AMENDED CLINICAL TRIAL MASTER PROTOCOL 01

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) with or without other anticancer therapies for the treatment of adults and adolescents with relapsed or refractory B cell lymphoma**
Protocol number:	**ACT16941 Master**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 with or without other anticancer therapies for the treatment of adults and adolescents with relapsed or refractory B cell lymphoma (Master Protocol)**
Acronym	**Pegathor Lymphoma 205**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin,** **France**
Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Master Protocol 01	All	28 April 2022, version 1 (electronic 1.0)
Clinical Trial Master Protocol		16 July 2021, version 1 (electronic 1.0)

Amended protocol 01 (28 April 2022)

This amended protocol (Amendment 01) 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 rationale for this amendment is to change from an every 3 weeks (Q3W) to an every 2 weeks (Q2W) investigational medicinal product (IMP) dosing schedule in one of the cohorts, and in response to requests from Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page and 1.1 Synopsis	The following study name: “Pegasus Lymphoma 205” has been removed from the protocol title and the new study acronym “Pegathor Lymphoma 205” has been added on the cover page.	For consistency across the program.
Cover page	The NCT number has been added.	This study has been registered on clinicaltrials.gov, the NCT number is applicable.
1.1 Synopsis- Figure 1, 4.1 Overall Design 6.1.1 Investigational medicinal product-Table 3, and 9.5 Interim analyses	The “Study Committee” has been renamed as “Study Board” and its composition and role have been clarified in Section 4.1.	For consistency with Sanofi standard terminology.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design	The following sentence “Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected.” has been deleted.	Reduction in protocol complexity and patient/site burden.
1.1 Synopsis, 4.1 Overall design	The following sentence has been removed “delay of >14 days between end of Cycle 1 and start of Cycle 2 because of toxicity will be considered a DLT”.	To align with the dosing schedule changes for one of the cohorts.
1.1 Synopsis, 4.1 Overall design	The following sentence has been deleted “or until start of another anticancer therapy or final cohort cut-off, whichever comes first” for the reason leading to EOT for the participants who discontinue study treatment with PD.	For consistency and clarification.
1.1 Synopsis, 6.1.2.1 Premedication for SAR444245, Table 7 Risk assessment	[redacted]	[redacted]
1.1 Synopsis, 6.1.2.1 Premedication for SAR444245	Oral administration of diphenhydramine is now permitted, in addition to IV administration. Intravenous administration of acetaminophen is now permitted, in addition to oral administration.	To allow local approved administration route to be used.
1.2 Schema	“FDG-PET must be performed for the 9-week and 18-week on-treatment assessment” has been added for Figure 2 and Figure 3.	For clarity.
	For Figure 3, the previous “Cycle 2-8” of the treatment period has been changed to “Cycle 2-16”, and previous “Cycle 8 and subsequent” has been changed to “Cycle 17 and subsequent”.	To align with the dosing schedule changes for one of the cohorts.
1.4 Biomarker flowcharts	[redacted]	[redacted]
5.1 Inclusion criteria, 8.2.5 Pregnancy testing, 8.3.5 Pregnancy, 10.2 Appendix 2 Clinical laboratory tests -Table 5 footnote e	In I04, the requirement for contraception for male participants has been changed from “at least 210 days [corresponding to time needed to eliminate study intervention(s) plus an additional 90 days (a spermatogenesis cycle)] after the last dose of study intervention” to “at least 3 days [corresponding to time needed to eliminate SAR444245] after the last dose of SAR444245”.	To change measures for male participants as per Clinical Trials Facilitation and Coordination Group (CTFG) guideline on “recommendations related to contraception and pregnancy testing in clinical trials version 1.1” of 21 Sept 2020. As SAR444245 is not genotoxic, there is no need to extend the requirement for contraception to 90 days (3 months) for male participants, but to take into account the 5 half-lives of the study intervention before its elimination.
	The recommended duration for continuing contraception after last dose of study intervention has been changed for female participants from 180 days to 120 days (or refer to the individual	None of the products in combination is genotoxic in this study, there is no need to extend the requirement for contraception to 30 days (1 month) corresponding to a menstrual cycle for female participants.

