of observation for collection of adverse events extends from the signature of the ICF until 30 days after the last administration of SAR440234. Serious adverse events, AESIs, pregnancy, and overdose reports should be assessed and reported as described in the protocol. SAEs and ongoing treatment-related AEs should be followed beyond EOT until resolution or stabilization.

t **Concomitant medication assessment:** The period of collection of concomitant medications extends from the signature of the ICF until EOT, and post EOT if associated with ongoing SAEs or ongoing treatment-related AEs.

x **The investigations and test scheduled for Day 42** may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion. If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment.

Abbreviations: AE=adverse event, AESI=adverse events of special interest, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AP=alkaline phosphatase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CD123=cluster of differentiation 123, CR=complete response, CRi=complete response with incomplete count recovery, CRP=C-reactive protein, CRS=cytokine release syndrome, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, FISH=fluorescent in situ hybridization, GGT=gamma glutamyl transferase, ICF=informed consent form, ICU=intensive care unit, INR=international normalized ratio, IV=intravenous, LDH=lactate dehydrogenase, MRD=minimal residual disease, PO=oral, PT=prothrombin time, RP2D=recommended Phase 2 dose, SAE=serious adverse event, SGOT=serum glutamate-oxalate transferase, SGPT=serum glutamate-pyruvate transferase.

1.2.4 Expansion Part: Treatment Cycle 2 and Subsequent, End of Treatment, and Follow-up

Evaluation[a]	Treatment Cycle 2 and Subsequent										EOT[b]	FU[c]
	Week 1			Week 2		Week 3	Week 4	Week 5	Week 6			
	D1[d]	D2, D3, D4	D5, D6, D7	D8	D9, D10, D11	D15	D22	D29	D36	D42		
Disease assessment												
Bone marrow aspiration[e]										X[f]		
Blood hematology[g]	X	X[f]	X[f]	X		X	X	X	X	X[y]	X	
Immunophenotyping (blood and bone marrow)[h]										X[f]	X	
Extramedullary leukemic localizations[i]	X									X[f,y]	X	
Minimal residual disease[j]										X	X	
Other clinical assessments												
ECOG PS, Body Weight	X			X		X	X	X	X	X[y]	X	
Physical examination[k]	X			X		X	X	X	X	X[y]	X	
Vital signs[l]	X	X[f]		X	X[f]	X	X	X	X	X[y]	X	
Other laboratory tests												
Coagulation[m]	X			X		X	X	X	X	X[y]	X	
Blood chemistry[n]	X	X[f]		X	X[f]	X	X	X	X	X[y]	X	
Serum or urine pregnancy test[o]											X	
Urinalysis[p]											X	
12-lead ECG											X	
Pharmacokinetics	See Pharmacokinetics/Pharmacodynamics Flow-Charts											
Anti-drug antibodies	See Pharmacokinetics/Pharmacodynamics Flow-Charts											
Cytokines[q]	See Pharmacokinetics/Pharmacodynamics Flow-Charts											

Evaluation[a]	Treatment Cycle 2 and Subsequent										EOT[b]	FU[c]
	Week 1			Week 2		Week 3	Week 4	Week 5	Week 6			
	D1[d]	D2, D3, D4	D5, D6, D7	D8	D9, D10, D11	D15	D22	D29	D36	D42		
CRP/ferritin[r]	See Pharmacokinetics/Pharmacodynamics Flow-Charts											
SAR440234 administration[s]	D1			D8		D15	D22	D29	D36			
Hospitalization[t]	X			X		X	X	X	X			
AE assessment[u]	Continuous										X	
Concomitant medication[v]	Continuous											
Disease status[w]										X	X	X

a **Evaluation:** Assessments should be performed prior to administration of SAR440234 (end of the previous cycle) unless otherwise indicated, at the end of the patient's participation in the trial, and at follow-up. Results should be reviewed by the Investigator prior to the administration of the next dose. If the patient is unable to attend monthly study visits, the investigator must obtain study follow up information via telephone call and record review from the patient's treating physicians.

b **End of treatment (within 30 days after the last administration of SAR440234):** Obtain end of treatment assessments. If the patient does not plan to return for an EOT visit, the EOT evaluation must be performed on the day that the decision is made that the patient will not continue SAR440234.

c **Post-study follow-up** for disease status, IMP-related AEs, and SAEs: Patients without documented disease progression at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with monthly follow-up visits until initiation of another anti-cancer therapy, disease progression, study cut-off date, or death. If the patient is unable to attend monthly study visits, the investigator must obtain study follow up information via telephone call and record review from the patient's treating physicians.

d **Day 1:** Cycles run consecutively so that Day 1 of each cycle is normally 7 days after the start of the last infusion in the previous cycle.

e **Bone marrow aspiration** will be performed for morphology (% of blasts) on Day 42 (±2 days) of Cycle 2 for evaluation of disease status. Subsequent bone marrow aspirates will be performed when clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, anemia Grade 4 occurs with onset in >14 days before or after Day 42.

f **Flagged assessments:** Cycle 2 only. Not required during Cycle 3 and subsequent cycles unless clinically indicated.

g **Blood hematology:** Daily during Week 1 of Cycle 2, then weekly thereafter (on IMP administration days and on Day 42). Hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count.

h **Immunophenotyping** of the peripheral blood and bone marrow is required on Day 42 (±2 days) of Cycle 2 (to assess CD123- expression and to monitor T-cell subpopulations and activation status). Bone marrow aspiration is not required for immunophenotyping at the end of subsequent cycles and at EOT unless clinically indicated.; the test will be done using blood.

i **Extramedullary leukemic localizations at physical examination:** Evaluation for hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, as clinically indicated.

j **MRD assessment:** MRD evaluation will be performed on the bone marrow if the patient enters CR or CRi. If MRD is positive, the MRD assessment will be repeated on subsequent bone marrow evaluations, or as clinically indicated.

k **Physical examination**: Examination of major body systems, including cardiovascular, respiratory, neurologic, and digestive.

l **Vital signs**: Temperature, blood pressure, heart rate, respiration rate, and oxygen saturation 5 minutes before starting infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then as clinically indicated at least until 72 hours from the start of the infusion. During infusion, vital signs must be monitored as follows: temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate every 30 minutes. Specific guidance on monitoring of vital signs during CRS are provided in Section 6.7.

m **Coagulation:** PT/INR, aPTT, fibrinogen.

n **Blood chemistry:** *Liver tests*: SGOT (AST), SGPT (ALT), GGT, total bilirubin, direct bilirubin, AP. *Renal function tests and electrolytes*: Sodium, potassium, calcium, magnesium, phosphorus, bicarbonate, BUN, creatinine, and estimated creatinine clearance (Cockcroft-Gault formula), uric acid. Others: LDH, albumin, and total protein. Patients should be monitored every 8 hours after the start of drug administration and for at least 72 hours after the end of infusion for signs and symptoms of tumor lysis: serum creatinine, potassium, calcium, magnesium, phosphorus, and uric acid. Blood chemistry will also be rechecked 8 hours or less prior to each administration of SAR440234.

o **Serum or urine pregnancy test:** Women of childbearing potential must have a negative serum or urine pregnancy test result at the end of study evaluation (Day 30 of the last cycle).

p **Urinalysis:** Dipstick for pH, protein, glucose, at baseline, then as clinically indicated and at EOT.

q **Plasma cytokines (including interleukin-6 and interferon-γ):** will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional sample will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.

r **Serum CRP/ferritin:** will be collected at the same time points as cytokines.

s **SAR440234 administration:** Systematic prophylactic premedication with dexamethasone 20 mg IV 4 and 1 hour prior to infusion of SAR440234 and montelukast 10 mg oral (PO) 4 hours prior to infusion are required. Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. Specific instructions for the preparation and administration of SAR440234 are provided in the Pharmacy Manual.

t **Hospitalization:** During Cycle 2, if the patient has tolerated the SAR440234 infusion during Cycle 1, the patient will be hospitalized only for the duration of each subsequent infusion (1 to 19 hours).

u **Adverse event assessment:** The period of observation for collection of adverse events extends from the signature of the ICF until 30 days after the last administration of SAR440234. Serious adverse events, AESIs, pregnancy, and overdose reports should be assessed and reported as described in the protocol. Serious adverse events and ongoing treatment-related adverse events should be followed beyond EOT until resolution or stabilization.

v **Concomitant medication assessment:** The period of collection of concomitant medications extends from the signature of the ICF until EOT, and post EOT if associated with ongoing SAEs or ongoing treatment-related AEs.

w **Disease status:** The treating physician will collect monthly the patient's disease status (CR, CRi, stable disease, relapse, or progressive disease) until the patient dies or starts new anti-neoplastic therapy, to collect either the date of progressive disease or the initiation of further antitumor therapy.

y **The investigations and test scheduled for Day 42** may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion. If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment.

Abbreviations: AE=adverse event, AESI=adverse events of special interest, ALT=alanine aminotransferase, ANC=absolute neutrophil count, AP=alkaline phosphatase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CD123=cluster of differentiation 123, CR=complete response, CRi=complete response with incomplete count recovery, CRP=C-reactive protein, D=day, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group performance status, EOT=end of treatment, FU=follow-up, GGT=gamma glutamyl transferase, ICF=informed consent form, INR=international normalized ratio, LDH=lactate dehydrogenase, MRD=minimal residual disease, PO=oral, PT=prothrombin time, SAE=serious adverse event, SGOT=serum glutamate-oxalate transferase, SGPT=serum glutamate-pyruvate transferase.

1.3 PHARMACOKINETIC, PHARMACODYNAMIC, BIOMARKER AND IMMUNOGENICITY FLOW CHARTS

1.3.1 Cycle 1: Week 1

	Screening	Cycle 1													
Week within Cycle		**Week 1**													
Day within Cycle	**D-14 to D-1**	**Day 1**									**Day 4 (Week 1 Dose Levels ≥3 only)**				
Time (decimal hours)		SOI	EOI	EOI +1h	EOI +2h	EOI +5h	EOI +7h	EOI +24h	EOI +48h	72h[a, e]	SOI	EOI	EOI +2h	EOI +5h	EOI +24h
Indicative clock time (based on a 2h infusion)	8:00 AM	8:00 AM	10:00 AM	11:00 AM	12:00 PM	3:00 PM	5:00 PM	10:00 AM	10:00 AM	8:00 AM	8:00 AM	10:00 AM	12:00 AM	3:00 PM	10:00 AM
Treatment (IV infusion)															
SAR440234		X----------X									X----------X				
Pharmacokinetics															
SAR440234[b, c, d]		P00[e]	P01[f]	P02	P03	P04	P05	P06	P07	P08[a, e]		P09[f, g]	P10[g]	P11[g]	P12[g]
Immunogenicity															
ADA[b, c, d]		AB00[e]													
Biomarkers															
Cytokines[b, c, i, j]	CS00	C00[e]	C01[f]	C02	C03	C04	C05	C06	C07	C08[a, e]		C09[f,g]	C10[g]	C11[g]	C12[g]

a Sample to be drawn immediately before starting the next infusion if the patient is continuing to be treated in the study and there is no dose delay.
b Refer to laboratory manual for sample collection, processing, and shipping.
c The sampling time-points for PK, ADA and cytokines may be modified during the course of the study (ie, omitting samples) based on the updated knowledge of SAR440234 behavior.
d Sampling for PK analysis and ADA detection will be stopped in all patients at the second study cut-off date.
e Pre-dose samples to be collected strictly before start of SAR440234 infusion.
f End of infusion sample to be collected within 10 minutes before the actual end of infusion.
g Samples to be collected from Dose Level 3.
h Mid of infusion sample to be collected during SAR440234 infusion only for infusion length ≥5 hours.
i An additional sample (CA00, CA01...) must be collected in case of Grade ≥2 CRS if it occurs, or as soon as it is diagnosed.
j CRP/ferritin will be measured at the same times as cytokines.

Abbreviations: AB=antibody, ADA=anti-drug antibody (ie, anti-SAR440234 antibody), C=cytokines, CRS=cytokine release syndrome, CS=cytokines screening, EOI=end of infusion, h=hours, IV=intravenous, P=plasma, PK=pharmacokinetic, SOI=start of infusion

1.3.2 Cycle 1: Week 2 and Week 3

	Cycle 1 Continued														
Week within Cycle	**Week 2**									**Week 3**					
Day within Cycle	**Day 8**									**Day 15**					
Time (decimal hours)	SOI	MOI	EOI	EOI +2h	EOI +5h	EOI +24h	EOI +48h	72h	168h[a, e]	SOI	MOI	EOI	EOI +2h	EOI +5h	EOI +24h
Indicative clock time (based on a 2h infusion)	8:00 AM	9:00 AM	10:00 AM	12:00 PM	3:00 PM	10:00 AM	10:00 AM	8:00 AM	8:00 AM	8:00 AM	9:00 AM	10:00 AM	12:00 PM	3:00 PM	10:00 AM
Treatment (IV infusion)															
SAR440234	X----------X									X----------X					
Pharmacokinetics															
SAR440234[b, c, d]	P13[a, e]	P14[h]	P15[f]	P16	P17				P18[a, e]		P19[h]	P20[f]	P21	P22	P23
Immunogenicity															
ADA[b, c, d]	AB01[e]								AB02[e]						
Biomarkers															
Cytokines[b, c, i, j]	C13[a, e]	C14[h]	C15[f]	C16	C17	C18	C19	C20	C21[a, e]		C22[h]	C23[f]	C24	C25	C26

a Sample to be drawn immediately before starting the next infusion if the patient is continuing to be treated in the study and there is no dose delay.
b Refer to laboratory manual for sample collection, processing, and shipping.
c The sampling time-points for PK, ADA and cytokines may be modified during the course of the study (ie, omitting samples) based on the updated knowledge of SAR440234 behavior.
d Sampling for PK analysis and ADA detection will be stopped in all patients at the second study cut-off date.
e Pre-dose samples to be collected strictly before start of SAR440234 infusion.
f End of infusion sample to be collected within 10 minutes before the actual end of infusion.
g Samples to be collected from Dose Level 3.
h Mid of infusion sample to be collected during SAR440234 infusion only for infusion length ≥5 hours.
i An additional sample (CA00, CA01...) must be collected in case of Grade ≥2 CRS if it occurs, or as soon as it is diagnosed.
j CRP/ferritin will be measured at the same times as cytokines.

Abbreviations: AB=antibody, ADA=anti-drug antibody (ie, anti-SAR440234 antibody), C=cytokines, CRS=cytokine release syndrome, CS=cytokines screening, EOI=end of infusion, h=hours, IV=intravenous, MOI=mid of infusion; P=plasma, PK=pharmacokinetic, SOI=start of infusion

1.3.3 Cycle 1: Weeks 4, Week 5, and Week 6

	Cycle 1 continued																	
Week within Cycle	**Week 4**										**Week 5**				**Week 6**			
Day within Cycle	**Day 22**										**Day 29**				**Day 36**			
Time (decimal hours)	SOI	MOI	EOI	EOI +2h	EOI +5h	EOI +24h	EOI +48h	72h	96h	168h[a, e]	SOI	EOI	EOI +2h	EOI +5h	SOI	EOI	EOI +2h	EOI +5h
Indicative clock time (based on a 2h infusion)	8:00 AM	9:00 AM	10:00 AM	12:00 PM	3:00 PM	10:00 AM	10:00 AM	8:00 AM	8:00 AM	8:00 AM	8:00 AM	10:00 AM	12:00 PM	3:00 PM	8:00 AM	10:00 AM	12:00 PM	3:00 PM
Treatment (IV infusion)																		
SAR440234	X----------X										X----------X				X----------X			
Pharmacokinetics																		
SAR440234[b, c, d]	P24[e]	P25[h]	P26[f]	P27	P28	P29	P30	P31	P32	P33[a, e]		P34[f]	P35		P36[e]	P37[f]	P38	
Immunogenicity																		
ADA[b, c, d]	AB03[e]									AB04[a,e]								
Biomarkers																		
Cytokines[b, c, i, j]	C27[e]	C28[h]	C29[f]	C30	C31	C32	C33	C34		C35[a, e]		C36[f]	C37	C38	C39[e]	C40[f]	C41	C42

a Sample to be drawn immediately before starting the next infusion if the patient is continuing to be treated in the study and there is no dose delay.
b Refer to laboratory manual for sample collection, processing, and shipping.
c The sampling time-points for PK, ADA and cytokines may be modified during the course of the study (ie, omitting samples) based on the updated knowledge of SAR440234 behavior.
d Sampling for PK analysis and ADA detection will be stopped in all patients at the second study cut-off date.
e Pre-dose samples to be collected strictly before start of SAR440234 infusion.
f End of infusion sample to be collected within 10 minutes before the actual end of infusion.
g Samples to be collected from Dose Level 3.
h Mid of infusion sample to be collected during SAR440234 infusion only for infusion length ≥5 hours.
i An additional sample (CA00, CA01...) must be collected in case of Grade ≥2 CRS if it occurs, or as soon as it is diagnosed.
j CRP/ferritin will be measured at the same times as cytokines.

Abbreviations: AB=antibody, ADA=anti-drug antibody (ie, anti-SAR440234 antibody), C=cytokines, CRS=cytokine release syndrome, CS=cytokines screening, D=day, EOI=end of infusion, h=hours, IV=intravenous, MOI=mid of infusion; P=plasma, PK=pharmacokinetic, SOI=start of infusion

1.3.4 Cycle 2 and Subsequent Cycles

Cycle	Cycle 2									Subsequent cycles			End of Treatment
Week within Cycle	Week 1					Week 3		Week 5		Week 1			
Day within Cycle	Day 1					Day 15		Day 29		Day 1			(EOT)[i]
Time (decimal hours)	SOI	MOI	EOI	EOI +2h	EOI +5h	SOI	EOI	SOI	EOI	SOI	EOI	EOI +2h	
Indicative clock time (based on a 2h infusion)	8:00 AM	9:00 AM	10:00 AM	12:00 PM	3:00 PM	8:00 AM	10:00 AM	8:00 AM	10:00 AM	8:00 AM	10:00 AM	12:00 PM	8:00 AM
Treatment (IV infusion)													
SAR440234	X----------X					X----------X		X----------X		X----------X			
Pharmacokinetics													
SAR440234[a, b, c]	P00[d]	P01[e]	P02[f]	P03		P04[d]		P05[d]		P00[d]	P01[f]	P02	
Immunogenicity													
ADA[a, b, c]	AB00[d]					AB01[d]		AB02[d]		AB00[d]			ABF00
Biomarkers													
Cytokines[a, b, g, h]	C00[d]	C01[e]	C02[f]	C03	C04								

a Refer to laboratory manual for sample collection, processing, and shipping.
b The sampling time-points for PK, ADA and cytokines may be modified during the course of the study (ie, omitting samples) based on the updated knowledge of SAR440234 behavior.
c Sampling for PK analysis and ADA detection will be stopped in all patients at the second study cut-off date.
d Pre-dose samples to be collected strictly before start of SAR440234 infusion.
e Mid of infusion sample to be collected during SAR440234 infusion only for infusion length ≥5 hours.
f End of infusion sample to be collected within 10 minutes the actual end of infusion.
g An additional sample (CA00, CA01...) must be collected in case of Grade ≥2 CRS if it occurs, or as soon as it is diagnosed.
h CRP/ferritin will be measured at the same times as cytokines.
i EOT evaluation must be performed within 30 days of the last administration of SAR440234. If a patient does not plan to return for an EOT visit, EOT evaluation must be performed on the day that the decision is made to discontinue SAR440234.

Abbreviations: AB=antibody, ADA=anti-drug antibody (ie, anti-SAR440234 antibody), C=cytokines, CRP=C-reactive protein, CA=additional cytokines sample, CRS=cytokine release syndrome, CS=cytokines screening, EOI=end of infusion, EOT=end of treatment, h=hours, IV=intravenous, MOI=mid of infusion; P=plasma, SOI=start of infusion

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2.1 LIST OF TABLES

2.2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
ADI:	actual dose intensity
AESI:	adverse event of special interest
ALL:	acute lymphocytic or lymphoblastic leukemia
ALT:	alanine aminotransferase
AML:	acute myeloid leukemia
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
AUC:	area under the curve
BUN:	blood urea nitrogen
CR:	complete response
CRi:	complete response with incomplete hematological recovery
CRO:	contract research organization
CRP:	C-reactive protein
CRS:	cytokine release syndrome
CTC:	common terminology criteria
DLT:	dose-limiting toxicity
DRF:	discrepancy resolution form
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
FIH:	first-in-human
GCP:	good clinical practice
GGT:	gamma glutamyl transferase
GLP:	Good Laboratory Practice
GM-CSF:	granulocyte macrophage-colony stimulating factor
HR-MDS:	high risk myelodysplasia
HSC:	hematopoietic stem cells
ICH:	International Council for Harmonisation
ICU:	intensive care unit
IEC:	institutional ethics committee
IFN:	interferon
Ig:	immunoglobulin
IL:	interleukin
IMP:	investigational medicinal product
IRB:	institutional review board
IV:	intravenous
IWG:	International Working Group
LSC:	leukemic stem cell
LSC:	leukemic stem cell
MABEL:	minimal anticipated biological effect level

MAD:	maximum administered dose
MDS:	myelodysplastic syndrome
MRD:	minimal residual disease
MTD:	maximum tolerated dose
NCCN:	National Comprehensive Cancer Network
NCI:	National Cancer Institute
NIMP:	noninvestigational medicinal product
ORR:	overall response rate
PD:	progressive disease
PO:	orally
R/R AML:	relapsed or refractory acute myeloid leukemia
RDI:	relative dose intensity
R-IPSS:	Revised International Prognostic Scoring System
RP2D:	recommended Phase 2 dose
SAE:	serious adverse event
SD:	stable disease
StD:	standard deviation
TCE:	T-cell engager
TEAE:	treatment-emergent adverse event
TLS:	Tumor lysis syndrome
TNF:	tumor necrosis factor
ULN:	upper limit of normal
WHO:	World Health Organization

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults and is the leading cause of fatal leukemia in the United States. First-line treatment for AML has changed little over the last 30 years, although the approval of 3 new drugs for AML in 2017, midostaurin (1), enasidenib (2), and CPX-351, suggests that a new era of AML therapy is beginning. AML induction regimens typically include cytosine arabinoside and anthracyclines. Allogeneic stem cell transplant is offered to patients with high risk disease in first or subsequent remissions. Despite this aggressive therapeutic approach, from 2007 to 2013 only 26.9% of patients diagnosed with AML survived 5 years (3). Relapse of AML is common and salvage treatment with cytotoxic chemotherapy is rarely curative (4).

There is growing evidence to suggest that AML derives from leukemic stem cells (LSCs) that give rise to leukemic blasts in vitro and in vivo models. It is hypothesized that the persistence of LSCs causes relapse after an initial remission. Thus the eradication of LSCs may be a requirement for cure and is an important therapeutic goal. One potential therapeutic target in AML is the surface receptor CD123, the interleukin (IL)-3 receptor alpha chain (IL-3R α) that is expressed at high levels on LSCs. Similar to normal hematopoietic stem cells (HSCs), LSCs have been shown to express CD34, but lack CD38 (CD34+CD38-), as well as other markers. While CD123 is expressed in both normal HSCs and AML LSCs, CD123 is expressed in a higher proportion of AML LSCs than normal HSCs (5, 6, 7, 8) and is more intensely expressed on AML LSCs than normal HSCs (9, 10, 11).

CD123 is strongly expressed in LSCs and blasts in the majority of patients with AML, regardless of prognostic risk group based on cytogenetic and molecular analysis (12). CD123 is also expressed in a variety of other hematologic malignancies, including myelodysplastic syndrome (MDS), B lineage acute lymphocytic or lymphoblastic leukemia (B-ALL), Hodgkin lymphoma, hairy cell leukemia, and chronic myeloid leukemia (7, 11, 13, 14).

No CD123-targeted therapy has been approved yet, but novel therapies targeting CD123 are currently under development, either as monoclonal antibodies, antibody drug conjugates (NCT02848248, NCT01632852, NCT02472145), or bispecific antibodies (NCT02715011, NCT02152956, NCT02730312). T-cell engagers (TCE) are bispecific molecules that aim to enhance the patient's immune response to tumors by stimulating the patient's T-cells to attack tumor cells.

SAR440234 is a monoclonal antibody TCE that is being developed as a potential therapy for hematologic malignancies. One arm of SAR440234 targets the CD3ε subunit of the T-cell co-receptor at the surface of the T-cell. The other arm targets CD123 on the malignant cell. Co-engagement of T-cell and malignant cell by the bispecific construct leads to the formation of a cytolytic synapse that induces T-cell activation and results in tumor cell specific killing. This process is human leukocyte antigen-independent, but requires the presence of the selected tumor

antigen at the surface of the tumor cell. Clinical proof of concept of T-cell redirected tumor cell killing has been achieved by the registration of blinatumomab, Blincyto®, a CD19-CD3 TCE for the treatment of ALL.

Despite advances in understanding the pathophysiology of AML and recognizing its molecular heterogeneity, developing viable therapeutics for patients with AML has proved to be a challenge. Novel agents are needed to achieve better responses that prolong overall survival, particularly for patients with relapsed or refractory disease. Consequently the proposed primary indication is relapsed or refractory acute myeloid leukemia (R/R AML) and high risk myelodysplasia (HR-MDS) patients who are ineligible for or have exhausted standard therapeutic options. As B-ALL leukemic cells often express CD123, this population is also included in the Dose Escalation Part. If B-ALL patients tolerate the study treatment well, SAR440234 may be investigated further in this population in subsequent studies.

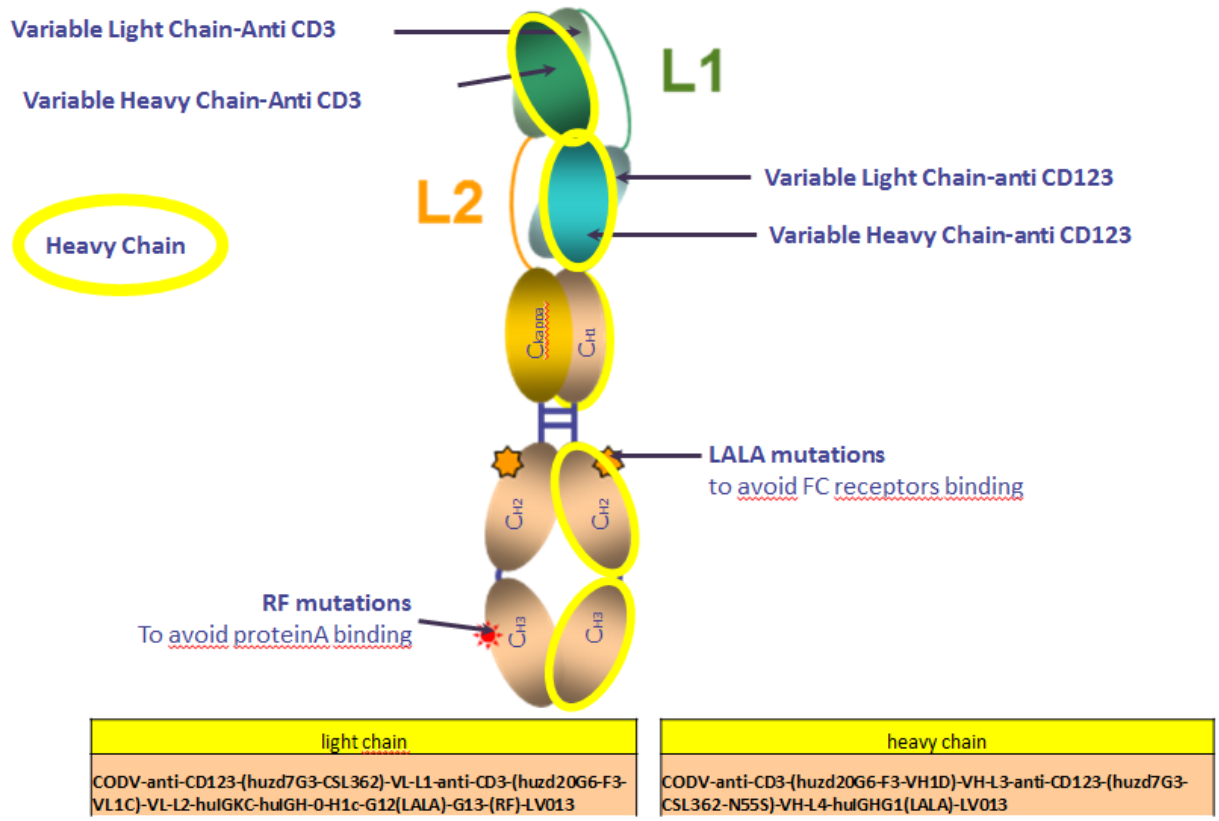
4.2 SAR440234

SAR440234 (CD3-CD123 TCE) is a humanized bispecific monoclonal antibody that binds selectively to the human CD123 tumor antigen and CD3 subunit of the T-cell co-receptor.

The structure is composed of a CODV-Fab fragment (CL kappa/CH1) grafted to an Fc IgG1 with LALA mutation to suppress Fc effector function (light chain position 366/367; heavy chain position 358/359). The so-called light chain is composed of 578 amino acids and has a molecular weight of 63 035.52 Da; the heavy chain is composed of 570 amino acids and has a molecular weight of 62800.90 Da.

The structure is illustrated in Figure 1.

Figure 1 - SAR440234 structure



SAR440234 (LC80781, [hz20G6 x hz7G3-N55S with Fc-IgG1-LaLa backbone]) is a novel fully human bispecific antibody TCE molecule that is proposed for the treatment of cancer. The proposed primary indication for SAR440234 CD3-CD123 TCE is AML.

SAR440234 is designed to simultaneously bind CD3, the human T-cell co-receptor molecule, and CD123, the human IL3 receptor alpha chain subunit (IL-3Rα) and thereby co-engage T-cells with CD123-expressing tumor cells, resulting in presentation of tumor cells for T-cell directed tumor-specific killing.

CD123 is aberrantly over-expressed in AML and in other hematological malignancies (MDS, systemic mastocytosis, blastic plasmacytoid dendritic cell neoplasm, B-ALL, and hairy cell leukemia). CD123 is expressed on AML blasts (~80% of positive samples, 63% with more than 80% CD123-positive blasts) and on CD34-positive/CD38-negative AML leukemic stem cells (~90% CD123-positive LSCs) (12). It has little expression outside the hematopoietic system. Thus, CD123 represents an attractive target for therapy in patients with AML.

In vitro studies have shown that SAR440234 induces T-cell activation and cytotoxic activity. Inhibition of AML tumor cell growth was seen with SAR440234 in animal tumor models.

4.3 NONCLINICAL TOXICOLOGY

Based on significant sequence homology of human CD3ε and CD123 compared to cynomolgus monkey in contrast to rodents, on similar binding affinity to both targets for human and cynomolgus monkey, and on overall similar staining pattern in cross-reactivity studies performed with SAR440234 on human and cynomolgus monkey normal tissues, the cynomolgus monkey was selected as the relevant species for in vivo toxicology evaluation.

Tissue cross-reactivity using normal human and cynomolgus monkey frozen tissues was assessed by immunohistochemistry using SAR440234 conjugated with digoxigenin (SAR440234-DIG). SAR440234-DIG-specific staining was observed in lymphoid tissues, bone marrow and on infiltrating/circulating cells and/or endothelial cells in most tissues in both species demonstrating overall similar staining distribution on human and cynomolgus monkey tissues. The localization of the staining was as expected, based on the reported distribution of CD3 and CD123 antigens.

Consequently, the in vivo general toxicity studies were conducted in cynomolgus monkeys, only. In the repeat-dose monkey studies, a progressive weekly intra-monkey dose escalation was used in an attempt to mitigate the cytokine release observed after a single administration. The doses used in the 3 conducted monkey toxicity studies were: [redacted] in the single-dose exploratory study, [redacted] in the weekly (x4) exploratory study and [redacted] (3 males), and [redacted] (5 females) in the weekly (x6) Good Laboratory Practice (GLP) study.

Safety pharmacology endpoints were evaluated in the weekly monkey GLP study. No SAR440234-related effects were noted on electrocardiogram (ECG), blood pressure and respiration rate in this study up to the highest dose tested of [redacted] Transient clinical signs and transient increased body temperature noted in the study were considered a consequence of the cytokines release and not a direct effect of SAR440234 on the central nervous system.

The main adverse effects noted in monkeys consisted of marked increases in the levels of cytokines (IL-2, IL-6, IL-10, interferon [IFN]γ and/or tumor necrosis factor [TNF]α) within the 24 hours following compound administration at [redacted] and above, associated with transient clinical signs (such as raised hair, hunched posture, impaired mobility, subdued/sluggish behavior, lethargy and/or emesis), transient increases in body temperature within the 24 hours following compound administration and transient increases in C-reactive protein (CRP) and ferritin (evaluated in the weekly monkey GLP toxicity study only). These effects resulted in preterminal euthanasia of the monkeys in the single-dose and weekly monkey GLP studies at high doses of 7.5 µg/kg and above.

The main target organs identified in the animals that were euthanized at scheduled necropsy consisted of minimally increased cellularity of intravascular neutrophils in the lungs in the single-dose monkey study and minimal to slight increased germinal centers in the spleen in the weekly GLP monkey study.

In addition, minimal to mild and transient increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, bilirubin and/or fibrinogen were noted mainly in the single-dose monkey study.

The local tolerance of SAR440234, evaluated in the weekly monkey GLP study, was good, as no compound-related macroscopic or microscopic findings were noted at the injection sites at any dose level.

Overall, test article-treated monkeys were exposed to SAR440234, with quantifiable plasma concentrations at least at the end of the 1-hour intravenous (IV) infusion (C_{eoi}). After repeated administration, C_{eoi} were maintained throughout the different administrations at [redacted], but decreased dramatically at [redacted] after the fourth administration, most probably due to the presence of anti-drug antibody (ADA, ie, anti-SAR440234 antibody) in the majority of the animals. Consequently, cytokine release mitigation by progressive intra-monkey dose escalation was demonstrated in the weekly monkey exploratory study at the dose of [redacted] only. It was not possible to conclude on mitigation in the weekly monkey GLP study due to the dramatic decrease in exposure after repeated administration.

Modulation of pharmacodynamic biomarkers in blood and/or bone marrow (depletion of CD123+ cells) was evidenced in the 3 monkey studies from the lowest dose tested [redacted] and this dose was the no-observed adverse effect level in these 3 monkey studies.

Most of the effects of SAR440234 described above are perfectly in line with the review article on 17 Investigational New Drugs (different CD3 bispecific formats) published by FDA in September 2017: “An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection”(15).

4.4 PHARMACOKINETICS IN ANIMAL

The nonclinical pharmacokinetics of SAR440234 were investigated in the toxicological species (cynomolgus monkeys) following an IV (1-hour infusion) administration of ^{3}H-SAR440234 to overcome the limitation of the immunoassay sensitivity. Following a single IV (1 hour) administration to cynomolgus monkeys, the radioactivity exhibited a bi-compartmental pharmacokinetic profile. The volume of distribution ranged from [redacted] and clearance ranged from [redacted]. Terminal elimination half-life was around [redacted] Exposure assessed by area under the curve (AUC) increased slightly less than expected by dose increase, with a [redacted] increase in AUC for a [redacted] increase in dose [redacted].

As the drug substance is a therapeutic protein, no other evaluation was conducted for absorption, distribution, elimination or excretion. It is generally recognized that antibodies are metabolized by degradation into small peptides and individual amino acids following endogenous catabolism, therefore no metabolism studies were conducted.

4.5 STUDY DESIGN RATIONALE

4.5.1 Choice of starting dose

The first-in-human (FIH) study is proposed as a single agent trial in patients with R/R AML, HR-MDS, and B-ALL. This trial is intended to establish proof-of-concept for this drug, based on clinical, pharmacokinetic, and biomarker evaluation; to assess the safety and preliminary anti-leukemic activity of SAR440234; and to define the optimal single agent dose for future studies. The FIH Phase 1/2A study will include a Dose Escalation Part to determine the recommended dose, followed by an Expansion Part at the recommended Phase 2 dose (RP2D). SAR440234 falls into the class of potent immunomodulatory agonists, and as recommended by ICHS9 guidances, it is proposed to use a conservative minimal anticipated biological effect level (MABEL) approach to define the starting dose for the FIH study.

The most sensitive and relevant assays using in vitro human material were selected for the MABEL determination. The anti-tumor efficacy of SAR440234 on disseminated human primary AML in vivo in the NSG mouse model was not incorporated in the MABEL determination, as the translational value of this model was uncertain.

In vitro, in a depletion assay using peripheral blood mononuclear cells from human healthy donors, SAR440234 depleted CD123-positive monocytes with a first effective concentration producing 80% effect (EC_{80}) of [redacted]. This activity was associated with a 20% cell depletion.

The MABEL was calculated using the most sensitive data on CD123-positive cell depletion (C_{MABEL}) with pharmacokinetic modeling to determine the FIH dose, according to the equation: $Dose = C_{MABEL} \times Vc_{human}$. It is a conservative approach (Duff method, 2006 [16]), assuming the total dose is administered as a bolus and instantly distributed into total plasma volume.

$V_{C\,human}$, volume of the central compartment in human, was obtained from pharmacokinetic parameters determined in monkeys from 2-compartment model analysis and scaled to human, according to the following equation: $Vc_{human} = Vc_{monkey} \times \left(\frac{BW_{human}}{BW_{monkey}} \right)^{\alpha}$, with BW_{human}=70 kg, BW_{monkey}=3 kg and α=1 (17)

$V_{C\,human}$ was determined as [redacted]

The FIH dose was determined as $Dose =$ [redacted] $ng/mL \times$ [redacted] $mL/kg =$ [redacted] ng/kg and the nearest convenient dose was set to 1 ng/kg.

In conclusion, the recommended starting dose for FIH administration is [redacted]

4.5.2 Clinical rationale

The proposed primary indications for SAR440234 are R/R AML, and HR-MDS. As discussed above, CD123 is highly expressed in most AML blasts, on CD3-positive/CD38-negative AML leukemic stem cells, and in B-ALL cells (18). CD123 has little expression outside the hematopoietic system. For these reasons, CD123 is an important therapeutic target in patients with AML and other hematologic malignancies that express CD123.

Because CD123 is expressed in the leukemic blasts from a majority of patients with AML, the selection of patients for CD123-expressing leukemic blasts in the FIH phase 1 is not recommended. Nonetheless, in vitro experiments have demonstrated that CD123 density might influence SAR440234 efficacy (sanofi, unpublished data). Thus, in the clinic, CD123 expression prevalence and cell density will be monitored in leukemic cells, blasts and LSCs, and in normal cells known to express CD123, such as basophils, plasmacytoid dendritic cells, and monocytes. The depth of CD123-positive cell depletion will be utilized as a pharmacodynamic monitoring marker of SAR440234 efficacy.

In the literature, very little has been reported about the T-cell subpopulation presence and state of activation or exhaustion in patients with AML. Because SAR440234's mechanism of action relies on its ability to recruit and activate T-cells, T-cell sub-populations will be monitored in the FIH study. In addition to monitoring CD123-expression and T-cell sub-populations, clinical sites participating in the testing of SAR440234 will be asked to provide data on the cytogenetic profile and molecular alterations observed in the leukemic cells of AML and MDS patients entering the clinical trial, as is now routine in the risk-stratification of AML and MDS patients (19). The sites will be required to obtain and record the results in the clinical database.

4.5.3 SAR440234 dose and regimen

A dose escalation single agent trial will be initiated in patients with R/R AML, HR-MDS, and B-ALL. This trial is intended to establish proof-of-concept for this drug, based on clinical, pharmacokinetic, and biomarker evaluation; to assess the safety and preliminary anti-leukemia activity of SAR440234; and to define the optimal dose of drug as a single agent.

Use of intra-patient dose escalation is proposed. This dosage strategy has already demonstrated its benefit in approved drugs, such as Blincyto®, with the same objective of cytokine release syndrome (CRS) mitigation. The strategy of intra-patient dose escalation is currently being used for other drugs under development.

In the first 2 dose levels (DL1 and DL2), SAR440234 will be administrated once weekly. After evaluation of the first 2 dose levels, a 2-step dosing increase in the first week of administration will be implemented to reach higher exposure in a shorter time frame.

A weekly schedule (bi-weekly during Cycle 1, Week 1 in DL ≥3) will be evaluated with drug administration on Days 1, 4 (DL ≥3 only), 8, 15, 22, 29, and 36 of a 6-week cycle that will be repeated, provided that the patient is achieving clinical benefit.

Cycles run consecutively so that Day 1 of each cycle is normally 7 days after the start of the last infusion in the previous cycle. If bone marrow hypocellularity Grade 4 or hematological toxicity Grade 3 or 4 is diagnosed, the interval between doses must be extended until toxicity is resolved. If the interval between doses is or exceeds 10 days, the treatment must be restarted with the lead-in doses appropriate for the selected dose level.

Systematic premedication with the corticosteroid, dexamethasone (two doses of 20 mg IV), and leukotriene inhibitor montelukast (one dose of 10 mg by mouth) are planned starting with the first dose of SAR440234 tested. Dexamethasone and/or tocilizumab will be used to treat Grade ≥2 CRS, as described below and in Section 6.7. Dexamethasone has been chosen because it penetrates the blood-brain barrier (20).

Use of intra-patient dose escalation is proposed. This dosage strategy has already demonstrated its benefit in approved drugs, such as Blincyto®, with the same objective of CRS mitigation. The strategy of intra-patient dose escalation is currently being used for other drugs under development, as well.

4.5.4 Cytokine release syndrome

Cytokine-associated toxicity, also known as CRS, is a nonantigen specific toxicity that occurs as a result of potent immune activation. It manifests clinically when large numbers of lymphocytes (B-cells, T-cells, and/or natural killer cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. Cytokine release syndrome has classically been associated with therapeutic monoclonal antibody infusions and in these settings, symptom onset typically occurs within minutes to hours after the infusion begins (21, 22, 23). Cytokine release syndrome has also recently been reported following administration of bispecific antibodies for leukemia, infusion of haploidentical mononuclear cells to patients with refractory leukemia, and adoptive immunotherapies for cancer, most notably T-cells engineered to express chimeric antigen receptors (18, 24, 25, 26, 27).

The timing of symptom onset and CRS severity depends on the inducing agent and the magnitude of immune cell activation. The incidence and severity of the syndrome also appears greater when patients have large tumor burdens, presumably because this leads to higher levels of T-cell activation. As with CRS associated with monoclonal antibody therapy, CRS associated with adoptive T-cell therapies has been associated with elevated IFN-γ, IL-6, and TNFα levels, and increases in IL-2, granulocyte macrophage–colony-stimulating factor (GM-CSF), IL-10, IL-8, IL-5, and fractalkine have also been reported (26, 28). Emerging evidence implicates IL-6 as a central mediator of toxicity in CRS. IL-6 is a pleiotropic cytokine with anti-inflammatory and proinflammatory properties. However, real time analysis of a broad panel of cytokines will not significantly impact management of individual patients with CRS, thus it is recommended that treatment decisions are based on clinical parameters (29).

In this FIH trial, plasma levels of cytokines, including IL-6 and IFN-γ, will be collected, as well as assays for serum CRP and ferritin. Sampling will be performed following the initial dose and after each dose increase, in order to assess for signs of CRS. C-reactive protein is an acute phase reactant produced by the liver, largely in response to IL-6. Serum CRP levels may serve as a surrogate for increases in IL-6 bioactivity (30). During CRS, serum CRP levels may increase by several logs. The serum CRP assay is rapid, inexpensive, and readily available in most hospitals.