Section # and Name	Description of Change	Brief Rationale
	substudy protocol), and the requirement of extension extra 30 days (1 month) has been removed.	Regulatory Authority (Italy) request.
5.1 Inclusion criteria	In I04, the requirement for the use of a male condom has been updated.	For consistency between recommended male and female contraception.
5.2 Exclusion criteria	In E 01, the Lansky Scale has been changed from "< 50%" to "⩽ 60%".	To align with the ECOG performance status as per Regulatory Authority (ANSM) request.
5.2 Exclusion criteria	In E 11, a note has been newly added to refer to substudy protocol.	Cohort specific requirement has been added for one of the substudies.
5.2 Exclusion criteria	E 19 has been changed from "Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention, including premedication to be administered in this study, as well as PEG or any pegylated drug" to "Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein".	To clarify that patients with known hypersensitivity to any excipient of the study interventions or to E. coli-derived protein must be excluded.
5.2 Exclusion criteria	E 23 "Participants treated under anti-hypertensive treatment who cannot temporarily (at least 36 hours) withhold antihypertensive medications prior to each SAR444245 dosing" has been deleted.	Temporary withholding of anti-hypertensive drugs is based on the physician's decision based on individual patients.
5.2 Exclusion criteria	E24 "Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease [GVHD])." has been removed from master protocol and added to relevant substudy.	For clarification.
5.2 Exclusion criteria	E 25 has been changed from: Participation in a concurrent clinical study in the treatment period To Current enrollment or past participation in a study of an investigational treatment or has used an investigational device within 28 days prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational treatment.	For clarification.
5.2 Exclusion Criteria, 10.2 Appendix 2: Clinical laboratory tests,	Requirement for human immunodeficiency virus (HIV) has been added at screening for participants in France and specified in exclusion criteria E16,	Regulatory Authority (ANSM) request.

Section # and Name	Description of Change	Brief Rationale
and 10.7 Appendix 7: Country-Specific Requirements	Clinical laboratory tests and Country-specific requirements sections.	
5.4 Screen failures	The following text has been added “A participant may be rescreened only once”.	For clarity.
6.1.3 Hydration guidelines for SAR444245 administration	[redacted]	[redacted]
6.1.4 Readiness for treatment of severe cytokine release syndrome	The following statement “alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following tocilizumab availability.
6.2 Preparation/handling/ storage/accountability	The following text regarding DTP shipment of IMP has been deleted: “(except for DTP shipment, for which a courier company has been approved by the Sponsor)”.	Direct-to-patient shipment of IMP is not possible in this study.
6.8.2 Prohibited concomitant medications, 10.10 Appendix 10 Risk assessment Table 7	The following sentence in Section 6.8.2 has been deleted: “Participants requiring medication(s) that are metabolized by the liver and have narrow therapeutic index require close monitoring (drug blood levels or other surrogate of drug exposure) when on study treatment. If a participant cannot be closely monitored, he/she should be removed from the trial.” In Table 7, the row for drug-drug interactions has been deleted.	Based on new de-risking in-vitro data.
8 Study Assessments and Procedures 8.2 Safety assessment, 8.2.3 Electrocardiograms and LVEF,	The assessment of troponin level has been added. The following text has been added: “A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiogram and troponin level”. Troponin has been added as an example of cardiac enzymes within additional evaluation to carry out when clinically indicated. The following text has also been added for evaluations during treatment and post treatment follow-up: “During treatment, or post treatment follow-up: Troponin will be performed at Cycle 4 Day 1. In	To allow assessment of any potential cardiotoxicity.

Section # and Name	Description of Change	Brief Rationale
	case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, troponin elevation, etc.), Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation".	
and 10.2 Appendix 2 Clinical laboratory tests-Table 5	Troponin has been added to "other screening tests".	
8.1 Efficacy assessments	Table 7 for imaging or disease assessment collection plan has been added.	For clarity.
8.2.2 Vital signs	"In an in-patient setting" has been added for Cycle 1 Day 1 vital sign collection for the safety run-in participants.	For clarity.
8.3.1 Time period and frequency for collecting AE and SAE information	The instruction to stop collecting AE and SAE information should the participant initiate another anticancer therapy has been removed. All AEs and SAEs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards.
8.3.8 Adverse event of special interest	SARS-CoV-2 infection/COVID-19 disease has been removed from AESIs.	COVID19 infection is removed from AESI considering progress of the vaccination and change in severity of the symptoms associated with new variants.
8.6 Biomarkers	The following sentence has been added for [redacted] "This method will only apply to samples from clinical sites not exhibiting feasibility constrains on handling/shipment".	To improve flexibility in case local constrains exist.
8.6 Biomarkers	Concerning collection of samples, the following text "will be stored for a period of up to 15 years after the last participant's last visit for potential re-analyses" has been changed to "may be used for further research if consent is provided (see Section 8.9)".	Harmonization per Sanofi standard terminology.
8.9 Use of biological samples and data for future research and 10.5 Appendix 5: Genetics	The text has been revised to state that the duration of storage for biological samples and relating data is up to 25 years. The duration of biological sample storage was previously given as a maximum of 15 years.	For consistency with the latest Sanofi standards.
9.3 Populations for Analyses	The efficacy population definition has been revised to "All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment".	To characterize the efficacy excluding participants newly enrolled.