In some series, peak CRP levels and fold-change in CRP have identified patients at risk for severe CRS (26). It is important to emphasize, however, that CRP levels are also elevated during infection and cannot be used to distinguish between inflammation caused by infection and inflammation related to CRS. Extreme elevations in serum ferritin have been observed in many patients with CRS after chimeric antigen receptor T-cell infusion, which supports a resemblance between CRS and macrophage activation syndrome/hemophagocytic lymphohistiocytosis.

To assess and record the severity of CRS in individual patients, the National Cancer Institute (NCI) Consensus Guidelines 2014 will be used (29, 31), and the mitigation strategy for CRS (Appendix H), is based on these guidelines. This grading system defines mild, moderate, severe, and life-threatening CRS, regardless of the inciting agent, and provides treatment recommendations with corticosteroids and/or tocilizumab (29). Tocilizumab is a humanized, immunoglobulin (Ig)G1k antihuman IL-6R mAb approved for treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and polyarticular juvenile rheumatoid arthritis (32, 33). Emerging clinical experience at several institutions has demonstrated that tocilizumab is an effective treatment for severe or life-threatening CRS (28). The FDA has approved tocilizumab for the treatment of chimeric antigen receptor T-cell induced severe or life-threatening CRS. The recommended dose of tocilizumab for treatment of CRS is 12 mg/kg IV for patients weighing <30 kg and 8 mg/kg IV for patients weighing ≥30 kg. Doses of tocilizumab should not exceed 800 mg per infusion. It is also recommended that tocilizumab should not be started in patients with an absolute neutrophil count (ANC) <2000/microliter, platelet count <100 000/microliter, or with an ALT or AST >1.5 times the upper limit of normal (ULN).

4.6 BENEFIT RISK ASSESSMENT

Severe CRS is an anticipated risk due to release of cytokines following T-cell activation. Anemia, leukopenia, and thrombocytopenia are other anticipated risks that commonly occur during treatment for hematologic malignancies. The safety monitoring and risk mitigation plan includes the following measures:

- Systematic premedication with dexamethasone and montelukast will be provided starting with the first dose of SAR440234 tested.
- Treatment with tocilizumab will be started if CRS Grade 2 is diagnosed. Two doses of tocilizumab will be available on site for each patient under treatment.
- A conservative MABEL approach is planned to define a very low dose as the starting dose in humans.
- Careful intra-patient dose escalation with conservative increases for each dose level will be performed. The dose escalation cohort will be initiated at a lower dose at the first infusion in each patient. The purpose of this design is to minimize exposure to sub-therapeutic doses while maintaining patient safety, particularly in the context when the FIH starting dose is very low. This strategy will facilitate rapid attainment of active therapeutic doses.
- Extensive clinical monitoring will be conducted during the Dose Escalation Part, including frequent assessment of vital signs during infusion and at specific time points post infusion. During Cycle 1 and the first 2 doses of Cycle 2 in the Dose Escalation Part, patients will

be hospitalized for the duration of each SAR440234 infusion (1 to 19 hours) and for the first 72 hours after the infusion is completed. During Cycle 1 and the first 2 infusions of Cycle 2 in the Expansion Part, patients will be hospitalized for the duration of the SAR440234 infusion (1 to 19 hours), and for 72 hours after completion of each infusion. During the remaining infusions of Cycle 2 and beyond in the Expansion Part, if the patient has tolerated the SAR440234 infusion well, the patient will be hospitalized only for the duration of each subsequent infusion (1 to 19 hours). The 2014 NCI Consensus Guidelines will be used to grade and guide the management of CRS (Appendix H).

- A DLT observation period of 42 days from the first administration of IMP in the first cycle, with administration of IMP on Day 1, Day 4 (DL ≥3), Day 8, and weekly thereafter, including at least 3 maximal subsequent doses in each dose level, will be followed to monitor for delayed effects of SAR440234 and for effects that occur only after the highest dose in Cycle 1.
- Continuous monitoring of vital signs will be implemented if CRS Grade ≥2 develops; blood chemistry will be tested every 8 hours. Any patients with Grade 2 or greater CRS must be admitted to the ICU.
- During the first cycle, patients will be monitored every 8 hours after the start of IMP administration and for at least 72 hours after the end of the SAR440234 infusion for signs and symptoms of tumor lysis, including serum creatinine, potassium, magnesium, phosphorous, calcium, and uric acid.
- Complete blood counts including white blood cell differential and ANC will be assessed daily during Cycle 1, the first 2 weeks of Cycle 2, and weekly thereafter for the duration of the treatment. Patients who develop Grade 3 or Grade 4 febrile neutropenia should receive broad spectrum antimicrobial therapy according to the hospital site's protocol. SAR440234 treatment should be discontinued for Grade 4 febrile neutropenia. Transfusion with red blood cells and platelets should be provided as needed.
- The study will be conducted at a limited number of sites, which will be selected based on their experience with potent immune modulating agents, treatment of leukemia, and CRS. Appropriate training will be provided, and the sites will be closely monitored.

The product is intended to be administered by IV infusion after reconstitution and dilution of lyophilized drug product in single use vials. While designing the strategy to ensure accuracy and control of the actual dose administered in each dose level, the following factors were considered: the extremely low starting dose, the wide range of doses expected during the dose escalation, the high potency of SAR440234, the risk of CRS, and the intended concentration of drug product formulation proposed for the FIH study. Hospital sites will be selected based on their demonstrated experience in complex administration procedures. Training will be reinforced at the sites, and procedures specified to minimize the risk of human error during dilution and potential product adsorption during drug preparation and infusion. The clinical administration protocol guidelines have been developed accordingly.

A solution for coating is supplied with SAR440234 that is used to coat infusion bags prior to dilution, which prevents adsorption of SAR440234 onto bags and infusion materials.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES:

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 at the RP2D in patients with R/R AML or HR-MDS.

5.2 SECONDARY OBJECTIVES:

- 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.

5.3 EXPLORATORY OBJECTIVES:

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.
- 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.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

Sequential cohort(s):

This Phase 1/2A Study is an open-label, nonrandomized, dose escalation and dose expansion, safety, efficacy, pharmacokinetic, and pharmacodynamic evaluation study of SAR440234 administered as a single agent IV infusion every week to patients ≥16 years of age with R/R AML, HR-MDS, or B-ALL.

The study will be performed in 2 parts: a Dose Escalation Part and an Expansion Part both with SAR440234 used as monotherapy. Enrollment of patients in the Expansion Part will start after completion of the Dose Escalation Part and identification of the MTD/RP2D.

6.2 STARTING DOSE AND DOSE ESCALATION PART

The rationale for selecting the starting dose and the dose escalation design are described in Section 4.5.1 and in Section 1.1, respectively.

6.2.1 Starting dose and dose levels

SAR440234 will be administered IV on Day 1, Day 4 (DL ≥3), Day 8, and weekly thereafter in Cycle 1 for a 42-day cycle. The dosing regimen will be weight-based; however, if a patient weighs >140 kg, the patient's weight will be capped at 140 kg for dose calculations. The administration of the investigational medicinal product (IMP) will begin at [redacted], representing the selected safe starting dose for an FIH trial, based on the MABEL, and by integration of all available in vivo and in vitro data at the start of the study.

A 3+3 dose escalation scheme will be used, based on DLTs observed during the first 42 days following the first administration of IMP in the first cycle (the DLT observation period). The goal is to treat 3patients per dose level in order to follow a 3 +3 design. In this FIH study, potential DLTs are defined as the following:

- Any Grade ≥3 nonhematological AE, unless either caused by disease progression or an obviously unrelated cause or caused by a laboratory abnormality without associated clinical consequences that resolves within 5 days (AE's related to cytopenias that were present prior to starting SAR440234 or to underlying leukemia will not be considered DLT's).

- Grade 4 hematological toxicities as defined in NCI-CTCAE v4.03, ie, new onset or worsening of life-threatening hematological abnormalities after administration of SAR440234 (AE's related to cytopenias that were present prior to starting SAR440234 or to underlying leukemia will not be considered DLT's).
  - Grade 4 bone marrow hypocellularity, if not caused by disease progression and not improved to baseline value or Grade ≤1 within 14 days,
  - Grade 4 decreased neutrophils, if not present at baseline and not resolved to baseline value or Grade ≤1 within 14 days,
  - Grade 4 febrile neutropenia not resolved within 7 days,
  - Grade 4 decreased platelet count, if not present at baseline and not improved to baseline value or Grade ≤1 within 14 days,
  - Grade 4 anemia, if not improved to baseline value or Grade ≤1 within 14 days.
- Grade 3 or Grade 4 CRS.
- Grade 2 CRS if it persists for >48 hours or is present <48 hours before the time when the next planned dose of SAR440234 is due.
- Any treatment-emergent adverse event (TEAE) that, in the opinion of the Principal Investigator and Sponsor, is of potential clinical significance such that further dose escalation would expose patients to unacceptable risk.
- IMP-related adverse reaction (unless caused by disease progression or an obviously unrelated cause) lasting more than 2 weeks with failure to recover to baseline or improve to Grade ≤1.

During the Dose Escalation Part, escalation to the next dose level cohort will occur after the last patient has completed the DLT observation period for the previous dose level. Within a dose level, subsequent patients will initiate treatment at least 1 week after the first patient in that dose level started treatment with SAR440234.

The occurrence of DLTs will inform the dose recommendation that will be used during the Expansion Part.

Response will be evaluated by a bone marrow aspirate at the end of Cycle 1 (Day 42 ±2 days). Patients may continue treatment with the IMP as long as clinical benefit is possible, or until disease progression, unacceptable adverse reaction, patient's decision to stop the treatment, or other reason for discontinuation (Section 6.5). Bone marrow aspirate will be performed on Day 42 (±2 days) of Cycle 2. Additional bone marrow aspirate is required if onset of cytopenia >14 days before or after Day 42. Subsequent bone marrow aspirates will be performed when clinically indicated, as determined by the treating physician. Additional bone marrow aspirate shall be performed as clinically indicated or if any of the following occurs: if decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, or anemia Grade 4 occurs with onset in >14 days before or after Day 42.

Response assessment will be performed according to the International Working Group (IWG) 2003 recommendations for AML (19) and the revised 2000 criteria for HR-MDS (34), and the 2016 National Comprehensive Cancer Network (NCCN) Guidelines for ALL (Appendix D, Appendix F, and Appendix H).

If at the end of a cycle the patient exhibits clinical benefit by symptoms or response criteria and does not meet study treatment discontinuation criteria, the patient may continue therapy until an unacceptable AE, disease progression, patient's decision to stop the treatment, or any other reason.

To minimize the risk of severe CRS, an intra-patient dose escalation in Cycle 1 is proposed, as shown in Table 1. Lead-in doses include the first 2 doses in DL1 and DL2 (ie, Week 1 and Week 2 administered doses), the first 3 doses in DL3 to DL5, and the first 4 doses in DL6 to DL8. After the lead-in doses, each patient will receive a fixed dose until the end of treatment, unless the dose needs to be decreased for safety reasons. DL1 to DL8 will achieve a range of lead-in doses from [redacted] and a range of final doses from [redacted]. During each cycle, pharmacokinetic and pharmacodynamic data will be collected that will be used, together with acute safety monitoring, in both the Dose Escalation and Expansion Parts.

Table 1 - Intra-patient dose escalation: Cycle 1

Dose Level	Cycle 1 (doses in ng/kg)						
	Week 1		Week 2	Week 3	Week 4	Week 5	Week 6
	Day 1	Day 4	Day 8	Day 15	Day 22	Day 29	Day 36
DL1	[redacted]						
DL2							
DL3							
DL4							
DL5							
DL6							
DL7							
DL8							

DL=dose level

For subsequent cycles, patients will maintain the maximum weekly dose that they achieved in Cycle 1, as shown in Table 2.

Table 2 - Patient dosing after Cycle 1

	Cycle ≥2 (doses in ng/kg)					
Dose Level	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
DL1	[redacted]					
DL2						
DL3						
DL4						
DL5						
DL6						
DL7						
DL8						

DL=dose level

6.2.2 Dose-limiting toxicity

The DLT observation period is 42 days from the first administration of IMP in the first cycle, with administration of IMP on Day 1, Day 4 (DL ≥3), Day 8, and weekly thereafter. A new dose level may begin 42 days after the last patient at a particular dose level receives his or her first dose of SAR440234.

The goal is to treat 3 patients per dose level in order to follow a 3 +3 design. For a given dose level, the second and third patients will be treated after the first patient at this dose level has been treated for 1 week. In the event of a DLT, the dose level will be expanded to a total of 6 patients, who will be treated at the same dose level that the DLT occurred (3 +3 design). If 1 of the 6 patients experience an IMP-related DLT at the dose level, the dose escalation will proceed with 3 patients per dose level. If ≥2 of 6 patients experience an IMP-related DLT, the MAD has been reached and the dose escalation will be stopped. The dosing plan for DL1to DL8 is summarized in Table 3.

Table 3 - Dose Escalation Part from DL1 to DL8

DLT observed at Cycle 1, in the first 3 patients	DLT observed in the whole cohort
DLT in 0/3 → escalate to the next dose level	-
DLT in 1/3 → add 3 more patients at the same level	- 1 DLT/ 6 patients → escalate to the next level - ≥2 DLTs/ 6 patients → define MAD
DLT in ≥2/3 → no additional patients	Defines MAD

DLT=dose-limiting toxicity; MAD=maximum administered dose

Inclusion of B-ALL patients

At any DL ≥3, patients with B-ALL (see inclusion criterion I 01) may also be recruited in the Dose Escalation Part.

Study continuation

The duration of each cycle of treatment is 42 days, with weekly administration of IMP (except for Cycle 1 Week 1 in DL ≥3 when 2 administrations will be given).

The criteria for retreatment of patients are described in Section 6.5.

The dose given in the second or subsequent cycles will be the last dose given in the previous cycle. If there is a ≥10-day interval between administrations of SAR440234, the next infusion must start with the lead-in doses appropriate for the selected dose level.

Additional pharmacokinetic data, safety and disease response will be assessed as indicated in the flow charts (Section 1.2) and when clinically indicated.

A Study Committee including the main Investigators, Sponsor's clinical team, and ad hoc experts, when appropriate, will regularly review the safety data, and will make recommendations as appropriate. The Study Committee will also decide the RP2D, including the recommended lead-in dose and schedule, for the Expansion Part in R/R AML and HR-MDS patients.

Additional (optional) cohort(s) beyond DL8, or intermediate dose levels, may be evaluated; the decision to proceed with these optional cohort(s), however, will be discussed with the Study Committee and will be based on the available safety, exploratory, and pharmacokinetic data.

It is anticipated that the number of patients enrolled in the Dose Escalation Part will be 30 to 40.

6.3 MAXIMUM ADMINISTERED DOSE / MAXIMUM TOLERATED DOSE

The dose escalation will end when the MAD is reached, which will be defined as the dose at which ≥33% of evaluable patients have experienced an IMP-related DLT during the DLT observation period in a cohort of 6 patients.

The MTD will be defined as the highest dose level at which no more than 1 patient of a maximum of 6 patients experienced an IMP-related DLT.

The patient population evaluable for MTD determination in the Dose Escalation Part will consist of all patients who receive at least 5 out of 6 weekly IV administrations of SAR440234 in DL1 and DL2, patients who receive at least 6 out of 7 IV administrations of SAR440234 in DL ≥3, and patients who discontinue the IMP before completion of Cycle 1 because of a DLT.

A patient who discontinues the IMP before the end of the DLT observation period or does not receive the planned dose for any reason other than DLT, will be replaced by enrolling another patient. The first 3 patients treated during the Dose Escalation Part of TED15138 will be replaced. Another 3 patients will be enrolled in DL1 and the trial will proceed according to the 3+3 design.

The dose level below the MAD will be considered the preliminary MTD, providing DLTs are observed in fewer than 2 of 6 treated patients (or fewer than one-third if more than 6 patients) at that dose level. Intermediate dose levels may be evaluated according to Study Committee recommendations. The MTD is generally the highest dose level at which at most 1 patient of a dose level cohort experiences a DLT.

Although the dose escalation process is guided by the safety evaluation during the DLT observation period, cumulative or irreversible toxicities observed in subsequent administrations should also be considered for the dose escalation and dose selection decisions (ie, smaller increases in dose, expansion of a given dose level, or an intermediate dose level), upon agreement between the participant Investigators and the Sponsor.

In the absence of an MTD, pharmacokinetic and pharmacodynamic parameters may help to define the recommended dose of SAR440234 to be tested in the expansion cohort part of the study.

6.4 RETREATMENT OF PATIENTS

Patients may continue treatment with the IMP as long as clinical benefit is possible, or until disease progression, unacceptable adverse reaction, patient's decision to stop the treatment, or other reason for discontinuation (Section 6.8.1). Details of the criteria to be followed for retreatment of patients following an AE or an interruption in treatment are provided in Section 6.5.

6.5 DOSE DELAYS/MODIFICATIONS

Whenever possible, treatment should be performed on the scheduled days. Doses to be given are those planned unless a dose modification is warranted due to AE. Dose delays, omissions and modifications in response to AEs are delineated in (Section 6.5.3 to Section 6.5.5) and summarized in Table 5 (infusion-related reactions), Table 6 (CRS), Table 7 (hematological AEs), Table 8 (bone marrow hypocellularity Grade 4), and Table 9 (other AEs). The reasons for dose delays or modifications should be documented.

6.5.1 Dose delays

If any infusion (excluding Day 4 infusion) cannot be made on the scheduled day, a time window of +1 or -1 day is allowed. Subsequent infusions should be administered according to the regular weekly schedule.

Dose delay of ≥3 days: If the infusion is administered ≥3 days later than planned, dosing must restart with the lead-in dose (Table 4).

If a Day 4 infusion cannot be made on the scheduled day: The infusion will be made on the next possible day, keeping a 4-day interval before the next infusion. If the infusion cannot be administered within 10 days of the last infusion, dosing must restart with the lead-in dose (Table 4).

6.5.2 Dose modifications

When more than 1 AE is present, treatment modifications will be in accordance with the guidelines for the most severe AE.

Dose modifications, if required, will be a reduction of 1 step (Table 4) from the last administered dose. For example, if the last administered dose was [redacted] (Step 5), a 1 step dose reduction would be to [redacted] (Step 4). Otherwise, the lead-in dose will be based on the last administered dose.

Table 4 - Definition of dose steps

Step	Target Dose (ng/kg)	Lead-in Dosing When Restarting Treatment (if Applicable)
1	[redacted]	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		

IV=intravenous

The target dose is the dose that will be given every 7 days after lead-in dosing. When there is a dose delay of 2 days (ie, <10 days from the last infusion), the dose may be given without the lead-in dose.

If there is a dose delay of ≥3 days (ie, the interval after the last infusion is >10 days) due to an AE, the dose should be reduced and the lead-in dose for the appropriate step should be administered before administering the reduced dose. For example, a 1-step dose reduction from [redacted] to [redacted] would require the lead-in doses for [redacted]. According to the scheme in Table 4, dosing would commence as follows: [redacted] on Day 8, followed by the planned dose of [redacted] IV on Day 15 and every 7 days thereafter.

If an AE requiring dose reduction and lead-in dosing occurs following the [redacted] dose, the 1 ng/kg weekly dose will be administered.

If an AE requiring dose reduction occurs following the [redacted] dose, the IMP will be discontinued.

After a safe and effective dose has been defined, individual patients who are still on study treatment at a different dose may be considered for treatment at another dose or schedule from which they were originally assigned, if this dose and schedule is thought to be safer and/or more effective, and the Sponsor and Investigator agree that it would be beneficial for the patient. If the dose exceeds the originally assigned dose, lead-in dosing will be administered.

6.5.3 Dose delay/modification for cytokine release syndrome and infusion-related reactions

Infusion-related reactions and CRS will be graded according to the 2014 NCI Consensus Guidelines (Appendix H). Recovery is defined as resolution to Grade 1 or less. CRS-like symptoms or signs that occur during infusion will be referred to as infusion-related reactions, while CRS-symptoms or signs that develop or persist after the infusion ends will be referred to as CRS. The patient's temperature, heart rate, blood pressure, oxygen saturation, and respiratory rate will be assessed every 30 minutes during the infusion. If clinical signs of an **infusion-related reaction Grade 1** develop, the infusion will be interrupted, and the patient will be treated with acetaminophen, diphenhydramine, and ranitidine, or similar agents. If the reaction remains at Grade 1 or less, the infusion will resume at 50% of the previous rate after up to 60 minutes of interruption. Up-titration of the rate may be attempted according to Section 8.1.2, provided that the AE remains Grade ≤1. If more than 60 minutes of interruption are required, the AE will be treated as for a Grade 2 infusion-related reaction.

If the **infusion-related reaction is Grade ≥2**, interrupt the infusion and treat the reaction. For Grade 2 infusion reactions, if the AE improves to Grade 1 or less within 48 hours, retreatment will be reattempted on the next scheduled day without a dose escalation, following premedication with dexamethasone, montelukast, acetaminophen, diphenhydramine, and ranitidine, or similar agents. If tolerated well, dose escalation (if planned) may resume with the next dose. If the infusion-related reaction persists for >48 hours, it will be managed as for a Grade 3 infusion-related reaction.

For **Grade 3 or Grade 4 infusion-related reactions**, interrupt the infusion and treat the reaction. The next dose will be omitted. After the AE resolves, treatment will restart on the next subsequent scheduled dosing day with additional premedication. Dose reduction by 1 step must be applied (Table 4). Treatment will restart with the lead-in dose.

For **CRS Grade 1**, no dose modifications or delays are required.