Section # and Name	Description of Change	Brief Rationale
9.5 Interim analysis	The following sentence has been added "Occurrence of any treatment related Grade 3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger ad hoc DMC."	For clarity.
10.1.6 Dissemination of clinical study data	The text has been revised as follows: "Sanofi shares information about clinical trials and results on publicly accessible websites for each completed sub study and final study results".	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials.
10.1.9 Study and site start and closure	The wording has been revised to specify "provided by the Sponsor" after "study treatment".	For clarification
10.4.2 Contraception guidance	The duration for study intervention may affect ova or sperm have been updated from "ova up to 180 days and sperm up to 210 days" to "ova and sperm for up to the number of days specified respectively for each cohort in the inclusion criteria".	To align with the updates of I04.
10.7 Appendix 7 Country-Specific Requirements	Country-specific requirements for France has been added.	Regulatory Authority request.
10.14 Appendix 14 Definition of line of therapy	Section newly added to clarify the definition of line of therapy. The subsequent section has been re-numbered accordingly.	For clarity.
Throughout the document	Minor editorial updates.	For clarity and consistency.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) with or without other anticancer therapies for the treatment of adults and adolescents with relapsed or refractory B cell lymphoma

Brief title: A study of SAR444245 with or without other anticancer therapies for the treatment of adults and adolescents with relapsed or refractory B cell lymphoma (Master Protocol)

Rationale:

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the interleukin (IL)-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. The first in human clinical study with SAR444245 (TCD16843/HAMMER, hereafter referred to as HAMMER) demonstrated that treatment with SAR444245 leads to expansion of CD8+ T cells and natural killer (NK) cells (with higher IL-2 βγ receptor expression) with negligible IL-2Rα induced effect on immunosuppressive Treg cells expansion, vascular leak syndrome related eosinophils expansion and IL-5 release.

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with other anticancer therapies or as a monotherapy, in trial participants with relapsed or refractory B cell lymphoma.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with or without other anticancer therapies in specific cohort of relapsed or refractory B cell lymphoma. Common protocol elements are contained in this document (“Master Protocol”) and cohort-specific protocol elements are contained in separate substudy protocols. This design has the flexibility to open new treatment cohorts as new treatment become available and close existing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity.

The information that is introductory and common to all cohorts is included in the present document (“Master Protocol”), and cohort-specific elements are included in separate substudies.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 with or without other anticancer therapies.	• Refer to individual substudy.
Secondary	
• To confirm the dose and to assess the safety profile of SAR444245 when combined with or without other anticancer therapies.	• Incidence of treatment emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus gradings (1).
• To assess other indicators of antitumor activity.	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of partial response (PR) or complete response (CR) determined by Investigator per Lugano response criteria 2014 (2). • Duration of response (DoR) defined as the time from first documented evidence of PR or CR until progressive disease (PD) determined by Investigator per Lugano response criteria 2014 (2), or death from any cause, whichever occurs first. • Clinical benefit rate (CBR) including CR or PR at any time or stable disease (SD) of at least 6 months (determined by Investigator per Lugano response criteria 2014) (2). • Progression free survival (PFS) defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator per Lugano response criteria 2014 (2) or death due to any cause, whichever occurs first.
• To assess the plasma concentrations of SAR444245 when given with or without other anticancer therapies.	• Plasma concentrations of SAR444245.
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245.

Overall design:

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 with or without other anticancer therapies in adults and adolescents with relapsed or refractory B cell lymphoma.

Brief summary:

A graphical presentation of the study schema is shown in Figure 1.

A safety run-in will confirm the dose of SAR444245 in each substudy. Participants who fulfill the eligibility criteria of any cohort may be enrolled to the safety run-in of that cohort. After a maximum of 10 participants have been enrolled into a specific cohort, enrollment will be paused for that cohort.

Once a total of at least 6 participants are evaluable for DLT in a specific cohort, safety data for these participants will be reviewed by the Study Board (SB). The Study Board will comprise the Investigators or designees participating in the safety run-in part of applicable cohorts and the Sponsor clinical team members. DLT-evaluable participants include all treated participants in the safety run-in part who have been observed for the DLT observation period (defined in the individual substudy). Any participant who experienced a DLT at any time during the DLT observation period will also be DLT-evaluable.

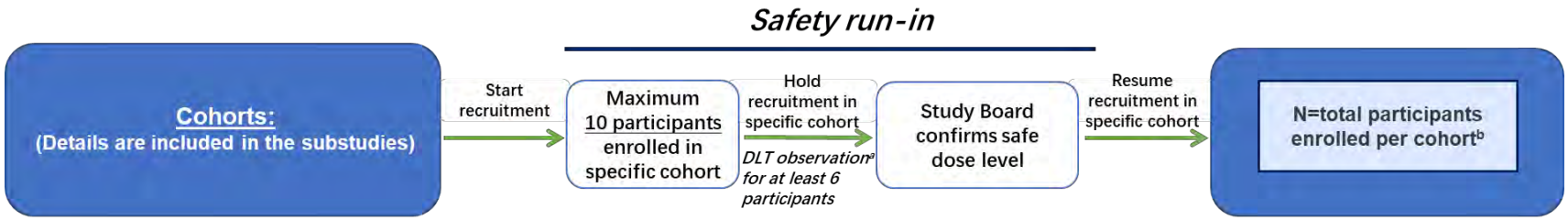
If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from SB. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants for that specific cohort (for example, if 10 Cohort A participants are enrolled in the safety run-in, and treated at the confirmed safe dose, approximately 15 additional participants will be enrolled into Cohort A to have the total number of 25 participants).