For **CRS Grade 2** that resolves within 48 hours, the next dose should be given on schedule, but without a dose escalation. For **CRS Grade 2 that persists for >48 hours or is present <48 hours before the next dose is scheduled, or a first episode of CRS Grade 3**, the next dose will be omitted. After resolution of the AE, treatment will resume with the lead-in dose and a 1-step dose reduction. For **CRS Grade 3** that fails to resolve to ≤Grade 1 within 72 hours, SAR440234 will be permanently discontinued. For a second or subsequent episode of CRS Grade 3, SAR440234 will be permanently discontinued. If CRS Grade >2 persists for >14 days after the last infusion, SAR440234 will be permanently discontinued.

For **CRS Grade 4**, the SAR440234 infusion must be stopped; no re-start is allowed. Treatment must be permanently discontinued.

Guidelines for the resumption of treatment and dose modification following treatment interruptions are provided in Table 5 (secondary to infusion-related reactions) and Table 6 (secondary to CRS).

Table 5 - Recommendations for resumption of treatment and dose modification following infusion-related reactions during SAR440234 infusion

Grade[a]	During SAR440234 Infusion (Infusion-related reaction)
1	Interrupt infusion and treat reaction, then resume the SAR440234 infusion at 50% of the rate previously achieved, and increase per Section 8.1.2, provided the event remains at Grade 1 or below. If AE requires interruption for >1 hour, treat as for Grade 2 event.
2	Interrupt infusion and treat reaction, then administer next dose on the next scheduled day without a dose escalation, but with additional premedication, provided AE has resolved within 48 hours. If tolerated well, dose escalation (if planned) may resume with subsequent doses. If AE persists for >48 hours, treat as for Grade 3 event.
3 or 4	Interrupt infusion and treat reaction. Omit next dose. After AE resolved, restart treatment on the next scheduled dosing day with additional premedication. Dose reduction by 1 step must be applied (Table 4). Treatment will restart with the lead-in dose. The reaction is a DLT if CRS occurs during Cycle 1.

a Grade of CRS according to the 2014 National Cancer Institute Consensus Guidelines (Appendix H)
AE=adverse event, DLT=dose-limiting toxicity

Table 6 - Recommendations for resumption of treatment and dose modification following cytokine release syndrome after SAR440234 infusion is completed

Grade[a]	After SAR440234 Infusion completed	
	Duration of event <48 hours and event resolved >48 hours before next dose is due	Duration of event >48 hours and/or persistent <48 hours before next dose is due
1	Administer the next dose when planned and escalate the dose (if planned).	
2	Administer the next dose when planned, but do not escalate next dose. If tolerated well, dose escalation may resume subsequently.	Omit next dose. After AE resolved, restart treatment. Dose reduction by 1 step must be applied (Table 4). Treatment will restart with the lead-in dose. The reaction is a DLT if CRS occurs during Cycle 1. If CRS Grade >2 persists for >14 days after the last infusion, SAR440234 will be permanently discontinued.
3	Omit next dose. After AE resolved, restart treatment. Dose reduction by 1 step must be applied (Table 4). Treatment will restart with the lead-in dose. Do not escalate past the target dose. The reaction is a DLT if CRS occurs during Cycle 1 If it fails to resolve to Grade ≤ 1 within 72 hours or if it recurs again, treatment will be permanently discontinued	
4	Permanent discontinuation.	

a Grade of CRS according to the 2014 National Cancer Institute Consensus Guidelines (Appendix H)
AE=adverse event, CRS=cytokine release syndrome, DLT=dose-limiting toxicity

6.5.4 Dose delay/modification for hematological adverse events due to SAR440234

If a patient experiences hematologic AEs (e.g. decreased neutrophil count, decreased platelet count, febrile neutropenia, or anemia) related to the underlying hematologic malignancy or baseline cytopenias and the investigator and Sponsor agree that continuing treatment is safe, the patient will continue treatment with SAR440234 without dose delay and/or modification.

If the AE does not appear to be related to the underlying hematologic malignancy or baseline cytopenias, dose delay and/or modification must be applied as in the following.

Decreased neutrophil count Grade 4, decreased platelet count Grade 4, or febrile neutropenia Grade 3 and Grade 4, and anemia Grade 4:

- If the AE resolves before the time of the next schedule infusion or within ≤10 days after the last infusion, treatment will be given as planned after recovery with dose reduction by 1 step.
- If the AE resolves in 10 to 14 days after the last infusion, omit 1 dose. After recovery, treatment will resume with dose reduction by 1 step, and will restart with the lead-in dose.
- If the AE persists >14 days after the last infusion, a bone marrow aspirate will be performed.
  - If <3 infusions of SAR440234 have been administered, the study treatment will be permanently discontinued,
  - If ≥3 infusions of SAR440234 have already been administered, the patient will resume the study treatment, once the AE has resolved, if there is perceived benefit, and the Investigator and Sponsor agree. Dose reduction by 1 step must be applied, and treatment will resume with the lead-in dose.

Bone marrow hypocellularity Grade 4 for at least 14 days

- The infusion(s) must be omitted until recovery of hypocellularity to baseline or Grade ≤1 and will be documented by a bone marrow aspirate.
- If bone marrow hypocellularity resolves in ≤21 days after the last infusion (ie, 2 doses omitted), treatment will resume with dose reduction by 1 step, and will resume with the lead-in dose.
- If bone marrow hypocellularity persists for >21 days after the last infusion, the following guidelines apply:
  - If <3 infusions of SAR440234 have been administered, the study treatment will be discontinued permanently,
  - If ≥3 infusions of SAR440234 have already been administered, the patient will resume the study treatment, once the AE has resolved, if there is evidence of clinical benefit, and the Investigator and Sponsor agree. Dose reduction by 1 step must be applied, and treatment will resume with the lead-in dose.

Guidelines for the resumption of treatment following treatment interruption secondary to hematological AEs are summarized in Table 7 and Table 8.

Table 7 - Dose delays and modifications for hematological adverse events

Adverse Event	Condition to Continue Treatment	Duration of Adverse Event		
		Resolved in ≤10 days after last infusion	Resolved in 11 to 14 days after last infusion	Persists >14 days after last infusion
Grade 4 decreased neutrophil count Grade 4 decreased platelet count Grade 3 or Grade 4 febrile neutropenia Grade 4 anemia	Recovery to Baseline or Grade ≤1	Administer as planned after recovery. Dose reduction by 1 step.	Omit 1 dose. After AE resolved, restart treatment. Dose reduction by 1 step and restart treatment with the lead-in dose. Do not escalate past the target dose.	If <3 infusions administered before onset of AE, then permanent discontinuation[a] If ≥3 infusions administered before onset of AE, then resume when AE has resolved, if there is evidence of clinical benefit. Dose reduction by 1 step and restart treatment with the lead-in dose.

a If permanent discontinuation is mandated but there is evidence of clinical benefit and the AE has resolved, study treatment may continue if the Investigator and the Sponsor agree

AE=adverse event

Table 8 - Dose delays and modifications for bone marrow hypocellularity Grade 4

Adverse Event	Condition to Continue Treatment	Duration of Adverse Event	
		Resolved in ≤21 days after last infusion	Persists >21 days after last infusion
Grade 4 bone marrow hypocellularity	Recovery to Baseline or Grade ≤1	Omit doses until recovery. Dose reduction by 1 step and restart treatment with the lead-in dose. Do not escalate past the target dose.	If <3 infusions administered before onset of AE, then permanent discontinuation[a] If ≥3 infusions administered before onset of AE: omit 1 dose. Restart treatment when AE has resolved, if there is evidence of clinical benefit. Dose reduction by 1 step and restart treatment with the lead-in dose.

a If permanent discontinuation is mandated but there is evidence of clinical benefit and the AE has resolved, study treatment may continue if the Investigator and the Sponsor agree

AE=adverse event

6.5.5 Dose delay/modification for other adverse events not including hematological adverse events or cytokine release syndrome due to SAR440234

Resolution of an AE requires recovery to baseline or Grade ≤1.

If the AE is related to the underlying hematologic malignancy or baseline cytopenias and the investigator and Sponsor agree that continuing treatment is safe, the patient will continue treatment with SAR440234 without dose delay and/or modification.

If the AE does not appear to be related to the underlying hematologic malignancy or baseline cytopenias, dose delay and/or modification must be applied as in the following.

For patients with AEs that are not hematological and/or not CRS or infusion-related reactions, the administration of SAR440234 should be modified as follows:

Grade 1:

- Continue treatment as planned.

Grade 2:

- If the AE is resolved before the time of the next scheduled infusion, or within ≤10 days after the last infusion, treatment will continue without change after recovery.
- If the AE is resolved >10 days after the last infusion, omit 1 dose. After recovery, treatment will restart with the lead-in dose (Section 6.5.2) as appropriate to achieve the same step that was administered prior to the onset of the AE.
- If the patient experiences a third episode of the same AE, the study treatment will be permanently discontinued.

Grade 3:

- If the AE is resolved before the time of the next scheduled infusion, or within ≤10 days after the last infusion, treatment will be continued with a dose reduction of 1 step (Section 6.5.2) after recovery.
- If the AE is resolved in 10 to 14 days after the last infusion, omit 1 dose. After recovery, treatment will resume with dose reduction by 1 step. Treatment will restart with the lead-in dose.
- If the AE is not resolved in ≤14 days after the last infusion, treatment will be permanently discontinued.
- If the patient experiences a second episode of the same AE, the study treatment will be permanently discontinued.

Grade 4:

- The next infusion will be omitted.
- If the AE resolves in ≤14 days after the last infusion, if there is perceived benefit, and the Investigator and Sponsor agree, treatment will restart with the lead-in dose. Dose reduction by 1 step will be applied.
- If the AE is not resolved in ≤14 days after the last infusion, treatment will be permanently discontinued.
- If the patient experiences a second episode of the same AE, the study treatment will be permanently discontinued.

Guidelines for the resumption of treatment following treatment interruption secondary to AEs other than hematological AEs, CRS, or infusion-related reactions are provided in Table 9.

Table 9 - Dose delay and dose modification for adverse events not including hematological adverse events, cytokine release syndrome, or infusion-related reactions

Grade	Condition to Continue Treatment	Duration of adverse event			Second Episode	Third Episode
		Resolved in <10 days after last infusion	Resolved in 10 to 14 days after last infusion	Persisting >14 days after last infusion		
1	Not applicable	No change			No change	No change
2	Recovery to Baseline or Grade ≤1	Administer as planned on recovery with dose as planned.	Omit 1 dose Restart after AE resolved. Treatment will restart with the lead-in dose. May escalate to planned dose level.	Omit 1 dose. Restart after AE resolved. Treatment will restart with the lead-in dose. May escalate to planned dose level.	Allowed. Same recommend-ation as for first episode.	Permanent discontinua-tion[a]
3	Recovery to Baseline or Grade ≤1	Administer as planned on recovery. Dose reduction by 1 step.	Omit 1 dose. Restart after AE resolved. Dose reduction by 1 step and treatment will restart with the lead-in dose. Do not escalate past target dose.	Permanent discontinuation[a]	Permanent discontinua-tion[a]	Not applicable
4	Recovery to Baseline or Grade ≤1	Omit 1 dose. Restart after AE resolved if evidence of clinical benefit. Treatment restart will be with dose reduction by 1 step and with the lead-in dose. Do not escalate past target dose.		Permanent discontinuation[a]	Permanent discontinua-tion[a]	Not applicable

a If permanent discontinuation is mandated but there is evidence of clinical benefit and the AE has resolved, study treatment may continue if the Investigator and the Sponsor agree

AE=adverse event

6.6 EXPANSION COHORT TO CONFIRM THE MTD

Approximately 37 patients will be treated at the RP2D of SAR440234 to collect safety, pharmacokinetic, pharmacodynamic, and preliminary efficacy data. Patients treated at the RP2D in the Dose Escalation Part (except B-ALL patients) together with the patients treated in the Expansion Part to a total of the first 17 patients treated at the RP2D (Stage 1 Phase 2), will be included in the efficacy analysis.

Additional or unexpected toxicities will also be explored using all the data gathered during the study course (not only at the RP2D). The occurrence of cumulative toxicity, and toxicities meeting the DLT criteria observed after the DLT observation period, if any, will also be assessed. The preliminary antitumoral activity (ie, tumor response) of the drug will be evaluated according to the IWG 2003 recommendations for AML (19) and the revised 2000 criteria for HR-MDS (34), and the 2016 NCCN Guidelines for ALL (Appendix D, Appendix F, and Appendix G).

6.7 GUIDELINES FOR MANAGEMENT OF ADVERSE EVENTS

6.7.1 Recommendations for management of Cytokine Release Syndrome

SAR440234 will be administered by IV infusion in cycles of 42 days, with weekly administration of IMP (except for Cycle 1 Week 1 in DL ≥3 when 2 administrations will be given). Before the start of each infusion, the following evaluation must be made: blood pressure, heart rate, oxygen saturation, respiration rate, and body temperature. Blood chemistry and complete blood count with differential must be obtained <8 hours before starting the SAR440234 infusion and should be within the range prescribed in the inclusion criteria (Section 7.2) and exclusion criteria (Section 7.3).

Dexamethasone 20 mg IV will be administered as premedication 4 hours and 1 hour prior to each initial IMP administration.

Montelukast 10 mg oral (PO) will be given once, 4 hours before the start of SAR440234 infusion.

Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. This rule will be applied for the same patient who experiences a CRS event for subsequent infusions and for all patients subsequently enrolled at that dose level or higher.

If CRS occurs, it will be graded according to the 2014 NCI Consensus Guidelines (Table 10) and will be managed as described in Table 11 (31). Patients may require high dose vasopressors, as described in Table 12. Guidelines for when and if a patient may resume treatment with SAR440234 if CRS or an infusion-related reaction develops during or after an infusion of SAR440234 are provided in Table 5 and Table 6 (Section 6.5).

Table 10 - Grading of cytokine release syndrome according to 2014 National Cancer Institute Consensus Guidelines

Grade	Definition
1	Symptoms are not life-threatening and require symptomatic treatment only; eg, fever, nausea, fatigue, headache, myalgias, malaise
2	Symptoms require and respond to moderate intervention Oxygen requirement <40% fraction of inhaled oxygen or hypotension responsive to fluids or low-dose pressors or Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention Oxygen requirement <40% fraction of inhaled oxygen or hypotension requiring high-dose or multiple pressors or Grade 3 organ toxicity or Grade 4 transaminitis
4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
5	Death

Table 11 - Evaluation and management of cytokine release syndrome

Grade	Evaluation	Treatment
1	Monitoring at least every 30 minutes: • BP, HR, temperature, respiratory rate, oxygen saturation. • Symptom assessment.	Symptomatic treatment with acetaminophen and/or antihistamine, if needed
2	As for Grade 1, with addition of the following: Continuous monitoring of: • BP. • Oxygen saturation. • HR. Monitoring at least every 8 hours, or more frequently if needed, of: • PaO_2. • ECG. • Blood chemistry.	As for Grade 1, with addition of the following: • Mandatory transfer of the patient to ICU. • IV fluid resuscitation and institution of vasopressors. • Supplemental oxygen. • Start tocilizumab: - 8 mg/kg IV once for patients weighing ≥30 kg, - 12 mg/kg IV once for patients weighing <30 kg, - If insufficient improvement in CRS within 12 hours, repeat tocilizumab at the same dose every 12 hours for a total of 3 doses.
3	As for Grade 2, with the addition of echocardiography if there is concern for cardiac dysfunction.	As for Grade 2, with addition of the following: • High-dose or multiple vasopressors Table 12 to treat hypotension or poor perfusion. • If no improvement in CRS within 24 hours, start dexamethasone 10 mg IV every 6 hours.
4	As for Grade 3.	As for Grade 3, with the addition of mechanical ventilation if required.

BP=blood pressure, CRS=cytokine release syndrome, ECG=electrocardiogram, HR=heart rate, ICU=intensive care unit, IV=intravenous, PaO_2=partial pressure of oxygen in arterial blood
NOTE: Grading of CRS is based according to 2014 National Cancer Institute Consensus Guidelines (see Table 10).

For each patient treated, the hospital must have an available bed in the intensive care unit (ICU) in case the patient develops hemodynamic or respiratory compromise. The ICU should be staffed by a critical care physician who has experience in treating CRS. In addition, the ICU must have the necessary equipment to commence immediate treatment and monitoring of a patient with CRS Grade ≥2 before he/she is admitted to ICU. Vital signs monitoring shall be made continuously if CRS Grade ≥2 develops.

High dose vasopressors are described in Table 12.

Table 12 - High dose vasopressors

Vasopressor	Dose
Norepinephrine monotherapy	≥20 mg/min
Dopamine monotherapy	≥10 mg/kg/min
Phenylephrine monotherapy	≥200 mg/min
Epinephrine monotherapy	≥10 mg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥10 mg/min
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent to ≥20 mg/min

All doses are required for ≥3 hours

Dexamethasone, vasopressors, and oxygen must be tapered quickly after resolution of CRS.

Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. This rule will be applied for the same patient who experienced a CRS event for subsequent infusions and for all patients subsequently enrolled at that dose level or higher.

Symptomatic treatment and/or pre-medication may include: diphenhydramine 25 to 50 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent), and acetaminophen 650 to 1000 mg PO 15 to 30 minutes (but no longer than 60 minutes) prior to infusion, or during infusion at the Investigator's discretion.

For patients with CRS Grade ≥2, tocilizumab will be administered at 8 mg/kg infused over 1 hour for patients weighing ≥30 kg (maximum dose 800 mg) or 12 mg/kg infused over 1 hour for patients weighing <30 kg. Another 8 mg/kg or 12 mg/kg dose IV may be administered in patients weighing ≥30 kg (maximum dose 800 mg) or 12 mg/kg for patients weighing <30 kg, respectively, if there is insufficient clinical improvement 12 to 24 hours after the first dose. Up to 3 doses of tocilizumab may be given.

6.7.2 Tumor Lysis Syndrome (TLS)

Blood chemistry (creatinine, potassium, calcium, magnesium, phosphorus, and uric acid) will be monitored every 8 hours for 72 hours after start of infusion to monitor for tumor lysis. If it occurs, appropriate treatment will be initiated that will include correction of serum calcium, potassium, or phosphorus abnormalities, and treatment of hyperuricemia with allopurinol and/or rasburicase, as indicated in Appendix J (35).

6.7.3 Hematological adverse events

Patients will receive packed red blood cells and platelet transfusions to manage anemia and thrombocytopenia, if needed. In addition, G-CSF may be administered to patients with neutropenia, except in Cycle 1 of the Dose Escalation Part. Antibiotics will be provided to patients with febrile neutropenia, in accordance with local practice. Details on the management of hematological toxicity are provided in Section 6.5.4.

6.7.4 Other adverse events

Other toxicities must be managed as clinically indicated. Details on dose delay and modification of dosing for patients with other toxicities are provided in Section 6.5.5.

6.7.5 Initiation of a new cycle of therapy

In the Dose Escalation Part, at the end of Cycle 1, 43 days after the first SAR440234 infusion, a patient may begin Cycle 2 if he or she did not experience a DLT. Details on the start of the next infusions are provided in Section 6.5.

In the Dose Escalation Part Cycle 2 and beyond, and for the Expansion Part Cycle 1 and beyond, details on the start of the next infusions are provided in Section 6.5.

6.8 DURATION OF STUDY PARTICIPATION

6.8.1 Duration of study participation for each patient

The duration of the study 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 DL ≥3 when 2 administrations will be given). After study treatment discontinuation, patients will return to the study site 30 days after the last IMP administration for end of treatment assessments. If a patient discontinues SAR440234 prior to day 42, the day 42 evaluation must be performed on the day that the decision is made that the patient will not continue treatment with SAR440234. EOT evaluation for a patient must be performed within 30 days of the last administration of SAR440234 received by the patient. If a patient does not plan to return to the study site for an EOT visit, the EOT evaluation must be performed on the day that the decision is made that the patient will not continue treatment with SAR440234.

Patients may continue treatment with the IMP as long as clinical benefit is possible, or until disease progression, unacceptable adverse reaction, patient's decision to stop treatment, or other reason for discontinuation. During the follow-up period, IMP-related AEs and all serious adverse events (SAEs) (regardless of relationship to study treatment) present at the time of study treatment discontinuation will be followed every month until resolution or stabilization, or until initiation of another antineoplastic therapy. If a patient is unable to attend monthly follow-up visits, the investigator will obtain follow up information via telephone call and record review from the treating physicians.

Clinical benefit is defined as: CR, CRi, PR, reduction of blast count, stabilization of symptoms and conditions, or any other clinical benefit identified and documented by the Investigator.

Patients without documented disease progression at the end of a treatment visit who have not yet started treatment with another anti-cancer therapy will proceed with monthly follow-up visits until initiation of another anti-cancer therapy, disease progression, study cut-off date, or death, whichever comes first. If a patient is unable to attend monthly follow-up visits, the investigator will obtain follow up information via telephone call and record review from the treating physicians.

The first cut-off date will be at the end of the first cycle of the last patient treated in the Dose Escalation Part in order to have at least the first cycle evaluable for all patients for determination of the MTD and for the RP2D.

The second cut-off date will be when the last patient in the Expansion Part will have been treated for 2 cycles (approximately 3 months), or has early progression, whichever occurs first, in order to assess tumor response. After the second cut-off date, ongoing patients will receive study treatment until disease progression or occurrence of an AE leading to treatment discontinuation, whichever is earlier, and they will only be followed for study treatment administration, SAEs, study treatment-related AEs, and reason for end of treatment.

6.8.2 Determination of end of clinical trial (all patients)

The clinical trial will end 30 days after the last IMP administration.

6.9 INTERIM ANALYSIS

An interim analysis is planned after the first 17 patients of the Expansion Part. Refer to Section 13.5 for details on interim analysis.

6.10 STUDY COMMITTEES

The Study Committee will include the Principal Investigator or delegate at each site, clinical team members from the Sponsor, and independent ad hoc experts, when appropriate. The Study Committee will review clinical data, including SAEs, adverse events of special interest (AESIs), DLTs, and deaths, on a regular basis. The Study Committee will decide whether or not to escalate to the next dose level based on their knowledge of the whole safety profile and on the design of the study. The Study Committee will also make recommendations on the choice of the RP2D. Decisions regarding patient treatment and cohort expansion will be discussed and will be clearly documented in the discussion minutes.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

It is anticipated that approximately 72 patients (67 to 77 patients) will be enrolled in this study: 30 to 40 patients in the Dose Escalation Part and 37 patients in the Expansion Part (Section 13.1).

7.2 INCLUSION CRITERIA

I 01. Confirmed diagnosis of primary or secondary AML (any subtype except acute promyelocytic leukemia) according to World Health Organization (WHO) classification or MDS with a Revised International Prognostic Scoring System (R-IPSS) risk category of intermediate or higher (36) (Appendix E). Patients must have exhausted available treatment options and must not be eligible for any treatment known to provide clinical benefit.

I 02. Patients with AML must have relapsed or refractory disease that has been resistant to available therapies, as defined by any 1 of the following criteria:

- Leukemia refractory to ≥2 intensive remission induction attempts,
- Leukemia in first relapse within 1 year following allogeneic stem cell transplant,
- Leukemia in second or higher relapse,
- Not eligible for intensive remission induction therapy and have persistent leukemia despite ≥2 cycles of therapy, including any of the following: hypomethylating agent (eg, decitabine or 5-azacitidine), chemotherapy, or targeted agents (eg, gemtuzumab ozogamicin or enasidenib).

I 03. During the Dose Escalation Part, patients with B-ALL without extramedullary lesions, in second or subsequent relapse, could also be recruited at any DL ≥3 during the 3 +3 escalation period. B-ALL patients should have completed previously ≥1 cycle of a salvage regimen, including any of the following: chemotherapy, blinatumomab, tyrosine kinase inhibitors, cellular therapy (eg, tisagenlecleucel), or targeted agents (eg, inotuzumab ozogamicin). Patients must have exhausted available treatment options and must not be eligible for any treatment known to provide clinical benefit.

I 04. Patients with HR-MDS must have >10% blasts in the bone marrow at the time of enrollment and fit one of the following categories:

- Not eligible for induction therapy and having completed ≥2 cycles of therapy, including any of the following: hypomethylating agent (eg, 5-azacitidine or decitabine), chemotherapy, or targeted agents.
- Not eligible for allogeneic stem cell transplant and having completed ≥1 course of induction therapy.

I 05. Signed written informed consent.

7.3 EXCLUSION CRITERIA

Patients who have met the above inclusion criteria listed in Section 7.2 for one of R/R AML, B-ALL, or HR-MDS, will be screened for the following exclusion criteria:

E 01. Age <16 years old.

E 02. Eastern Cooperative Oncology Group (ECOG) performance status >2 (11).

E 03. Abnormal laboratory parameters, including the following:

- Total bilirubin >1.5 x ULN unless Gilbert's syndrome is present,
- ALT, AST, or alkaline phosphatase >2.5 x ULN,
- Serum creatinine >2 x ULN and/or creatinine clearance <30 mL/min,
- Grade 4 hematological toxicity: febrile neutropenia, bone marrow hypocellularity, symptomatic disseminated intravascular coagulation, life-threatening anemia, or life-threatening thrombotic thrombocytopenic purpura,
- White blood cell count > 30,000/mm^3.
    - If the white blood count exceeds 30,000/mm^3, hydroxyurea may be used to reduce the white blood cell count to < 30,000/ mm^3 at start of treatment.
    - Hydroxyurea may be administered to patients at the Investigator's discretion during Cycle 1, but must be stopped ≥1 day prior to Cycle 2, Day 1.

E 04. Graft-versus-host disease following allogeneic stem cell transplantation requiring treatment with more than 10 mg of oral prednisone or equivalent daily. The stem cell transplant and/or donor lymphocyte infusion should have been performed more than 3 months before study treatment start.

E 05. History of an active or chronic autoimmune condition that has required or requires therapy.

E 06. Prior treatment with an anti-CD123-directed agent.

E 07. Second primary malignancy that requires active therapy. Adjuvant hormonal therapy is allowed.

E 08. Previous treatment with chemotherapy, radiotherapy, or immunotherapeutic agents in the 4 weeks prior to IMP administration (Cycle 1 Day 1), except for hydroxyurea.

E 09. Previous treatment with any other investigational agent in the 4 weeks prior to IMP administration (Cycle 1 Day 1).

E 10. Receiving at the time of first IMP administration concurrent steroids >10 mg/day of oral prednisone or the equivalent for ≥3 months, except steroid inhaler, nasal spray, or ophthalmic solution.

E 11. Requirement for tocilizumab for any other diagnosis within ≤14 days before the first administration of SAR440234.

E 12. Known contraindication to any of the noninvestigational medicinal products (NIMPs) (dexamethasone and tocilizumab), acetaminophen, diphenhydramine, ranitidine, montelukast or similar agents.

E 13. Evidence of active central nervous system leukemia at the time of enrollment.

E 14. Known acquired immunodeficiency syndrome (AIDS-related illnesses) or HIV disease requiring antiretroviral treatment, or having active hepatitis A, B or C infection, or tuberculosis.

E 15. Pregnant and breast-feeding women, female patients of childbearing potential, and male patients with female partners of childbearing potential who are not willing to avoid pregnancy by using an adequate method of contraception (2 barrier method or 1 barrier method with a spermicide, intrauterine device, or hormonal contraception with inhibition of ovulation, for 2 weeks prior to the first dose of SAR440234, during treatment, and 12 weeks after the last dose of study treatment). A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile.

E 16. Any country-related specific regulation that would prevent the patient from entering the study.

E 17. Any clinically significant, uncontrolled medical conditions that, in the Investigator's opinion, would expose excessive risk to the patient or may interfere with compliance or interpretation of the study results.

E 18. Patients weighing <60 kg (DL1, DL2, and DL3 only).

Patients who have been withdrawn from the study after the study treatment has started cannot be reincluded in the study. Their inclusion and treatment number must not be re-used.

Rescreening is permitted for patients who have not received treatment in this study.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

The IMP is presented as a lyophilisate powder for solution for IV injection at [redacted] (CD3-CD123) [redacted]

8.1.1 Dose of drug per administration

Starting dose of SAR440234 is described in Section 6.2.

8.1.2 Preparation, reconstitution, and administration of SAR440234

Dilution method, calculation of volume to be infused, and administration of SAR440234 are detailed in the Pharmacy Manual.

SAR440234 requires a [redacted], as detailed in the Pharmacy Manual. Special care should be taken to avoid accidental overdose with the medication.

Infusion-related reactions are expected, thus infusion rates should be gradually increased every 30 minutes, as tolerated, for each administration. Minimum and maximum infusion rates have also been defined for each dose level, as described in the Pharmacy Manual.

[redacted]

The infusion rate schedule for SAR440234 is described in the Pharmacy Manual.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Dexamethasone: 4 mg/mL for IV injection.

Tocilizumab: 200 mg/10 mL vial for IV injection.

Montelukast: 10 mg tablet for oral administration.

Dexamethasone 20 mg IV will be instituted as systematic premedication 4 hours and 1 hour prior to each initial IMP administration.

Montelukast tablets 10 mg will be given orally once, 4 hours before the start of SAR440234 infusion.

Dexamethasone 20 mg IV must be repeated 5 hours after the start of infusion if CRS Grade 2 has occurred in a previous patient or previous administration in the same patient. This rule will be applied for the same patient who experiences a CRS event for subsequent infusions and for all patients subsequently enrolled at that dose level or higher.

For each patient treated, the clinical site must have at least 2 full doses of tocilizumab in the clinical pharmacy ready for immediate administration in case of CRS Grade 2 or above. Guidelines for management of patients with CRS are included in Section 6.7.

For patients with Grade 2 CRS, tocilizumab will be administered at 8 mg/kg infused over 1 hour for patients weighing ≥30 kg (maximum dose 800 mg) or 12 mg/kg infused over 1 hour for patients weighing <30 kg.

If there is insufficient improvement in CRS within 12 hours, tocilizumab may be repeated at the same dose every 12 hours for a total of 3 doses. The interval between consecutive doses should be at least 8 hours. Subcutaneous infusion of tocilizumab is not approved for CRS treatment. Tocilizumab must not be used for prophylaxis of CRS. Patients with Grade 3 or Grade 4 CRS should be treated with tocilizumab as for patients with Grade 2 CRS. For patients with Grade 3 or Grade 4 CRS who do not respond to tocilizumab within 24 hours, dexamethasone 10 mg IV should be given every 6 hours.

For patients weighing ≥30 kg or more, tocilizumab should be diluted in 100 mL of 0.9% or 0.45% sodium chloride injection USP for IV infusion and administered by drip infusion over 1 hour. For patients weighing <30 kg, tocilizumab should be diluted in 50 mL of 0.9% or 0.45% sodium chloride USP for IV infusion and administered by drip infusion over 1 hour. Tocilizumab should not be given as a bolus or push.

8.3 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

SAR440234 will be supplied in boxes of [redacted].

Packaging is described in the Pharmacy Manual.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.4 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP/NIMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling the sanofi compound must be managed according to the rules provided by the Sponsor.

SAR440234 must be stored at [redacted]. All vials must be kept in their box until use.

Details of the storage conditions for the diluted solution are provided in the Pharmacy Manual.

8.5 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

The IMP will be dispensed in accordance with the Investigator's prescription, and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP; deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.5.7).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.5.1 Treatment accountability and compliance

Administration of the IMP will be supervised by the Investigator or Subinvestigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP. These records (eg, drug movement form) include the date the IMP is received from the Sponsor, dispensed for patient, and destroyed or returned to the Sponsor. The packaging batch number (PR Nr) on the vial must be recorded on the drug accountability form.

The person responsible for drug administration to the patient will record precisely the date, infusion rate, and start and stop times of the drug administration to the patient.

8.5.2 Return and/or destruction of treatments

All used and partially used IMP (SAR440234) will be destroyed at the study site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist).

All unused IMP may be destroyed at the site or retrieved by the Sponsor. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

A detailed treatment log form of the destroyed and/or returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

8.6 CONCOMITANT TREATMENT

All treatments being taken by the patient 14 days prior to registration onto the study, or at any time during the study in addition to the IMP are regarded as concomitant treatments, and the type, dose and route of administration must be documented on the appropriate pages of the eCRF. Hydroxyurea may be administered to patients at the Investigator's discretion during cycle 1 but must be stopped ≥1 day prior to the start of cycle 2.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the eCRF:

- Supportive treatment as medically indicated for the patient's wellbeing may be prescribed at the Investigator's discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the eCRF.

Details of specific treatments for the management of AEs are provided in Section 6.7.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies.
- Radiotherapy, even if palliative in intent, may not be given during the study.
- Prophylactic use of hematopoietic growth factors (eg, G-CSF, GM-CSF, erythropoietin) during the DLT observation period in the Dose Escalation Part only.
- Cytokine release may modulate CYP450 enzymes (decrease activity) and cause drug-drug interactions by increasing concentrations of drugs primarily metabolized by CYPs. Therefore, patients treated or intended to be treated with drugs known to be CYP substrates with a narrow therapeutic index (Appendix B) should be carefully monitored for toxicity. Cytokine release may also have an impact on transporters. Therefore, patients should be monitored closely when treated, or intended to be treated, with transporter substrates that have a narrow therapeutic index. These drugs include: digoxin, glyburide, and methotrexate.

8.7 POST INVESTIGATIONAL MEDICINAL PRODUCT

The patient's treatment plan after discontinuation of the IMP will be at the discretion of the treating physician.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 SAFETY

The major purpose of this Phase 1/2A study is to establish, based on DLTs, the MTD of SAR440234 administered IV weekly (except for Cycle 1 Week 1 in DL ≥3 when 2 administrations will be given) to patients with hematologic malignancy (R/R AML, B-ALL, or HR-MDS). Safety is thus the primary study endpoint and will be assessed continuously.

The safety profile will be assessed from the findings of physical examinations (preferably by the same physician in each center), laboratory tests, and reports of AEs, etc, and will be based on incidence, severity (as graded by the NCI-CTCAE v4.03; except for CRS, which will be graded according to the 2014 NCI Consensus Guidelines, Table 10), and cumulative nature of TEAEs (defined as AEs that develop or worsen in grade or become serious during the on-treatment period).

9.1.1 Dose-limiting toxicities

With an objective of defining the RP2D and dose schedule, the safety of SAR440234 will be evaluated using the following assessments during the Dose Escalation Part:

- Incidence of DLT (as defined in Section 6.2.1) observed during the DLT observation period (6 IMP administrations).
- Incidence of allergic reactions/hypersensitivity and CRS/acute infusion reactions.

Potential and IMP-related DLTs will be considered as AESIs. As such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of each event. The Investigator will attach the DLT-specific CRF page to the transmitted DLT/AESI form or will complete the specific DLT form in the electronic case report form (eCRF).

Potential DLTs are defined as the occurrence of any of the following related to the study therapy using NCI-CTCAE v4.03, or the NCI Consensus Guidelines for grading CRS (Table 10), as appropriate:

Hematological abnormalities:

- Grade 4 hematological toxicities, ie, new onset or worsening of life-threatening hematological abnormalities after administration of SAR440234:
  - Grade 4 bone marrow hypocellularity, if not caused by disease progression and not improved to baseline value or Grade ≤1 within 14 days,
  - Grade 4 decreased neutrophils, if not present at baseline and not resolved to baseline value or Grade ≤1 within 14 days,
  - Grade 4 febrile neutropenia not resolved within 7 days,

- Grade 4 decreased platelet count, if not present at baseline and not improved to baseline value or Grade ≤1 within 14 days,
- Grade 4 anemia, if not improved to baseline value or Grade ≤1 within 14 days.

Nonhematological abnormalities:

- Any Grade ≥3 nonhematological AE unless either caused by disease progression or obviously unrelated cause or caused by a laboratory abnormality without associated clinical consequences that resolves within 5 days.
- Any TEAE that, in the opinion of the Principal Investigator and Sponsor, is of potential clinical significance such that further dose escalation would expose patients to unacceptable risk.
- Grade 3 or Grade 4 CRS.
- Grade 2 CRS if it persists for >48 hours or is present <48 hours before the time when the next planned dose of SAR440234 is due.

Other: IMP-related adverse reaction leading to a delay or omission of more than 2 weeks between 2 planned administrations of SAR440234 due to failure to improve to baseline or Grade ≤1.

At the end of each appropriate cycle (ie, end of Cycle 1), each patient must be assessed by the Investigator as to whether or not the patient experienced a DLT. This information must be recorded on the appropriate eCRFs, and an electronic DLT notification (either DLT or not) will be sent to the Sponsor, before a subsequent cycle may begin.

The reported potential DLTs will be reviewed by the study committee in order to determine their relationship to the IMP.

9.1.2 Adverse events

Adverse events will be collected from the signing of the study main informed consent up to 30 days after the last IMP administration. During the follow-up period, ongoing SAEs regardless of relationship to IMP, and ongoing or new study treatment related AEs will be followed until resolution or stabilization. Adverse events encountered before the start of SAR440234 treatment will be summarized separately.

Pretreatment AEs, TEAEs, and post-treatment AEs will be graded according to the NCI-CTCAE v4.03, or the NCI Consensus Guidelines for grading CRS (Table 10) as appropriate, and will be coded to a “Preferred Term” and associated primary “System Organ Class” using the version of MedDRA (Medical Dictionary for Regulatory Activities). Adverse events will be summarized with respect to the type, frequency, severity, seriousness, and relatedness

The study-specific and general safety criteria are developed in Section 10.

9.1.3 Laboratory safety variables

The schedule for laboratory assessment is described in Study Procedures (Section 12) and Study Flowcharts (Section 1.2).

9.1.4 Clinical examinations

The schedule for clinical examinations is described in the Study Procedures (Section 12) and the Study Flowcharts (Section 1.2).

9.1.5 Immunogenicity

9.1.5.1 Sampling times

The blood collection time points are defined in the pharmacokinetic/pharmacodynamic flow charts (Section 1.3) to measure ADA in plasma and to conduct the immunogenicity analysis. The sampling times schedule for ADA detection may be modified (ie, samples omitted) based on updated knowledge of SAR440234 potential immunogenicity. Immunogenicity sampling will be stopped at the second study cut-off date in all patients.

It is of utmost importance to collect all blood samples at the specified times and according to the specifications.

Samples missed or lost for any reason should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be recorded precisely.

The remaining plasma samples will be kept for other possible exploratory analysis. The results of this analysis will not be included in the clinical study report but in a stand-alone report, if applicable.

9.1.5.2 Sample handling procedures

Detailed instructions for sample preparation and shipping for SAR440234 ADA assay samples will be provided to the study sites in a separate Laboratory Manual.

9.1.5.3 Bioanalytical method

The bioanalytical methods used for immunogenicity assessment will be performed according to a validated method under the responsibility of Sanofi Biomarkers and Clinical Bioanalyses Department (Alfortville, France).

9.1.6 Other safety endpoints

Safety assessments are described in the Study Procedures (Section 12) and the Study Flowcharts (Section 1.2).

9.2 PHARMACOKINETIC EVALUATION

9.2.1 Sampling times

The blood collection time points are defined in the pharmacokinetic/pharmacodynamic flow charts (Section 1.3) to measure SAR440234 concentrations in plasma and to conduct the pharmacokinetic analysis. The sampling times schedule may be modified (ie, samples omitted) based on updated knowledge of SAR440234's pharmacokinetic behavior. Pharmacokinetic sampling will be stopped at the second study cut-off date in all patients.

- It is of utmost importance to collect all blood samples at the specified times and according to the specifications.
- Samples missed or lost, for any reason should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. The dates and times of drug administration should also be recorded precisely.
- Remaining plasma samples will be kept for other possible exploratory analysis. Results of this analysis will not be included in the clinical study report but in a stand-alone report, if applicable.

9.2.2 Pharmacokinetic sample handling procedure

Detailed instructions for pharmacokinetic sample preparation will be provided to the study sites in a separate Laboratory Manual.

9.2.3 Bioanalytical method

The bioanalytical method used for pharmacokinetic assessment will be performed according to a validated method under the responsibility of Sanofi Biomarkers and Clinical Bioanalyses Department (BCB, Alfortville, France).

9.2.4 Pharmacokinetic parameters

The pharmacokinetic analysis will be carried out by Pharmacokinetic, Dynamic & Metabolism group (PKDM, Alfortville, France). Pharmacokinetic parameters will be calculated with PKDMS software (Pharsight), using noncompartmental methods from SAR440234 plasma concentrations. The parameters will include, but may not be limited to those listed in (Table 13). Additionally, a modeling approach may be used if deemed relevant and applicable.

Table 13 - List of pharmacokinetic parameters and definitions

Parameters	Definition
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 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)

9.3 PHARMACOGENETIC ASSESSMENT

Not applicable.

9.4 SPECIFIC ASSESSMENTS

9.4.1 Biomarker assessments

Exploratory endpoints include:

- 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 at the study sites in bone marrow aspirates 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.

Specific assessments are described below. Additional analysis, not specified in the protocol but related to the drug safety, action and/or effect of SAR440234, may be conducted on remaining samples pending evolving literature.

9.4.1.1 Cytokine and acute phase protein assessment

Plasma levels of pro-inflammatory cytokines, including IL-6 and IFN-γ, as well as blood levels of 2 acute phase proteins, CRP, and ferritin, will be assessed during the trial (Section 1.3). Samples will be collected at screening and for those patients who have already entered the trial at predose, and during Cycle 1 and Cycle 2. Planned sampling times for cytokine and acute phase protein assessment can be found in the pharmacokinetic/immunogenicity flow charts. The sampling times schedule for cytokines and acute phase protein assessment may be modified (ie, samples omitted) based on updated knowledge during the course of the study. Cytokine analysis will be performed in a centralized laboratory (contract research organization [CRO]). CRP and ferritin measurements will be performed locally at sites.

Additional samples for analysis of cytokines and acute phase proteins must be collected in case of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.

Refer to separate laboratory manual for details concerning handling procedures.

9.4.1.2 Immunophenotyping by flow cytometry

Immunophenotyping will be performed on blood and bone marrow samples at screening, and for those patients who have already entered the trial as planned in the study flow charts (Section 1.3). Analysis will include monitoring of CD123 expression on normal cells, of CD123 expression in leukemic cells and kinetics of this expression under treatment and of T-cell subpopulations (eg, CD4, CD8), and activation status among other potential subpopulations. Processing of samples and analysis will be performed in a centralized laboratory (CRO). Immunophenotyping sampling will be stopped at the second study cut-off date in all patients.

Refer to separate laboratory manual for details concerning handling procedures.

9.4.1.3 Disease molecular subtype

Information about disease molecular subtype will be collected at screening. Disease molecular subtype could be reassessed locally when clinically indicated.

9.4.1.4 Minimal residual disease

The modalities of MRD evaluation should be identified and a baseline level of disease involvement should be determined from the Screening bone marrow aspirate. MRD evaluation will be performed on the bone marrow if the patient enters CR or CRi. If MRD is positive, the MRD assessment will be repeated on subsequent bone marrow evaluations, or as clinically indicated. This assessment will be performed locally, if available.

9.5 SAMPLED BLOOD VOLUME

The volume of blood to be collected during the trial and a description of the samples and their processing are described in the laboratory manual.

9.6 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patients who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to oncology that are defined in the present protocol.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioanalytical method, or to identify new drug targets or biomarkers.

These samples will remain labeled with the same identifiers used during the study (ie, patient ID). They will be transferred to a sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see Section 16.3 and Section 16.5).