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an intravenous (IV) infusion over 30 minutes during each cycle (see Section 1.1 Study interventions for details). Overall safety monitoring will be performed throughout the study. If recommended by the Study Board, SAR444245 dose may be reduced to [redacted]µg/kg or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

The dose confirmation will follow modified toxicity probability interval 2 (mTPI2) design.

Dose limiting toxicity: Selected events occurring during the DLT observation period (defined in the individual substudy) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245. Please refer to the full list of events in Section 4.1 Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the Study Board will determine if the dose of SAR444245 needs to be reduced to [redacted] µg/kg or another lower dose level, in agreement with the Sponsor.

Figure 1 - Overall study schema



a The DLT observation period is defined in the individual substudy.
b Including participants enrolled in the safety run-in at the confirmed safe dose.

Abbreviations: DLT: dose limiting toxicity; N: number.

Special considerations pertaining to methodology

Interactive Response Technology will be used to control recruitment, assignment per site and facilitate the handling, management, and accountability of drug supply.

Number of participants:

Please refer to the individual substudy for the numbers of participants to be enrolled and treated at the confirmed safe dose.

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

The duration of the study for a participant will include:

- **Screening period**: Up to 28 days.
- **Treatment Period**: Enrolled participants will receive continuous treatment until PD, unacceptable adverse event (AE), or other full permanent discontinuation criteria as described in Section 7, or complete the maximum cycles allowed in the individual substudy. However, treatment beyond PD may be allowed for up to 9 weeks if the participant appears to be benefiting clinically after discussion with the Sponsor.
- **End of Treatment and Follow-up**: End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **End of Treatment (EOT)**:
    1. Participants who discontinue study treatment **without PD** or who **complete the maximum cycles allowed in the individual substudy without PD** (per Lugano response criteria 2014[2]), will be followed every 3 months ±7 days from last IMP administration, for safety (as per Schedule of Activities [SoA] in the individual substudy) and tumor imaging assessments, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.
    2. Participants who discontinue study treatment **with PD** (per Lugano response criteria 2014[2]) will be followed for safety in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status Updated survival status may be requested by the Sponsor at any time during the study. Survival Phone Call Follow up will continue until death, participant request to discontinue from follow-up, or cut-off date for final

analysis has been reached, or upon cancellation of Survival follow-up at the discretion of the Sponsor at any prior timepoint.

After the cohort cut-off date for the primary analysis, participants can continue to receive IMP, if clinical benefit is observed, until full permanent discontinuation criteria described in Section 7 are met and will continue to undergo all assessments as per the study schedule of activities in the individual substudy.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort last participant in (LPI).

Study interventions

Investigational medicinal product(s)

SAR444245

- Formulation: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- Route of administration: intravenous (IV) infusion.
- Dose regimen: refer to individual substudy.

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted.

See substudy protocols for other IMPs.

Non-investigational medicinal products

Premedication for SAR444245

All participants will receive the following premedication to prevent or reduce the acute effect of infusion-related reactions (IRR) or flu-like symptoms, 30 to 60 minutes prior to SAR444245 infusion (no longer than 60 minutes) for the first 4 cycles:

- Acetaminophen (paracetamol) 650 to 1000 mg IV or oral route (PO) (or equivalent), and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

SAR444245 premedication may be optional after 4 cycles:

- For a participant who has no IRR during the first 4 cycles: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the

subsequent infusions without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent infusions.

- If a participant develops an IRR Grade <2 during their first cycle only and then experiences no further IRRs during their next 3 cycles: The Investigator may consider omitting premedication for Cycle 5. If no IRR is observed during Cycle 5 without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during Cycle 5 without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent cycles.

Statistical considerations:

- **Analysis of primary endpoint:**

  Refer to individual substudy.

- **Analysis of secondary efficacy endpoints:**

  - Time to response (TRR) will be assessed on the subgroup of participants who have achieved objective response in the efficacy population.
  - Duration of response (DoR) will only be summarized on the subgroup of participants who have achieved objective response in the efficacy population.
  - Clinical benefit rate (CBR) will be estimated by dividing the number of participants with clinical benefit by the number of participants in the efficacy population.
  - Progression free survival (PFS) will be summarized on the efficacy population using Kaplan-Meier methods. The median PFS times and associated 90% confidence interval (CI) will be provided.

- **Analysis of secondary safety endpoints:**

  - Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class (SOC) and Preferred Term (PT) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V5.0) grade (all grades and Grade ≥3) for the exposed population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to full intervention discontinuation, TEAEs leading to partial intervention discontinuation (if applicable), TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) and participants who died by study period (treatment-emergent period, post-treatment period) and reasons for death will be summarized. Immune Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS) events will be graded using American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading and will be summarized separately.
  - Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number and percentage of participants with

laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided for the exposed population.