9.7 EFFICACY

In the Expansion Part, disease response for R/R AML and HR-MDS will be an additional primary endpoint:

- Preliminary anti-leukemia and anti-MDS activity as defined by IWG (34):
  - Overall response rate (ORR) including CR, CRi, and PR,
  - Duration of response,
  - Event-free survival.

9.7.1 Criteria for response (antitumoral activity)

The IWG and NCCN criteria will be followed, as appropriate, for assessment of response (Appendix D, Appendix F, and Appendix G).

10 PATIENT SAFETY

10.1 SAFETY ENDPOINTS ASSESSED IN THIS TRIAL

Refer to Section 9.1 for definition of safety criteria, parameters to be analyzed, and method of sample collection.

10.2 SAFETY INSTRUCTIONS

Please refer to Section 6.7.

10.3 ADVERSE EVENTS MONITORING

All AEs will be managed and reported in compliance with all applicable regulations and included in the final clinical study report.

10.4 DEFINITIONS OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

An **Adverse Event** is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Note: Examples of such events (list is not exhaustive) are intensive treatment in an emergency room or at home (for allergic bronchospasm, blood dyscrasias, or convulsions) or asymptomatic ALT increase ≥10 ULN that does not result in hospitalization, or development of drug dependency or drug abuse.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse events

All AEs regardless of seriousness or relationship to the IMP, spanning from the signature of the informed consent form (ie, occurring during the baseline period even in the absence of any administration of IMP), up to 30 days following the last administration of study treatment, are to be recorded on the corresponding page(s) included in the eCRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.

Vital signs or ECG abnormalities are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a seriousness criterion and/or is defined as an AESI (see Section 10.5.5).

Laboratory abnormalities are to be recorded as AEs only if they lead to treatment discontinuation and/or modification of dosing and/or fulfill a seriousness criterion and/or are defined as an AESI (see Section 10.5.5).

10.5.2 Serious adverse events

In the case of an SAE, an AESI, a pregnancy report, or an overdose, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send e-notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- SEND (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team. Care should be taken to ensure that the patient's identity is protected and the patient’s identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, patient status) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge. In addition, any effort should be made to document further each SAE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the eCRF system does not work.

10.5.3 Follow-up

- The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AEs (clinical signs, laboratory values or other, etc) until the return to normal or consolidation of the patient's condition. Ongoing related AEs at the end of study treatment will be followed until resolution or stabilization.
- In case of any SAE/AESI, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until outcome has been stabilized. This may imply that follow-up may continue after the patient has discontinued study treatment or has left the clinical trial and that additional investigations may be requested by the monitoring team;
- In case of any AE or AESI brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.5.4 Treatment discontinuation due to nonserious adverse event

In the case of a treatment discontinuation due to a nonserious AE:

- ENTER (within 24 hours) the information related to treatment discontinuation due to a non-SAE in the appropriate screens of the eCRF (AE with the box "action taken with IMP" ticked "permanently discontinued", together with the end of treatment form with reason that should be ticked "AE"); the system will automatically send the notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.

10.5.5 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the SAR440234 program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Investigational medicinal product related DLTs (as defined in Section 9.1.1) are considered as AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator will attach the DLT-specific eCRF page to the DLT/AESI form.

Additional AESIs include the following:

- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/NIMP:
  - Pregnancy in a female patient or in a female partner of a male patient will qualify as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4),
  - In the event of pregnancy in a female patient, treatment with the IMP should be discontinued,
  - Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) within the intended therapeutic interval, adjusted according to the tested drug
    - Infusion: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
    - Oral: increase of at least 30% of the dose to be taken.

  Of note, asymptomatic overdose has to be reported as a standard AE.
- Other project specific AESIs:
  - Cytokine release syndrome.

10.5.6 Laboratory abnormalities

Laboratory abnormalities should be monitored, documented, and managed according to the related flowchart (see Section 1.2). Laboratory values will be reported in the appropriate pages of eCRF.

Laboratory abnormalities should be reported as AE only in case they lead to an action on study treatment or if they are serious (see Section 10.5.1).

10.5.7 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines. Appropriate information (eg, samples, labels or documents, eg pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are unexpected and are at least reasonably related to the IMP (ie, suspected unexpected serious adverse reactions), to the regulatory authorities, institutional ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- The AESIs (eg, DLT, CRS) to those regulatory authorities who require such reporting.

Adverse events that are considered expected are specified by the reference safety information, ie, the Investigator Brochure.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

11 HANDLING OF PATIENT TEMPORARY AND PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

Pregnancy will lead to definitive treatment discontinuation in all cases.

11.1 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL MEDICINAL PRODUCT(S)

11.1.1 List of criteria for permanent treatment discontinuation

Patients may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation and this should be documented in the eCRF.

Treatment with the IMP should be discontinued in any of the following cases:

- At the patient's request, at any time and irrespective of the reason (patient's decision to stop treatment), or at the request of their legally authorized representative without any effect on their care. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical records check. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent. AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document any case of withdrawal of consent.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the patient's wellbeing. These situations include the following:
  - Disease progression,
  - Unacceptable AE,
  - Poor compliance to the study protocol,
  - Any other reason such as intercurrent illness that prevents further administration of study treatment,
  - Requirement for radiotherapy, even if palliative in intent.
- Patient is lost to follow-up.

If patients are clinically stable, possibly deriving clinical benefit from therapy, and tolerating the treatment well, the patient may continue on treatment.

11.1.2 Handling of patients after permanent treatment discontinuation

All permanent treatment discontinuation must be recorded by the Investigator in the appropriate screen of eCRF when considered as telephone call and record review if the patient is unable to attend monthly post-study visits. After study treatment is discontinued, patients must complete a visit within 30 days after the last administration of the IMP, as described in Section 12.7. If a patient does not plan to return for an EOT visit, the EOT evaluation must be performed on the day that the decision is made that the patient will not continue SAR440234. Post-study follow up must be performed by telephone call and record review if the patient is unable to attend monthly post-study visits.

Patients who have been withdrawn from the study treatment cannot be re-entered into the study.

Patients will be followed up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last.

If possible, after permanent discontinuation of treatment, patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

11.2 REPLACEMENT OF PATIENTS

During the Dose Escalation Part of the study, 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. Any patient who is not evaluable for DLT for any reason shall be replaced at the same dose level as described in Section 6.3. The first 3 patients treated during the Dose Escalation Part of TED15138 will be replaced. Another 3 patients will be enrolled in DL1 and the trial will proceed according to the 3+3 design. Patients treated in the Expansion Part of the study who are withdrawn from study treatment will not be replaced.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

During the course of the study, all patients entering the study must be evaluated according to the schedule outlined in the flow charts in Section 1.2 (overall assessments), Section 1.3 (pharmacokinetic, pharmacodynamics, biomarker, and immunogenicity assessments) and described below. The results of the evaluation will be recorded in the eCRF pages until the patient is not followed anymore.

During the Dose Escalation Part of the study, patients must be hospitalized as indicated below:

- Cycle 1 for DL1 and DL2: for the duration of the SAR440234 infusion (1 to 19 hours) and for 72 hours after completion of each infusion, for safety monitoring.
- Cycle 1 for DL ≥3: for the duration of the SAR440234 infusion (1 to 19 hours) and for 72 hours after completion of each infusion, for safety monitoring. In Week 1 only, patients will receive an infusion of SAR440234 on Day 4. Therefore, patients in DL ≥3 will be hospitalized continuously from Day 1 of Week 1 until 72 hours after completion of the third infusion, ie, for 11 days.
- Cycle 2 for all dose levels: for the duration of the SAR440234 infusion (1 to 19 hours) and for 72 hours after completion of each subsequent infusion in Week 1 and Week 2 only, for safety monitoring. Hospitalization for all the other infusions is on the day of infusion only.
- Cycle 3 and beyond for all dose levels: on the day of infusion, only.

During the Expansion Part of the study, patients will be hospitalized as indicated below:

- Cycle 1 if the RP2D is DL1 or DL2: for the duration of the SAR440234 infusion (1 to 19 hours) and for 72 hours after completion of each subsequent infusion, for safety monitoring.
- Cycle 1 if the RP2D is DL ≥3: for the duration of the SAR440234 infusion (1 to 19 hours) and for 72 hours after completion of each subsequent infusion, for safety monitoring. In Week 1 only, patients will receive an infusion of SAR440234 on Day 4. Therefore, patients in DL ≥3 will be hospitalized continuously from Day 1 of Week 1 until 72 hours after completion of the third infusion, ie, for 11 days.
- Cycle 2 and beyond for all dose levels: on the day of infusion only.

If a subsequent treatment cycle is delayed for ≥10 days, treatment should resume with the lead-in doses, and the hospitalization guidelines for a first cycle of treatment must be applied.

Patients who are not hospitalized will return to the site weekly for administration of SAR440234 and assessments as indicated in the study flow charts. An end of treatment visit will be performed 30 days after the last administration of the IMP (see flow charts for investigations to be performed). The patients will be followed until recovery or consolidation of any SAE or IMP-related AE.

12.2 BASELINE EVALUATION

The pretreatment examinations are to be performed within 14 days prior to the first administration of the IMP. The informed consent form will have to be signed by the patient before any procedure specific to the study can be performed. The following assessments are to be performed at this visit.

- Medical history and clinical examination: including medical, surgery, and disease history; prior anticancer therapies; physical examination; ECOG performance status, height, weight; vital signs (temperature, blood pressure, heart rate, respiration rate, oxygen saturation); and record of prior and concomitant medications.
- Laboratory assessments:
  - Coagulation: international normal ratio, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer,
  - Chemistry:
    - Liver function tests: AST, ALT, gamma glutamyl transferase (GGT), total bilirubin, direct bilirubin, alkaline phosphatase,
    - Electrolytes: sodium, potassium, calcium, magnesium, phosphorus, bicarbonate,
    - Renal function tests: BUN, creatinine, uric acid, estimated CrCl (Cockroft-Gault formula),
    - Others: LDH, albumin, and total protein.
  - Urinalysis: dipstick for pH, protein, glucose,
  - Serum or urine pregnancy test, when appropriate: a negative serum or urine pregnancy test result must be obtained within 14 days prior to the first dose of the IMP,
  - Serology tests: hepatitis B antigen, hepatitis C antibodies,
  - Pro-inflammatory cytokines, CRP, and ferritin,
  - Cytogenetic/FISH data collection.
- Disease assessment:
  - Bone marrow aspiration,
  - Bone marrow biopsy,
  - Hematology: hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count,
  - Immunophenotyping (peripheral blood and bone marrow),
  - Extramedullary leukemic localizations: hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, and any other examinations as clinically indicated to be performed to assess disease status at baseline,
  - Minimal residual disease Baseline assessment.
- 12-lead ECG.

All patients who signed the study informed consent form will be assigned a patient number. Each patient will receive an incremental identification number corresponding to his/her order of enrollment in the study. Those patients, who meet all the inclusion criteria and none of the

exclusion criteria, will be eligible for registration in the study. A written confirmation of each eligible patient identification and treatment dose level will be forwarded to the Investigator.

Adverse events will be collected from the time the informed consent is signed.

12.3 BEFORE THE FIRST INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION ON THE FIRST DAY OF TREATMENT

The following assessments are to be performed on Cycle 1 Day 1.

- Physical examination including height and weight; ECOG performance status; vital signs (temperature, blood pressure, heart rate, respiration rate, oxygen saturation).
- Laboratory assessments:
  - Coagulation: international normal ratio, prothrombin time, activated partial thromboplastin time, fibrinogen,
  - Chemistry:
    - Liver function tests: AST, ALT, GGT, total bilirubin, direct bilirubin, alkaline phosphatase,
    - Electrolytes: sodium, potassium, calcium, magnesium, phosphorus, bicarbonate,
    - Renal function tests: BUN, creatinine, uric acid, estimated CrCl (Cockroft-Gault formula),
    - Others: LDH, albumin, and total protein.
  - Pro-inflammatory cytokines, CRP, and ferritin,
  - SAR440234 pharmacokinetics and ADA (predose).
- Disease assessment:
  - Hematology: hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count,
  - Extramedullary leukemic localizations: hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration.

12.4 DURING THE TREATMENT PERIOD OF CYCLE 1

See flow charts in Section 1.2 and Section 1.3.

- Administration of SAR440234: Days 1, 4 (DL ≥3), 8, 15, 22, 29, and 36.
- Blood samples for serum CRP/ferritin, and cytokines (including IL-6 and IFN-γ), SAR440234, and ADA, will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional blood sample for analysis of CRP/ferritin and cytokines will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.
- AE enquiry and record.
- Changes in concomitant medications record.

- Physical examination including weight; ECOG performance status on IMP administration days.
- Vital signs (temperature, blood pressure, heart rate, respiration rate, oxygen saturation) 5 minutes before start of infusion, 0.5 hours after start of infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then daily. During infusion, temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate must be monitored every 30 minutes. Vital signs (heart rate, respiration rate) must be monitored continuously during CRS Grade ≥2, if this occurs.
- Laboratory assessments:
  - Coagulation: international normal ratio, prothrombin time, activated partial thromboplastin time on IMP administration days, daily after the first administration, for patients in Cycle 1 of the Dose Escalation Part,
  - Chemistry: on IMP administration days, and every 8 hours after the start of drug administration and for at least 72 hours after the end of infusions for patients in the Dose Escalation Part and the Expansion Part:
    - Liver function tests: AST, ALT, GGT, total bilirubin, direct bilirubin, alkaline phosphatase,
    - Electrolytes: sodium, potassium, calcium, magnesium, phosphorus, bicarbonate,
    - Renal function tests: BUN, creatinine, uric acid, estimated CrCl (Cockroft-Gault formula),
    - Others: LDH, albumin, and total protein.
- Pro-inflammatory cytokines, CRP, and ferritin as indicated in Section 1.3.1 and Section 1.3.3.
- ECG: must be monitored continuously during CRS Grade ≥2, if this occurs.
- Oxygen saturation (pulse oximetry): must be monitored continuously during CRS Grade ≥2, if this occurs.
- Disease assessment:
  - Bone marrow aspiration is required on Day 42 (±2 days). Additional bone marrow aspirate shall be performed as clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, anemia Grade 4 occurs with onset in >14 days before or after Day 42,
  - Hematology: hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count. Hematology will be evaluated daily during Cycle 1,
  - Immunophenotyping (peripheral blood and bone marrow) on Day 42 (±2 days),
  - Extramedullary leukemic localizations: hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration or others on Day 1,
  - Minimal residual disease, as clinically indicated.

The investigations and tests scheduled for Day 42 may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion:

- Extramedullary leukemic localization
- ECOG PS, Body Weight
- Physical examination
- Blood chemistry

If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment with SAR440234.

12.5 DURING FURTHER CYCLES

See flow charts in Section 1.2 and Section 1.3.4.

- Administration of SAR440234: Days 1, 8, 15, 22, 29, and 36.
- Blood samples for serum CRP/ferritin, and cytokines (including IL-6 and IFN-γ), SAR440234, and ADA, will be collected at the time points specified in the pharmacokinetic, pharmacodynamic, biomarker and immunogenicity flowcharts. An additional blood sample for analysis of CRP/ferritin and cytokines will be taken at onset of CRS Grade ≥2 if it occurs, or as soon as it is diagnosed.
- AE enquiry and record.
- Changes in concomitant medications record.
- Physical examination including weight; ECOG performance status on IMP administration days.
- Vital signs (temperature, blood pressure, heart rate, respiration rate, oxygen saturation) 5 minutes before start of infusion, 0.5 hours after start of infusion, at the end of infusion, 1 hour, 2 hours, and 4 hours post-infusion, then as clinically indicated at least until 72 hours from the start of infusion. During infusion, temperature, blood pressure, heart rate, oxygen saturation, and respiratory rate must be monitored every 30 minutes. Vital signs must be monitored continuously during CRS Grade ≥2, if this occurs.
- Laboratory assessments:
  - Coagulation: international normal ratio, prothrombin time, activated partial thromboplastin time, fibrinogen on IMP administration days.
  - Chemistry on IMP administration days and 3 subsequent days during Cycle 2, Week 1 and Week 2, then weekly thereafter:
    - Liver function tests: AST, ALT, GGT, total bilirubin, direct bilirubin, alkaline phosphatase,
    - Electrolytes: sodium, potassium, calcium, magnesium, phosphorus, bicarbonate,

  - Renal function tests: BUN, creatinine, uric acid, estimated CrCl (Cockroft-Gault formula),
  - Others: LDH, albumin, and total protein.

- Pro-inflammatory cytokines, CRP, and ferritin as indicated in Section 1.3.4.
- Disease assessment:
  - Bone marrow aspiration is required on Day 42 (±2 days). Additional bone marrow aspirate shall be performed as clinically indicated, or if any of the following occurs: decreased neutrophil count Grade 4, decreased platelet count Grade 4, febrile neutropenia Grade 3 and Grade 4, anemia Grade 4 occurs with onset in >14 days before or after Day 42,
  - Hematology: hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count, daily during Week 1 of Cycle 2, then weekly during all subsequent infusions and cycles,
  - Immunophenotyping (peripheral blood and bone marrow) on Day 42 of Cycle 2 only and in blood on Day 42 of Cycle 3 and subsequently. Further samples for immunophenotyping may be taken at the discretion of the Investigator and as clinically indicated,
  - Extramedullary leukemic localizations: hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, on Day 1 of each cycle.
  - Minimal residual disease, as clinically indicated.

All of these tests may be repeated when clinically indicated.

Blood hematology is not required in D2-D7 of cycle 3 and subsequent. Blood chemistry is not required in D2-D4 and in D9-D11 of cycle 3 and subsequent.

The investigations and tests scheduled for Day 42 may be performed on the next day if treatment continues after the current cycle; in this case the tests and investigations must be performed before start of next infusion:

- Blood hematology,
- Extramedullary leukemic localization,
- ECOG PS, Body Weight,
- Physical examination,
- Vital signs,
- Coagulation,
- Blood chemistry.

If the treatment won't be continued after the current cycle, all the planned tests and investigations for Day 42 must be performed on the day that the decision is made that the patient will not continue treatment with SAR440234.

12.6 END OF TREATMENT VISIT (TO BE PERFORMED WITHIN 30 DAYS AFTER THE LAST ADMINISTRATION OF THE INVESTIGATIONAL MEDICINAL PRODUCT)

See flow charts in Section 1.2.2, Section 1.2.4, and Section 1.3.4.

- AE enquiry and record.
- Changes in concomitant medications record.
- Physical examination including weight; ECOG performance status; vital signs (temperature, blood pressure, heart rate, respiration rate, oxygen saturation).
- Laboratory assessments:
  - Coagulation: international normal ratio, prothrombin time, activated partial thromboplastin time,
  - Chemistry:
    - Liver function tests: AST, ALT, GGT, total bilirubin, direct bilirubin, alkaline phosphatase,
    - Electrolytes: sodium, potassium, calcium, magnesium, phosphorus, bicarbonate,
    - Renal function tests: BUN, creatinine, uric acid, estimated CrCl (Cockroft-Gault formula),
    - Others: LDH, albumin, and total protein.
  - Urinalysis: dipstick for pH, protein, glucose,
  - Serum or urine pregnancy test.
- Disease assessment:
  - Hematology: hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count,
  - Immunophenotyping (peripheral blood),
  - Extramedullary leukemic localizations: hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration.
- 12-lead ECG.

Blood sampling for immunogenicity assessments of SAR440234 will be performed at the end of treatment visit. If the patient does not plan to return for an EOT visit, the EOT evaluation must be performed on the day that the decision is made that the patient will not continue treatment with SAR440234.

12.7 PERIOD POST END OF TREATMENT

Follow up will be performed for patients with ongoing SAEs regardless of relationship to IMP and ongoing IMP-related AEs 30 days after the last IMP administration, and for patients with new IMP-related AEs/SAEs. Those events will be followed until resolution or stabilization as described in Section 10.5.3 and Section 11.1.2. Follow-up visits are to be performed monthly until initiation of another anti-cancer therapy, disease progression, study cut-off date, or death. If a patient is unable to return to clinic for monthly follow-up visits, the investigator must obtain follow up information via telephone call and record review.

Patients achieving stable disease (SD), CR, CRi, or PR or non-CR/nonprogressive disease (PD) should be followed until disease progression or initiation of another specific antitumor treatment to collect either the date of PD or the initiation of further antitumor therapy.

The Site Investigator will evaluate the patient's symptoms, physical examination, vital signs, and laboratory tests each month. If the Investigator finds evidence to indicate a change in disease status, the Investigator will obtain a bone marrow aspirate to confirm the change. If there is no perceived change in disease status, additional testing is not required.

12.8 POST STUDY CUT-OFF PERIOD

If a patient continues to benefit from the treatment after the second study cut-off date, the patient can continue study treatment until disease progression, unacceptable toxicity or patient request. Such patients will be followed until 30 days after the last administration of the IMP and will continue to undergo select study assessments. The following information will be collected: IMP(s) administration, IMP-related AEs, and any SAEs.

No follow-up information will be collected after these patients discontinue study treatment, with the exception of all SAEs regardless of relationship to study treatments and all IMP-related AEs still ongoing at the end of study treatment and any new treatment-related AE/SAEs occurring after the end of study treatment which will be followed until resolution/stabilization.

13 STATISTICAL CONSIDERATIONS

The content of this section is the Statistical Analysis Plan for the study.

13.1 DETERMINATION OF SAMPLE SIZE

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

13.1.1 Dose escalation part

This study aims to establish the MTD as well as the RP2D of SAR440234 according to DLTs observed.

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 will be replaced. The first 3 patients treated during the Dose Escalation Part of TED15138 will be replaced. Another 3 patients will be enrolled in DL1 and the trial will proceed according to the 3+3 design.

13.1.2 Expansion part

A Simon's 2-stage design (optimal) will be used. If ≤3 responses (CR, CRi or PR) are observed on the first 17 patients treated, the alternative hypothesis of at least 40% response rate will be rejected. Otherwise, accrual will continue to the full sample size of 37 patients. Overall, this procedure has 90% statistical power (1-sided alpha of 10%) to reject a null response rate of 20% in a 1-sample test for a binomial proportion (East version 6.4, Cytel Software, Cambridge, MA). Eleven (11) responses on 37 patients will be necessary to reject the null hypothesis.

13.2 PATIENT DESCRIPTION

13.2.1 Disposition of patients

Disposition of patients will be depicted by intended dose level (including the Expansion Part) for both the patient study status and also for the patient analysis populations. For patient study status, the total number of patients for each one of the following categories will be presented in the clinical study report using a flow-chart diagram or summary table:

- Registered patients are patients who sign the study informed consent, and who plan to receive the study treatment.

The all-treated/safety population is defined in Section 13.3.1.

- Patients who discontinue study treatment and reasons for discontinuation.
- Patients evaluable for DLT assessment.
- Pharmacokinetic population.
- Pharmacodynamic population.
- Activity/efficacy population.

For all categories of patients, percentages will be calculated using the number of exposed patients (all-treated/safety population). Reasons for treatment discontinuation will be provided in tables giving numbers and percentages by dose level.

Additionally, the analysis populations for safety, efficacy, pharmacokinetics, and pharmacodynamics will be summarized in a table by patient counts for the all-treated/safety population.

13.2.2 Protocol deviations

Major protocol deviations, which compromise the evaluation of the MTD, will be derived adequately (mainly algorithmically and/or following medical review) and determination of deviations will be finalized based on data review conducted prior to database lock. Decisions made on a patient's status will be documented.

13.3 ANALYSIS POPULATIONS

13.3.1 All-treated/safety population

The all-treated/safety population is defined as all registered patients who have given their informed consent and who have received at least 1 dose (even incomplete) of SAR440234.

13.3.2 Patients evaluable for DLT assessment

The DLT-evaluable population in the Dose Escalation Part will include all patients who have received at least 5 out of 6 weekly IV administration of SAR440234 in DL1 and DL2, patients who have received at least 6 out of 7 IV administrations of SAR440234 in DL ≥3, and patients who discontinue the IMP before completion of Cycle 1 because of a DLT.

A complete safety evaluation should be performed during the DLT observation period, and a DLT form should be completed at the end of the cycle. This concerns both patients followed up to the end of the evaluation period and patients who experienced a DLT validated by the Study Committee. Patients with incomplete safety evaluation during the DLT observation period and who experience a DLT during this period will be considered as evaluable for DLT.

The first 3 patients treated will be excluded from the DLT-evaluable population.

13.3.3 Pharmacokinetic population

The pharmacokinetic population will include patients from the all-treated/safety population with at least 1 evaluable drug concentration after IMP administration (whatever the cycle and even if dosing is incomplete).

13.3.4 Activity/efficacy population

The activity/efficacy population will be defined as all patients with at least 1 post-Baseline evaluable disease assessment allowing status evaluation.

13.3.5 Anti-drug antibody population

The ADA population will include all patients from the all-treated/safety population with at least 1 available ADA result after IMP administration.

13.4 STATISTICAL METHODS

Unless otherwise specified, analyses will be descriptive and performed based on the all-treated/safety population.

Continuous data will be summarized using number of available data, mean, standard deviation (StD), median, minimum, and maximum for each dose level. Categorical and ordinal data will be summarized using number and percentage of patients in each dose level.

13.4.1 Demographics and baseline characteristics

Standard demographic and baseline characteristics (including age, race, gender, ECOG performance status), medical history, cancer diagnosis will be collected at baseline and described by dose level. Genetic and molecular profiles of disease, if available, will be collected before study treatment.

Parameters will be summarized by dose level and overall using descriptive statistics.

13.4.2 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed and summarized by dose level within the all-treated/safety population.

Duration of IMP exposure is defined as: last dose date – first dose date + 28 days, regardless of unplanned intermittent discontinuations.

In addition, in the Expansion Part of the study, dose information will be assessed for the following variables:

- The number of infusions.
- The cumulative dose at Cycle k is the sum of all doses from Cycle 1 to and including Cycle k, where k is based on Investigator's report.
- Actual dose intensity (ADI), defined as the cumulative dose divided by the number of weeks on study treatment.
- Relative dose intensity (RDI), defined as the ratio of the actual dose intensity to the planned dose intensity. The relative dose intensity is an indicator of the feasibility of the chosen schedule of administration.
- 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 and reason for dose reduction.

Dose information variables will be summarized descriptively (n, mean, standard deviation, median, Q1:Q3, minimum, and maximum). Analyses will be performed based on the number of patients and on the number of cycles.

13.4.3 Prior/concomitant medication/therapy

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

Medications of specific interest such as antibiotics and hematopoietic growth factors (G-CSF, GM-CSF and erythropoietin or red blood cells transfusion) will be summarized and listed by dose level.

Further treatment of interest for the analysis and given to the patient after withdrawal from IMP will be listed.

13.4.4 Analyses of safety data

13.4.4.1 Dose-limiting toxicities

The DLTs observed during DLT observation period will be summarized by dose level, as well as AEs that meet the DLT criteria in subsequent cycles. Details will be provided (characteristics of DLTs) by patient.

13.4.4.2 Analyses of adverse events

Adverse events will be collected from the time informed consent is signed until at least 30 days after the last administration of the IMP, and will be categorized according to NCI-CTCAE v4.03, except for CRS, which will be graded according to the 2014 NCI Consensus Guidelines (Table 10). All AEs will be classified by system organ class and preferred term according to the latest available version of the MedDRA dictionary.

Definitions

Period of observation: The observation period will be divided into 3 segments: pretreatment, on-treatment, and post-treatment. The pretreatment period is defined as the time from when the patients give informed consent up to the first administration of the IMP. The on-treatment period is defined as the time from the first dose of IMP up to 30 days after the last dose of IMP. The post-treatment period is defined as the time starting 31 days after the last dose of IMP to the study closure.

Pretreatment AEs are defined as any AE occurring during the pretreatment period.

Treatment-emergent AEs are defined as AEs that developed or worsened (according to the Investigator opinion) or became serious during the on-treatment phase.

Post-treatment AEs are defined as AEs that are reported during the post-treatment period.

The grade will be provided in the summary. For patients with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be the TEAEs. Pre- and post-treatment AEs will be described separately.

Adverse event incidence tables will present for each dose level, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the all-treated/safety population within each dose level.

Sorting within tables should ensure the same presentation for the set of all AE within the observation period (pre-, on-, and post-treatment). For that purpose, the table of all TEAEs presented by system organ class and preferred term will be sorted by internationally agreed order, unless otherwise specified. Full 4-level hierarchy will be provided, if needed.

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE,
  - Any Grade ≥3 TEAE,
  - Any Grade 3 or 4 TEAE,
  - Grade 5 TEAE (any TEAE with a fatal outcome during the treatment period),
  - Serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation.

Analysis of CRS

The following summaries will be provided:

- Number (%) of patients experiencing CRS (all grades and by grade).
- Number (%) of patients experiencing CRS by action taken with study treatment.
- Number (%) of patients with infusion of occurrence.
- Duration of CRS event (in hours).

13.4.4.3 Deaths

The following deaths summaries will be generated;

- Number (%) of patients who died by study period (pre-treatment, on-treatment, post-treatment).

A listing of deaths will be provided.

13.4.4.4 Clinical laboratory evaluations

For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used. Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. Each test result will be graded by NCI-CTC (v4.03). The number of patients with abnormal laboratory tests at baseline will be presented by grade. The frequency of patients in each grade of lab tests during treatment will be summarized. When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3 to 4 of abnormal laboratory tests. For patients with Grade 3 to 4 abnormal laboratory tests, additional analyses will be conducted to describe time to onset and dose to onset.

Further analyses could be provided to explore the dose and time to onset of safety endpoints of interest.

13.4.4.5 Vital signs

The summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study endpoint (baseline, each post baseline time point, last on treatment value and/or worst value) by dose level. Mean changes from baseline with the corresponding standard error (or boxplots) will be plotted over time (at same time points) in each dose level.

13.4.4.6 Immunogenicity

13.4.4.6.1 Immunogenicity status

The observation period for ADAs will be divided into 2 periods:

- The ADA pretreatment period will be defined as the time that informed consent is signed until the first study treatment administration.
- The ADA on-study observation period will be defined as the time from the first study treatment administration until the end of the study.

Patients with at least 1 evaluable ADA result during the ADA pretreatment period will be considered as evaluable at baseline. Patients with at least 1 evaluable ADA result during the ADA on-study observation period will be considered evaluable during the on-study observation period.

Definitions:

- *Pre-existing ADA*, defined as ADA that are present in samples drawn during the pretreatment period.
- *Treatment-induced ADA*, defined as ADA that developed at any time during the ADA on-study observation period in patients without pre-existing ADA (including patients without pretreatment samples).
- *Treatment boosted ADA*, defined as pre-existing ADA with a significant increase in the ADA titer during the study compared to the baseline titer.
- *ADA positive patients*, defined as patients with at least 1 treatment-induced or treatment-boosted ADA positive sample at any time following the first study treatment administration.
- *ADA prevalence*, defined as the sum of the number of patients with pre-existing ADA and the number of patients with treatment induced ADAs, divided by the number of evaluable patients.
- *ADA incidence*, defined as the number of ADA positive patients divided by the number of evaluable patients.

The immunogenicity of SAR440234 will be assessed by summarizing the number (%) of patients with pre-existing ADA and ADA negative at baseline, and by summarizing the number (%) of ADA positive patients (including treatment-induced ADA and treatment boosted ADA) during the on-study observation period.

ADA prevalence and ADA incidence will be also described.

A summary table will summarized the number of evaluable patients, number of positive, negative and inconclusive patients. The prevalence and the incidence will be also reported.

For all patients, an individual listing of immunogenicity sample results (positive, negative or inconclusive) will be provided together with the associated titer.

13.4.4.6.2 Immune response:

The following definitions will be used to describe the immune response:

- *Transient ADA response*: ADA detected only at 1 time point during treatment or ADA detected at ≥2 time points during treatment including EOT with less than a 16-week period between the first and last ADA-positive samples (irrespective of any negative samples in between) and the last sample should be ADA negative.
- *Persistent ADA response*: ADA detected at ≥2 time points during treatment including EOT with ≥16-week period between the first and the last ADA-positive samples (irrespective of any negative samples in between) and if the last 2 samples are positive, irrespective of the time period in between.
- *Indeterminate ADA response*: only the last sampling time point is positive.

13.4.4.6.3 Immunogenicity impact on pharmacokinetics

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

13.4.5 Analyses of pharmacokinetic variables

Individual concentrations and pharmacokinetic parameters of SAR440234 will be summarized by descriptive statistics (such as mean, geometric mean, median, SD, standard error of the mean, coefficient of variation, minimum, and maximum). Individual and mean profiles will be presented graphically. Dose proportionality and accumulation will also be assessed on relevant parameters in the pharmacokinetic population.

13.4.6 Analysis of cytokines

Individual concentrations of each measured cytokine will be tabulated and summarized by descriptive statistics (such as mean, geometric mean, median, SD, standard error of the mean, coefficient of variation, minimum, and maximum). Potential correlation with other parameters such as safety and pharmacokinetic endpoints will be also investigated.

13.4.7 Analysis of immunophenotyping data

CD123 receptor density at baseline and after treatment will be summarized with descriptive statistics. Subpopulation analyses including effector/target ratio will be tabulated with standard descriptive statistics.

13.4.8 Analyses of antitumor activity/efficacy variables

The ORR and other efficacy will be summarized using descriptive statistics by hematological malignancies. A 95% 2-sided confidence interval will be computed for ORR using the Clopper-Pearson method.

13.5 INTERIM ANALYSIS

In the Expansion Part, an interim analysis is planned when 17 patients are treated in order to decide, based on preset criteria, if the recruitment of planned additional patients is justified. If 3 or fewer responses (CR, CRi, or PR) are observed on the first 17 patients, the study will be stopped for futility.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator(s), in accordance, with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules, and regulations.

Information regarding the clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with sanofi public disclosure commitments.

14.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the study, including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, with the name of the patient filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

For patients age 16 to 18 years, the informed consent form should be signed, name filled in and personally dated by the patient's parent(s) or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants age 16 to 18 years will assent as detailed below or will follow the ethics committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

- Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.
- Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

- Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

In relation to the population of patients exposed in the trial (ie, pediatric/minor patients), the IRB/IEC should ensure proper advice from specialist with pediatric expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

The informed consent form and the assent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

14.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate ethics committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure with any addenda, Investigator's CV, etc) and the date of the review should be clearly stated on the written ethics committee (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the ethics committee (IRB/IEC) should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the ethics committee (IRB/IEC) and to health authorities (competent regulatory authority), as required by local regulation.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, discrepancy resolution form [DRF], or other appropriate instrument) in an accurate manner according to the instructions provided and to ensure direct access to source documents by the Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

15.2 RESPONSIBILITIES OF SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical, and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the Monitoring team must check the eCRF entries against the source documents, except for the preidentified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allowing the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRF (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

15.4 USE AND COMPLETION OF CASE REPORT FORMS AND ADDITIONAL REQUESTS

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to the Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

15.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document, which is maintained in the Sponsor trial master file.

16 ADDITIONAL REQUIREMENTS

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification, and training of each Investigator and Subinvestigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

16.2 RECORD RETENTION IN STUDY SITES(S)

The Investigator must maintain confidential all study documentation and take measures to prevent accidental or premature destruction of these documents.

It is recommended that the Investigator retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

16.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

16.4 PROPERTY RIGHTS

All information, documents, and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not cause the delegated Investigator staff/Subinvestigator to mention any information regarding the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market, or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

16.5 DATA PROTECTION

- The patient's personal data, which may be included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding the Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White) will be collected in this study because these data are required by several regulatory authorities (eg, on afro American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

16.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy as required by applicable law. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

16.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

16.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

16.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the IMP leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Noncompliance by the Investigator or Subinvestigator, or delegated staff with any provision of the clinical trial protocol, or breach of any applicable laws, regulations, or ICH GCP guidelines.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

16.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

16.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to Investigator.

16.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold his approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or of its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the Collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

17 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

18 BIBLIOGRAPHIC REFERENCES

1. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute cyeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-64.

2. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722-31.

3. SEER Cancer Stat Facts: Acute Myeloid Leukemia. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/statfacts/html/amyl.html.

4. Breems DA, Van Putten WL, Huijgens PC, Ossenkoppele GJ, Verhoef GE, Verdonck LF, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. J Clin Oncol. 2005: 20;23(9):1969-78.

5. van Rhenen A, Feller N, Kelder A, Westra AH, Rombouts E, Zweegman S, et al. High stem cell frequency in acute myeloid leukemia at diagnosis predicts high minimal residual disease and poor survival. Clin Cancer Res. 2005:15;11(18):6520-27.

6. Jin L, Lee EM, Ramshaw HS, Busfield SJ, Peoppl AG, Wilkinson L, et al. Monoclonal antibody-mediated targeting of CD123, IL-3 receptor alpha chain, eliminates human acute myeloid leukemic stem cells. Cell Stem Cell. 2009:2;5(1):31-42.

7. Jordan CT, Upchurch D, Szilvassy SJ, Guzman ML, Howard DS, Pettigrew AL, et al. The interleukin-3 receptor alpha chain is a unique marker for human acute myelogenous leukemia stem cells. Leukemia. 2000;14(10):1777-84.

8. Taussig DC, Pearce DJ, Simpson C, Rohatiner AZ, Lister TA, Kelly G, et al. Hematopoietic stem cells express multiple myeloid markers: implications for the origin and targeted therapy of acute myeloid leukemia. Blood. 2005;106(13):4086-92.

9. Testa U, Riccioni R, Diverio D, Rossini A, Lo Coco F, Peschle C. Interleukin-3 receptor in acute leukemia. Leukemia. 2004 ;18(2):219-26.

10. Testa U, Riccioni R, Militi S, Coccia E, Stellacci E, Samoggia P, et al. Elevated expression of IL-3R alpha in acute myelogenous leukemia is associated with enhanced blast proliferation, increased cellularity, and poor prognosis. Blood. 2002;100(8):2980-88.

11. De Waele M, Renmans W, Vander Gucht K, Jochmans K, Schots R, Otten J, et al. Growth factor receptor profile of CD34+ cells in AML and B-lineage ALL and in their normal bone marrow counterparts. Eur J Haematol. 2001;66(3):178-87.

12. Ehninger A, Krmaer M, Röllig C, Thiede C, Borhhauser M, von Bonin M, et al. Distribution and levels of cell surface expression of CD33 and CD123 in acute myeloid leukemia. Blood Cancer J. 2014;4:e218.

13. Florian S, Sonneck K, Hauswirth AW, Krauth MT, Schernthaner GH, Sperr WR, et al. Detection of molecular targets on the surface of CD34/CD38- stem cells in various myeloid malignancies. Leuk Lymphoma. 2006;47(2):207-22.

14. Muñoz L, Nomdedéu JF, López O, Carnicer MJ, Bellido M, Aventín A, et al. Interleukin-3 receptor alpha chain (CD123) is widely expressed in hematologic malignancies. Haematologica. 2001;86(12):1261-69.

15. Saber H, Del Valle P, Ricks TK, Leighton JK. An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. Regul Toxicol Pharmacol. 2017;90:144-52.

16. Duff GW. Expert Scientific Group on Phase One Clinical Trials: Final Report; 30th November 2006. Stationery Office 2006; 25-27.

17. Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? MAbs. 2011;3(1):61-6.

18. Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood. 2013;121(26):5154-57.

19. Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-49.

20. Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO; Medical Research Council Childhood Leukaemia Working Party. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol. 2005;129(6):734-45.

21. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med. 2006;355(10):1018-28.

22. Chatenoud L, Ferran C, Legendre C, Thouard I, Merite S, Reuter A, et al. In vivo cell activation following OKT3 administration. Systemic cytokine release and modulation by corticosteroids. Transplantation. 1990;49(4):697-702.

23. Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, Engert A. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood. 1999;94(7):2217-24.

24. Reagan JL, Fast LD, Safran H, Nevola M, Winer ES, Castillo JJ, et al. Cellular immunotherapy for refractory hematological malignancies. J Transl Med. 2013;11:150.

25. Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T-cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther. 2010;18(4):843-51.

26. Davila ML, Riviere I, Wang X, Bartido S, Park J, Curran K, et al. Efficacy and toxicity management of 19-28z CAR T-cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014;6(224):224ra25.

27. Brentjens R, Yeh R, Bernal Y, Riviere I, Sadelain M. Treatment of chronic lymphocytic leukemia with genetically targeted autologous T-cells: case report of an unforeseen adverse event in a phase I clinical trial. Mol Ther. 2010;18(4):666-68.

28. Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T-cells for acute lymphoid leukemia. N Engl J Med. 2013;368(16):1509-18.

29. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.

30. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111(12):1805-12.

31. Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016;2016(1):567-72.

32. Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected clinical conundrums. Semin Arthritis Rheum. 2014;43(4):458-69.

33. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(3):818-25.

34. Cheson BD, Bennett JM, Kantarjian H, Pinto A, Schiffer CA, Nimer SD, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000;96(12):3671-74.

35. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

36. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood. 2012;120(12):2454-65.

37. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

38. NCI-CTC Version 3.0 reference, accessible through the NCI website at http://ctep.info.nih.gov/reporting/ctc.html.

19 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.
3. Postmenopausal female:
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient,
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 6.8):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent,
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration (during the protocol-defined time frame).

- Refrain from donating sperm for the duration of the study and for 3 months after study completion or the last dose of study treatment.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below:

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]: – oral – intravaginal – transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]: - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: *a* Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. *b* Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be utilized during the treatment period and for at least 38 days after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

Appendix B List of CYP substrates with a narrow therapeutic range

Patients treated or intended to be treated with drugs presented as CYP substrates with narrow therapeutic range should be monitored carefully for safety. Examples of such drugs are as follows:

***In vivo* CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A Narrow Therapeutic Range Substrates**	
CYP enzyme	**NTR Substrates[a]**
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP2D6	Thioridazine
CYP3A	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, quinidine, sirolimus, tacrolimus, cisapride, astemizole, terfenadine, pimozide

a CYP substrates with a narrow therapeutic range – drugs with an exposure-response relationship that indicates that relatively small increases in their exposure levels by co-administered CYP inhibitors may lead to safety concerns

Abbreviations: CYP=cytochrome P450, NTR=narrow therapeutic range.

Appendix C ECOG Performance Status Scale

Performance Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair (37).

Appendix D Response Criteria for ALL

The following response criteria are extracted from the NCCN Guidelines, Version 2.2016, for ALL.

Response Criteria for Blood and Bone Marrow

- Complete response (CR):
  - No circulating blasts or extramedullary disease,
    - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/central nervous system involvement.
  - Trilineage hematopoiesis and <5% blasts,
  - ANC >1000/μL,
  - Platelets >100 000/μL,
  - No recurrence for 4 weeks.
- Complete response with incomplete blood count recovery (CRi):
  - Meet all criteria for CR except platelet count and/or ANC.
- Overall response rate (ORR = CR + CRi).
- Refractory disease:
  - Failure to achieve CR at the end of induction.
- Progressive disease (PD):
  - Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease.

Relapsed disease:

- Reappearance of blasts in blood or bone marrow (>5%) or in any extramedullary site after a CR.

Response Criteria for Mediastinal Disease

CT of chest with IV contrast and PET imaging should be performed to assess.

- Complete remission (CR): complete resolution of mediastinal enlargement by computed tomography. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative.
- Partial remission (PR): >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous positive PET scan, a post-treatment PET must be positive in at least one previously involved site.
- Progressive disease (PD): >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, a post-treatment PET must be positive in at least one previously involved site.