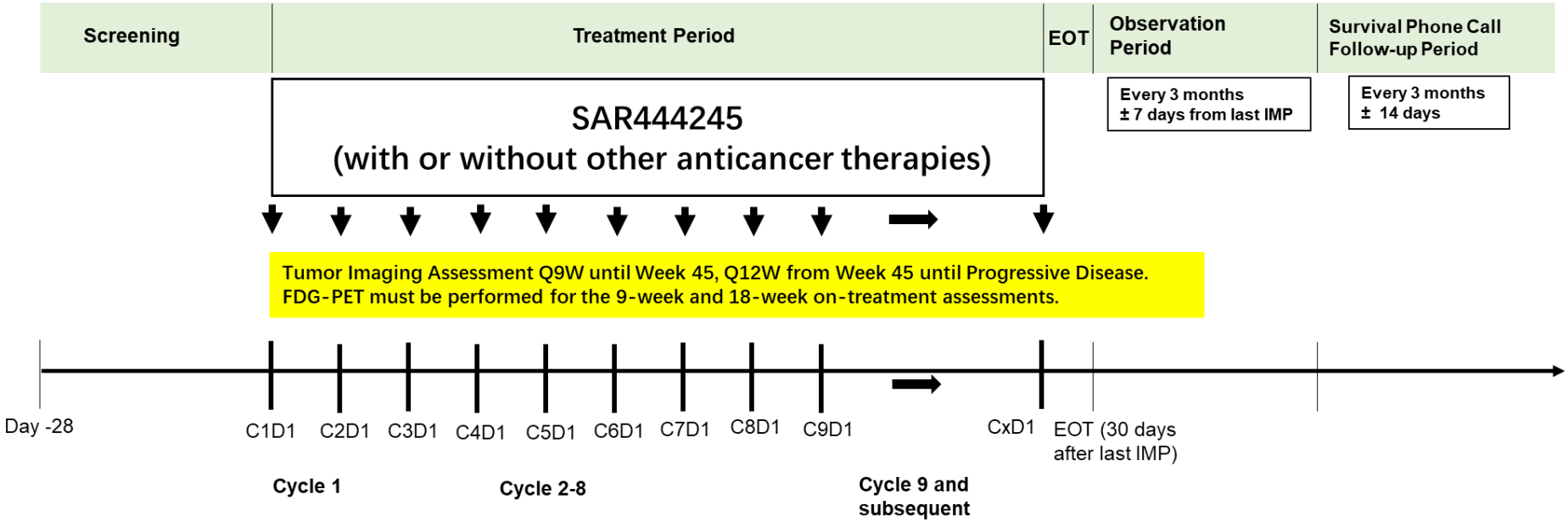
- **Analysis of other secondary endpoints:**
  - Plasma concentrations of SAR444245 will be summarized with descriptive statistics.

Data Monitoring/Other Committee: Yes (see Section 10.1.5 for details).

1.2 SCHEMA

1.2.1 Study design for Cohort testing Q3W regimen

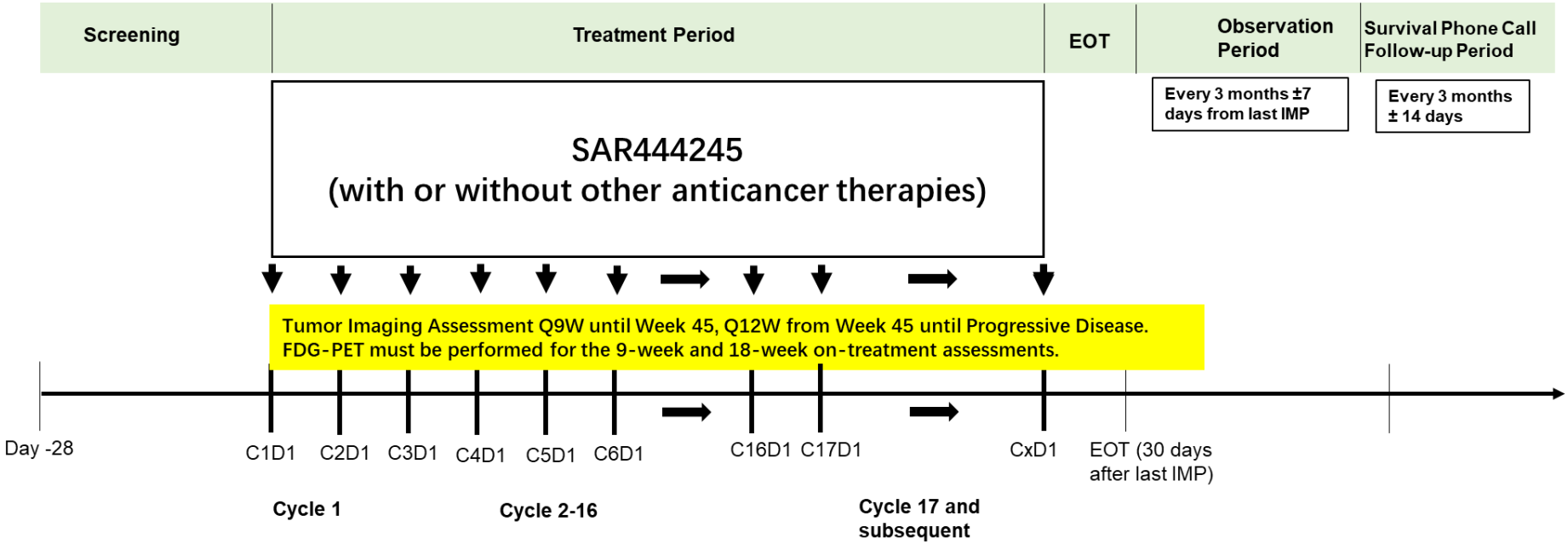
Figure 2 - Graphical study design-Cohort testing Q3W regimen



C=Study cycle (1 cycle = 21 days); D=Study day; EOT=end of treatment; FDG-PET=fluorodeoxyglucose-positron emission tomography; IMP=Investigational medicinal product; Q3W= every 3 weeks; Q9W= every 9 weeks; Q12W= every 12 weeks.

1.2.2 Study design for Cohort testing Q2W regimen

Figure 3 - Graphical study design-Cohort testing Q2W regimen



C=Study cycle (1 cycle=14 days); D=Study day; EOT=end of treatment; FDG-PET=fluorodeoxyglucose-positron emission tomography; IMP=Investigational medicinal product, Q3W= every 3 weeks; Q9W= every 9 weeks; Q12W= every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Please refer to individual substudy.

1.4 BIOMARKER FLOWCHARTS

Please refer to substudies for the individual biomarker flowcharts.

1.5 PHARMACOKINETIC FLOWCHARTS

The sampling time-points for pharmacokinetic (PK) and anti-drug antibodies (ADA) for/against SAR444245 and/or other IMPs may be updated during the course of the study based on the updated knowledge of drug behavior upon notification from the Sponsor.

Please refer to substudies for the individual pharmacokinetic flowchart.

2 INTRODUCTION

The purpose of this study is to evaluate the potential impact of SAR444245 with or without other anti-cancer therapies to improve outcome in adults and adolescents with B cell lymphoma, including classic Hodgkin lymphoma (cHL), primary mediastinal large B cell lymphoma (PMBCL), and diffuse large B cell lymphoma (DLBCL). Preclinical data, as described below, support the clinical study design. SAR444245 is a recombinant human interleukin 2 (IL-2) with a site-specific substitution of a non-native azido lysine amino acid residue which is bio-conjugated to a single linear 30 kDa PEG. SAR444245 is being developed as an immuno-oncology treatment to be administered every 2 weeks (Q2W) or less frequently (every 3 weeks [Q3W] in the present study) in patients with cancer. [redacted] The site-specific pegylation of IL-2 in SAR444245 provides a "non-alpha" pharmacologic profile for SAR444245 that is designed to prevent engagement of the high affinity IL-2Rα and keep comparable binding to IL-2Rβ, while maintaining CD8+ T cell and natural killer (NK) cells anti-tumor activity and resulting in an improved safety profile relative to aldesleukin. Aldesleukin is approved in the United States (US) for the following indications: the treatment of metastatic renal cell carcinoma (RCC) and metastatic melanoma, with the same or limited approval status in other countries. Its use has resulted in durable complete response (CR) in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, widespread use of aldesleukin is limited by its low response rate, short half-life ($t_{1/2}$), and severe toxicities, including primarily vascular leak syndrome (VLS), and cytokine release syndrome (CRS).

In contrast to native IL-2 and aldesleukin, SAR444245 does not have high potency at the IL 2Rα/β/γ receptor expressed on Treg cells because the site-specific pegylation blocks IL-2Rα engagement. Due to this re-programmed receptor bias, SAR444245 induces proliferation of peripheral CD8+ T and NK cells in vivo as observed in mice and non-human primates (NHP) with negligible effect on the expansion of immunosuppressive Treg cells. Furthermore, SAR444245 does not bind IL-2Rα, and does not activate cells that express low levels of the high affinity IL 2Rα, such as Type 2 innate lymphoid cells (ILC-2s), eosinophils, and endothelial cells. Thus, it is expected to have a greatly reduced risk of VLS, and therefore a wider therapeutic window as compared to aldesleukin. In preclinical NHP studies, no signs of VLS were observed at a dose of SAR444245 that was [redacted] higher than the dose eliciting maximal expansion of peripheral CD8+ T cells. Therefore, in the clinic, SAR444245 is expected to have a wider therapeutic window as compared to aldesleukin due to a greatly reduced risk of VLS.