- No response (NR): failure to qualify for PR or PD.
- Relapse: recurrence of mediastinal enlargement after achieving CR. For patients with a previous positive PET scan, a post-treatment PET must be positive in at least one previously involved site.

Further details are provided online at the following NCCN website:
https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site

Appendix E Revised International Prognostic Scoring System in MDS

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R[6])

	Score value						
Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetic[7]	**Very good**	**–**	**Good**	**–**	**Intermediate**	**Poor**	**Very poor**
Marrow blasts (%)	**≤2**	**–**	**>2-<5**	**–**	**5-10**	**>10**	**–**
Hemoglobin	**≥10**	**–**	**8-<10**	**<8**	**–**	**–**	**–**
Platelets	**≥100**	**50-<100**	**<50**	**–**	**–**	**–**	**–**
ANC	**≥0.8**	**<0.8**	**–**	**–**	**–**	**–**	**–**

IPSS-R Risk category (% IPSS-R pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

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For IPSS-R: Very Low/Low/Intermediate, see MDS-3 and MDS-4
For IPSS-R: Intermediate/High/Very High, see MDS-5

[6]Greenberg PL, Tuechler H, Schanz J, et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012;120:2454-2465.
Websites for accessing the IPSS-R calculator tool: http://www.ipss-r.com or http://mds-foundation.org/calculator/index.php. A mobile App for the calculator tool is also available.

[7]Cytogenetic risks: Very good = -Y, del(11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: (3 abnormalities); Very poor = complex: >3 abnormalities.

Appendix F Response criteria for AML

RESPONSE CRITERIA DEFINITIONS FOR ACUTE MYELOID LEUKEMIA[1]

- **Morphologic leukemia-free state**
  - **Bone marrow <5% blasts in an aspirate with spicules**
  - **No blasts with Auer rods or persistence of extramedullary disease**
- **If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in one week.**
- **A bone marrow biopsy should be performed if spicules are absent from the aspirate sample.**
- **Complete response (CR)**
  - **Morphologic CR - patient independent of transfusions**
    - **Absolute neutrophil count >1000/mcL**
    - **Platelets ≥100,000/mcL**
    - **No residual evidence of extramedullary disease**
  - **Cytogenetic CR - cytogenetics normal (in those with previously abnormal cytogenetics)**
  - **Molecular CR - molecular studies negative[2]**
  - **CRi - There are some clinical trials, particularly those that focus on the elderly or those with antecedent myelodysplasia, that include a variant of complete response referred to as CRi. This has been defined as <5% marrow blasts, either ANC <1000/mcL or platelets <100,000/mcL, and transfusion independence but with persistence of cytopenia (usually thrombocytopenia).**
  - **Responses less than CR may still be meaningful depending on the therapy.**
- **Partial remission[3]**
  - **Decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate and the normalization of blood counts, as noted above.**
- **Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (eg, bone marrow regeneration after consolidation therapy) or extramedullary relapse.**

[1]Cheson BD, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21(24):4642-4649.
[2]This is clinically relevant only in APL and Ph+ leukemia at the present time. Molecular remission for APL should be performed after consolidation, not after induction as in non-APL AML.
[3]Partial remissions are useful in assessing potential activity of new investigational agents, usually in phase I trials.

Appendix G Response criteria for HR-MDS

Based on the revised criteria for HR MDS (34).

Measurement of response/treatment effect in MDS

ALTERING DISEASE NATURAL HISTORY

1. Complete remission (CR)

Bone marrow evaluation: Repeat bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia.* When erythroid precursors constitute less than 50% of bone marrow nucleated cells, the percentage of blasts is based on all nucleated cells; when there are 50% or more erythroid cells, the percentage blasts should be based on the nonerythroid cells.

Peripheral blood evaluation (absolute values must last at least 2 months)†:
Hemoglobin greater than 11 g/dL (untransfused, patient not on erythropoietin)
Neutrophils 1500/mm^3 or more (not on a myeloid growth factor)
Platelets 100 000/mm^3 or more (not on a thrombopoetic agent)
Blasts, 0%
No dysplasia*

2. Partial remission (PR) (absolute values must last at least 2 months):
All the CR criteria (if abnormal before treatment), except:
Bone marrow evaluation: Blasts decreased by 50% or more over pretreatment, or a less advanced MDS FAB classification than pretreatment. Cellularity and morphology are not relevant.

3. Stable disease
Failure to achieve at least a PR, but with no evidence of progression for at least 2 months.

4. Failure
Death during treatment or disease progression characterized by worsening of cytopenias, increase in the percentage bone marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment.

5. Relapse after CR or PR—one or more of the following:
a) Return to pretreatment bone marrow blast percentage.
b) Decrement of 50% or greater from maximum remission/response levels in granulocytes or platelets.
c) Reduction in hemoglobin concentration by at least 2 g/dL or transfusion dependence.§

6. Disease progression
a) For patients with less than 5% blasts: a 50% or more increase in blasts to more than 5% blasts.
b) For patients with 5% to 10% blasts: a 50% or more increase to more than 10% blasts.
c) For patients with 10% to 20% blasts: a 50% or more increase to more than 20% blasts.
d) For patients with 20% to 30% blasts: a 50% or more increase to more than 30% blasts.
e) One or more of the following: 50% or greater decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.§

7. Disease transformation
Transformation to AML (30% or more blasts).

CYTOGENETIC RESPONSE
(Requires 20 analyzable metaphases using conventional cytogenetic techniques.)
Major: No detectable cytogenetic abnormality, if preexisting abnormality was present.
Minor: 50% or more reduction in abnormal metaphases.
Fluorescent in situ hybridization may be used as a supplement to follow a specifically defined cytogenetic abnormality.

HEMATOLOGIC IMPROVEMENT (HI)
(Improvements must last at least 2 months in the absence of ongoing cytotoxic therapy.)†
Hematologic improvement should be described by the number of individual, positively affected cell lines (eg, HI-E; HI-E 1 HI-N; HI-E 1 HI-P 1 HI-N).

1. Erythroid response (HI-E)
Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, transfusion independence.
Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

2. Platelet response (HI-P)
Major response: For patients with a pretreatment platelet count less than 100 000/mm^3, an absolute increase of 30 000/mm^3 or more; for platelet transfusion-dependent patients, stabilization of platelet counts and platelet transfusion independence.
Minor response: For patients with a pretreatment platelet count less than 100 000/mm^3, a 50% or more increase in platelet count with a net increase greater than 10 000/mm^3 but less than 30 000/mm^3.

3. Neutrophil response (HI-N)
Major response: For absolute neutrophil count (ANC) less than 1500/mm^3 before therapy, at least a 100% increase, or an absolute increase of more than 500/mm^3, whichever is greater.
Minor response: For ANC less than 1500/mm^3 before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm^3.

4. Progression/relapse after HI: One or more of the following: a 50% or greater decrement from maximum response levels in granulocytes or platelets, a reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.§

For a designated response (CR, PR, HI), all relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (eg, 1 month or longer).

**The presence of mild megaloblastoid changes may be permitted if they are thought to be consistent with treatment effect. However, persistence of pretreatment abnormalities (eg, pseudo-Pelger-Huet cells, ringed sideroblasts, dysplastic megakaryocytes) are not consistent with CR.*

†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 2-month period. Such patients can be included in the response category into which they fit at the time the therapy is started.

§In the absence of another explanation such as acute infection, gastrointestinal bleeding, hemolysis, and so on.

Appendix H Grading System and mitigation strategy for CRS, based on 2014 NCI Consensus guidelines

Grade	Toxicity	Intervention
Grade 1	• Fever, nausea, fatigue, headache, myalgias, malaise, without life-threatening complications.	• Vigilant supportive care. • Assess and treat infection if present. • Fluid resuscitation. • Provide antipyretics and analgesics, if needed.
Grade 2	• Oxygen requirement <40% FIO2. • Hypotension responsive to low-dose or single vasopressor. • Grade 2 organ toxicity	• As for Grade 1, but monitor cardiac and other organ function closely. • Consider corticosteroids and/or anti-IL6 therapy for patients with advanced age or multiple co-morbidities.
Grade 3	• Oxygen requirement >40% FIO2. • Hypotension responsive to high-dose or multiple vasopressors. • Grade 3 organ toxicity. • Grade 4 increase in ALT or AST.	• As for Grade 2, but with the addition of corticosteroids and/or anti-IL6 therapy.
Grade 4	• Life-threatening symptoms. • Requirement for mechanical ventilation. • Grade 4 organ toxicity, excluding increase in ALT or AST.	• As for Grade 2, but with the addition of corticosteroids and/or anti-IL6 therapy.
Grade 5	Death	

Grading system based on the 2014 NCI Consensus Guidelines (29, 31).

Appendix I National Cancer Institute common terminology criteria for adverse events

Refer to NCI-CTCAE v4.03 (38) in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

Appendix J Guidelines for the management of tumor lysis syndrome (TLS).

TLS is a metabolic derangement that is the result of rapid destruction of tumor cells. TLS is common in hematological malignancies and can cause several side effects; some of them may become life-threatening. Early recognition of TLS and initiation of therapy is essential.

Intravenous hydration is recommended for all patients prior to start of SAR440234 infusions and is left to Investigator judgment for further cycles.

The patients at greatest risk of TLS are those with a high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions should be taken (such as use of prophylactic uric acid lowering agents (eg, allopurinol or rasburicase) and regular measurement of electrolytes.

This appendix provides parameters to be checked in case of TLS suspicion and recommendations for TLS management. Abnormalities listed in this appendix do not exclusively support TLS diagnosis and any differential diagnosis also needs to be assessed, if appropriate.

TLS may present with laboratory parameters changes, clinical manifestations, or both as indicated in **Appendix Table 1**.

Appendix Table 1 - Tumor lysis syndrome definitions

Table I. Cairo–Bishop definition of laboratory tumour lysis syndrome.

Uric acid	$x \geq 476$ µmol/l or 25% increase from baseline
Potassium	$x \geq 6{\cdot}0$ mmol/l or 25% increase from baseline
Phosphorous	$x \geq 2{\cdot}1$ mmol/l (children), $x \geq 1{\cdot}45$ mmol/l (adults) or 25% increase from baseline
Calcium	$x \leq 1{\cdot}75$ mmol/l or 25% decrease from baseline

Modified from Hande and Garrow (1993).
Laboratory tumour lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 d before or 7 d after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Table II. Cairo-Bishop definition of clinical tumour lysis syndrome.

(1) Creatinine*: $x \geq 1{\cdot}5$ ULN† (age >12 years or age adjusted)
(2) Cardiac arrhythmia/sudden death*
(3) Seizure*

Modified from Hande and Garrow (1993).
Clinical tumour lysis syndrome (CTLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. CTLS is defined as the presence of LTLS and any one or more of the above-mentioned criteria.
*Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).
†Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1·5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: > 1 <12 years, both male and female, 61·6 µmol/l; ≥ 12 < 16 years, both male and female, 88 µmol/l; ≥16 years, female, 105·6 µmol/l; ≥16 years, male, 114·4 µmol/l.

During the 1st cycle of SAR440234 treatment, every 8 hours after the start of infusion for the next 72 hours, the monitoring of blood chemistry is mandatory (details are provided in protocol).

Cardiac monitoring and admission to the ICU is required if TLS is established, as well as continuing laboratory monitoring every 4-6 hours. Additional measures to treat metabolic derangements associated with TLS may be required, as shown in **Appendix Table 2**.

Prophylaxis against TLS may be required depending on the patient's risk for TLS, as described below.

Low-risk is defined as:

- Patients with low tumor burden (WBC ≤ 50 x 10^9/l and normal LDH level)
- Patients receiving low intensity cytoreductive therapy
- Normal pre-existing uric acid
- Adequate hydration
- No tumor infiltration in the kidney

High-risk is defined as:

- Hematological malignancies with high proliferative rate
- High tumor burden (WBC ≥ 50 x 10^9/l and high LDH level)
- Elevated uric acid level
- Patients receiving intensive cytoreductive therapy
- Poor hydration
- Leukemia infiltration of the kidney

Recommendations for **intravenous hydration** during SAR440234 treatment in patients at high risk for TLS, include the following:

- Normal saline solution 3 L/m^2/d, unless no symptoms of acute renal dysfunction and oliguria.
- Maintain urine output ≥ 100 ml/m^2/h.
- Diuretics may be required to maintain urine output at ≥ 100 ml/m^2/h: mannitol 0.5 mg/kg or furosemide 0.5 – 1.0 mg/kg.

For high risk patients, prophylactic treatment with **allopurinol** should begin 2 to 3 days before the start of antineoplastic therapy and continue for 10 to 14 days, as described in **Appendix Table 3**.

Rasburicase is indicated for patients with the following features:

- High-risk of TLS development
- Urgent need to initiate therapy in a patient with a high bulk of malignant disease
- In a situation where adequate hydration may be difficult or impossible
- Acute renal failure

The dose for rasburicase is indicated in **Appendix Table 3**. Redosing must be individualized.

Recommendations regarding the selection of allopurinol and/or rasburicase are summarized in **Appendix Table 4**.

Appendix Table 2 - Specific recommendations for treatment of TLS

Hyperphosphatemia: ≥ 2.1 mmol/L	Removing phosphates from i.v. solutions Oral phosphate binders: e.g. aluminum hydroxide orally at 50-150 mg/kg/24 h q6h Peritoneal dialysis, hemodialysis or continuous venovenous hemofiltration may be required in a case of severe hyperphosphatemia. **Calcium infusion is prohibited!**
Hypocalcemia: ≤ 1.75 mmol/L (serum) or ionized calcium is ≤ of ionized local limit	Treatment not required if asymptomatic. Symptomatic hypocalcemia (muscle cramps and spasms, paresthesias, arrhythmias, heart block, hypotension, confusion, delirium, hallucination, seizures) requires treatment: Calcium gluconate 50 – 100 mg/kg/dose i.v.
Hyperkalemia	Moderate and asymptomatic (≥ 6.0 mmol/L): Avoid i.v. and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate 1 g/kg with 50 % sorbitol po or per rectum Severe (>7.0 mmol/L) and/or symptomatic Same as above, plus Calcium gluconate (100–200 mg/kg) i.v. and/or Regular insulin (0.1 unit/kg i.v.) + D25 (2 mL/kg) i.v. Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemo- or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD or CVVHD)
Hyperuricemia: uric acid ≥ 476 mcmol/L	See **Appendix Tables 3** and **4** regarding selection and dose of hypouricemic agents: Allopurinol Rasburicase (recombinant urate oxidase).

Appendix Table 3 - Recommendations on the use of hypouricemic agents

Allopurinol 100 mg/m^2/dose q8 h (10 mg/kg/d divided q8 h) p.o. (maximum 800 mg/d) or 200–400 mg/m^2/d in 1–3 divided doses i.v. (maximum 600 mg/d) Reduce dose by 50% or more in renal failure Reduce 6-mercaptopurine and/or azathioprine doses by 65–75% with concomitant allopurinol Adjust doses of drugs metabolized by P450 hepatic microsomal enzymes with concomitant allopurinol
Rasburicase **Avoid in glucose-6-phosphate dehydrogenase deficient patients.** **Immediate and permanent stop of treatment if methemoglobinemia is result.** 0.05–0.20 mg/kg i.v. over 30 min To measure uric acid levels place blood sample immediately on ice to avoid continual pharmacological ex vivo enzymatic degradation. 10% incidence of antibody formation.

Appendix Table 4 - Recommendations on selection of hypouricemic agents

	Allopurinol	**Rasburicase**
Uric acid level	Normal	Elevated
Tumor type	Non-hematological Hodgkin's lymphoma, CML	Burkitt's lymphoma, lymphoblastic lymphoma, ALL, AML
Tumor burden		
WBC count	$\leq 50 \cdot 10^9$/L	$>50 \cdot 10^9$/L
LDH	$\leq 2 \cdot$ normal	$>2 \cdot$ normal
Cytoreductive intensity	Mild	Aggressive
Kidney tumor infiltration	Absent	Present

Appendix K Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Clinical Trial Summary.

Amended protocol [02] (15 February 2019)

Reasons for amendment

- **Modify allowed chemotherapy to permit use of hydroxyurea, if needed, to control the white blood count during Cycle 1**

In section: E03, E08, Clinical Trial Summary "Dose Escalation Part", Section 7.3 and Section 8.6

Rationale: Hydroxyurea may help to control the white blood count during the 6 weeks of the DLT observation period of the dose escalation and/or during lead-in dosing during Cycle 1 when SAR440234 dosing is likely to be subtherapeutic.

- **Clarify wording in the dose delay/reduction section to avoid misinterpretations**

In section: Section 6.5.4, and Section 6.5.5

Rationale: Dose delay and/or dose reduction are not required if the AE is related to underlying leukemia or baseline cytopenia and continuing SAR440234 treatment is considered safe.

- **Clarify wording of DLT definitions**

In section: Clinical Trial Summary "Dose Escalation Part" and Section 6.2.1

Rationale: AEs caused by the patient's underlying hematologic malignancy should not be considered investigational medical product (IMP)-related and thus should not be deemed DLTs.

- **Require performance of Day 42 assessment on the day that the patient discontinues therapy with SAR440234**

In section: Flow charts and Section 1.2.1-1.3.4, Section 6.8.1, Section 12.4, Section 12.5, Section 12.6, and Section 12.7

Rationale: Given the severity of illness and short life expectancy that many patients with relapsed or refractory hematologic malignancies exhibit, a patient may not survive long enough or be well enough to return to clinic for a Day 42 or EOT visit after discontinuing SAR440234.

- **Require performance of end of treatment (EOT) assessment within 30 days of last SAR440234 administration**

In section: Flow charts and Section 1.2.1-1.3.4, Section 6.8.1, Section 12.4, Section 12.5, Section 12.6, and Section 12.7

Rationale: Given the severity of illness and short life expectancy that many patients with relapsed or refractory hematologic malignancies exhibit, a patient may not survive long enough or be well enough to return to clinic for a Day 42 or EOT visit after discontinuing SAR440234.

- **Require follow up via telephone call and record review if a patient is unable to return to clinic for monthly study visits after discontinuing SAR440234**

In section: Flow charts and Section 1.2.1-1.3.4, Section 6.8.1, Section 12.4, Section 12.5, and Section 12.6, and Section 12.7

Rationale: Given the severity of illness and short life expectancy that many patients with relapsed or refractory hematologic malignancies exhibit, a patient may not survive long enough or be well enough to return to clinic for a Day 42 or EOT visit after discontinuing SAR440234.

- **Clarify enrollment schedule**

In section: Clinical trial summary, and Section 6.2.1

Rationale: Since each Cycle 1 Day 1 (C1D1) of each DL starts with a dose that was tested in the previous DL and the acute effects are expected to occur within 1 week of administration, subsequent patients within a DL may initiate treatment at least 1 week after the first patient in the same DL started treatment with SAR440234.

Amended protocol 01 based on Amendment 01

Reasons for amendment

- **Clarify some discontinuation criteria**

In section: Clinical trial summary, Section 6.5.4 of the protocol

Rationale: Description of treatment discontinuation for patients with Grade 3 febrile neutropenia or Grade 4 bone marrow hypocellularity has been removed because it was not consistent with the more detailed description in Section 6.5.4

- **Modify some Inclusion/Exclusion criteria**

In sections: Clinical trial summary, Section 7.2 and Section 7.3 of the protocol

Rationale:

- In I 02., the criteria for patients who have relapsed or refractory disease resistant to available therapies have been revised.
- In I 03., it has been clarified that patients with B-cell acute lymphoblastic leukemia without extramedullary lesions in second or subsequent relapse must have completed at least 1 cycle of a salvage regimen before being recruited for any dose level ≥3 during the dose escalation part.
- I 04. was revised to better define the criteria for inclusion of patients with high risk myelodysplasia (HR-MDS).
- I 01. and I 03 are revised to specify that patients must have exhausted available treatment options and must not be eligible for any treatment known to provide clinical benefit.
- E 03. is revised to exclude patients with a white blood cell count greater than 30,000/mm3.
- E 05. is added to exclude patients with history of active or chronic autoimmune condition that has required or requires therapy.

- **Define overdose of oral intake**

In section: Section 10.5.5 of the protocol

Rationale: A criterion for overdose with orally taken Investigational Medicinal Product (IMP)/Non-Investigational Medicinal Product (NIMP) has been added as montelukast (NIMP) may be taken orally.

In addition, other minor changes are listed in the description of changes (next section).

- **Update premedication prior to infusion. Additional premedication is now required: dexamethasone 20 mg IV and monteleukast 10 mg oral (PO) 4 hours prior to the start of SAR440234**

In section: Clinical trial summary, Section 1.2, Section 4.5.3, Section 6.7.1, and Section 8.2 of the protocol

Rationale: Provide maximal protection from acute reactions.

- **Update dose modification rules for Grade 3 and 4 CRS**

In section: Section 6.5.3 (Tables 5 and 6) of the protocol.

Rationale: To protect patients against the potentially life-threatening consequences of severe cytokine release syndrome (CRS). All patients who develop Grade 4 CRS at any time point in the study should immediately and permanently discontinue study drug. In addition, only patients who experience limited Grade 3 CRS (as defined by 1st occurrence of Grade 3 CRS with recovery to baseline or ≤ Grade 1 within 72 hours) should be permitted to resume treatment with appropriate dose reductions.

- **Add specific guidelines for the risk stratification, diagnosis, prevention, and treatment of tumor lysis syndrome.**

In section: Section 6.7.2 and Appendix J of the protocol

Rationale: To prevent potentially life-threatening consequences of tumor lysis syndrome, which could occur if SAR440234 is highly effective in a patient with a high burden of malignant disease.

- **Add magnesium to blood chemistry.**

In section: Sections 1.2, Section 6.7.2, and Section 12 of the protocol

Rationale: To prevent potentially life-threatening consequences of tumor lysis syndrome, which could occur if SAR440234 is highly effective in a patient with a high burden of malignant disease.

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