Furthermore, the site-specific pegylation extends the plasma $t_{1/2}$ of IL-2 in SAR444245 in mice and NHP to 9-13 hours versus 85 minutes for aldesleukin in patients.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models. SAR444245 is hypothesized to have a synergistic effect with immunotherapies. Refer to individual substudies for specific background and rationales. The first in human clinical study with SAR444245 (TCD16843/HAMMER, hereafter referred to as

HAMMER) demonstrated that treatment with SAR444245 leads to expansion of CD8+ T cells and natural killer (NK) cells (with higher IL-2 βγ receptor expression) with negligible IL-2Rα induced effect on immunosuppressive Treg cells expansion, vascular leak syndrome related eosinophils expansion and IL-5 release.

2.2 BACKGROUND

2.2.1 Rationale for B cell lymphoma and selected participant population

Lymphomas are an important cause of cancer death world-wide. There are many different sub-types of lymphoma. Immunotherapy has demonstrated efficacy in most types of B cell lymphoma, although the approach varies according to the subtype. There is still considerable unmet need for patients with B cell lymphoma, including cHL, PMBCL, and DLBCL, thus this study focuses on these indications. Non-Hodgkin lymphoma (NHL) is the most common type of lymphoma, while DLBCL is the most common type of aggressive NHL. In 2019, the annual incidence (US) for NHL was 80,000. Hodgkin lymphoma (HL) is a relative rare malignancy, but one of the most common hematologic malignancies in young adults. Primary mediastinal B cell lymphoma (PMBCL) is a rarer hematologic malignancy that is typically seen in young adult women and adolescents. In 2021, the US annual incidence for NHL and HL is expected 81,560 and 8,830 respectively (3). Hodgkin lymphoma (HL) and PMBCL are of special interest because they are the first hematologic malignancies in which checkpoint blockade with anti-PD1 therapy has been shown to be effective. Pembrolizumab monotherapy is approved in both indications in the relapsed or refractory setting, while nivolumab monotherapy is approved in relapsed or refractory HL only.

There is still a considerable area of unmet need for patients with relapsed or refractory NHL or HL. At diagnosis NHL and HL exhibit 5-year overall survival rates of 73.2% and 88.3%, respectively (3), however patients who develop relapsed or refractory disease exhibit a PFS of 14.7 months or 4-12 months for HL or NHL, respectively, if their disease persists despite intensive salvage therapy or if they are ineligible for intensive therapy (4, 5, 6, 7). Anti-PD1 monotherapy for patients with relapsed or refractory HL who have received 2 or more prior lines of systemic therapy has yielded ORR's of 65-87%, however CRR is 16-17% and PFS is 46% at 1 year (8, 9). Similarly for patients with relapsed or refractory PMBCL who have received a median of 3 prior lines of sytemic therapy, pembrolizumab monotherapy yields an ORR of 45-48%, however CRR is 13-33% and PFS is 38-47% at 1 year. These data highlight the need for more effective treatment combinations that synergize with checkpoint inhibitor therapy in HL and PMBCL (10).

For patients with relapsed or refractory DLBCL who are ineligible for intensive therapy, there are several treatment options; however, none of these regimens are considered curative and PFS is generally 1 year or less. The rituximab-based combination, rituximab+gemcitabine+oxaliplatin (RGemOx), is a well-tolerated form of chemoimmunotherapy that has been shown to be effective in relapsed or refractory DLBCL patients (ORR 43-61%) (5, 11). Recently published data supporting accelerated approvals of tafasitamab+lenalidomide and polatuzumab vedotin +bendamustine+rituximab demonstrate ORR of 43% and 70%, respectively, and PFS of 9-12 months (6, 7) in patients with relapsed or refractory DLBCL who were previously treated with rituximab or other anti-CD20 agents.

For patients who are eligible for intensive therapy for relapsed or refractory DLBCL, approved CD19-directed chimeric antigen receptor T-cell immunotherapy (CAR-T) achieves remarkable durations of response (median 9 months-not estimated) for patients who reach a CR, however about 50% of patients do not achieve a CR and thus will not receive a sustained benefit. Patients achieving a partial response (PR) exhibit a median duration of response of 2-3 months (12, 13).

There have been trials using IL-2 in lymphoma, below is the information from the trials.

In multiple Phase 1 or Phase 2 studies, aldesleukin has demonstrated preliminary effacicy and in generally tolerable as a combination with rituximab (375 mg/m^2 Q2W or QW for 4 infusions) in patients with NHL (14, 15, 16, 17, 18, 19). The response rate was approximately 10% (for rituximab-refractory) to 50%. Multiple CR cases were reported.

Phase 1/2 study of a modified non-alpha IL-2 (nemvaleukin alfa, ALKS 4230) in combination with pembrolizumab showed 1 PR from a PD1-naïve HL patient (20).

2.2.2 Current standard of care in B cell lymphoma

Standard of care in B cell lymphoma is provided in the individual substudy.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SAR444245 may be found in the Investigator's brochure (IB).

2.3.1 Risk assessment

Safety data from clinical studies conducted with SAR444245 in humans is currently limited to available data from the Phase 1/2 first-in-human study (TCD16843[HAMMER], hereafter referred to as HAMMER). Consequently, the assessment of the risks associated to SAR444245 is based on existing preclinical data and takes into consideration the known safety profile of the structurally similar product aldesleukin (Proleukin®) and current knowledge of the new-generation, investigational IL-2 analog NKTR-214 (bempegaldesleukin).

Table 8 summarizes potential risks for SAR444245 identified from preclinical experience and from the Phase 1/2 first-in-human (HAMMER) study.

2.3.1.1 Aldesleukin experience

There is currently one marketed IL-2 product, Proleukin (aldesleukin). It is an IL-2 therapeutic that is currently licensed in the US for the treatment of metastatic RCC and metastatic melanoma, and in several European countries for the treatment of metastatic RCC.

Aldesleukin is a human recombinant interleukin-2 which has been shown to possess the biological activities of human native IL-2 mediated through its binding with the high-affinity IL-2Rαβγ and intermediate-affinity IL-2Rβγ receptors. The widespread use of aldesleukin has been limited by its low response rate, a short t1/2 that requires dosing three times per day, and toxicities (21), which include life-threatening and sometimes fatal VLS. Vascular leak syndrome is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. It results in hypotension and reduced organ perfusion which, if severe, can result in death. It may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Aldesleukin has been associated with exacerbation of pre-existing or initial presentation of auto immune disease and inflammatory disorders. Exacerbation of Crohn's disease, scleroderma, thyroiditis, inflammatory arthritis, diabetes mellitus, oculo-bulbar myasthenia gravis, crescentic IgA glomerulonephritis, cholecystitis, cerebral vasculitis, Stevens-Johnson syndrome and bullous pemphigoid, have been reported following treatment with IL-2.

It was recognized early in clinical studies that eosinophilia appeared to mark the onset of VLS, with several reports of fast, dose-dependent elevation in eosinophils. Additional publications suggested a causal connection between the increase in peripheral IL-5 levels and identified ILC-2 as the source of this powerful chemoattractant and activator of eosinophils (22). Aldesleukin mediates activation of ILC-2s via interaction with the high affinity IL-2Rα chain that exists at low levels on ILC-2s.

Treatment with aldesleukin is associated with impaired neutrophil function (reduced chemotaxis) and the resulting increase in the risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy.

Proleukin toxicity threat mandates that it should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and cardiopulmonary or intensive care specialists must be available.

Proleukin has been shown to have embryo lethal effects in rats but there are no adequate well controlled studies in pregnant women; this information can be extrapolated to SAR444245. Also, since it is not known whether SAR444245 is excreted in human breast milk, nursing mothers cannot participate in this study.

High doses of aldesleukin (IL-2) were associated with decreased expression of enzymes of hepatic metabolism (22). As SAR444245 also exercises IL-2 activity, the Investigator should monitor clinical effects of narrow therapeutic index drugs that are hepatically metabolized.

2.3.1.2 SAR444245

2.3.1.2.1 Preclinical data

Among the potential risks, preclinical data for SAR444245 are lacking for infusion-related reactions (IRRs), immunogenicity (anti-drug antibodies), hypersensitivity, and immune-mediated adverse events. Those are, however, typical effects associated with the use of biologic drugs in oncology and should be considered for SAR444245.

Further, preclinical data for SAR444245 do not indicate the potential for nephrotoxicity, neurotoxicity, or pulmonary toxicity, which are known adverse effects for aldesleukin. However, mitigation strategies for nephrotoxicity and neurotoxicity are also proposed in the protocol.

Preclinical data for SAR444245 do not indicate higher risk for infections. However, infections are typically associated with the use of aldesleukin and are to be expected.

There are no preclinical data for tumor lysis syndrome (TLS) associated with the use of SAR444245, but it is known to occur when aldesleukin is combined with cisplatinum, vinblastine and dacarbazine (refer to Proleukin US label). The participants at greatest risk of TLS are those with high tumor burden prior to treatment, elevated uric acid level, poor hydration or tumor infiltration of the kidney, or receiving intensive cytoreductive therapy.

Cytokine release syndrome is a potentially life-threatening toxicity that has been described in the setting of immunotherapy with T cell engagement. It is characterized by a variety of symptoms including high fevers, hypotension, rigors, and malaise, and may progress to cytokine storm (uncontrolled immune hyperactivation involving myriad cytokines) with more severe and potentially life-threatening manifestations. As SAR444245 mediates immune activation, it may induce adverse events related to cytokine release (eg, fatigue, fever, chills, muscle pain, rash, nausea, symptoms of autoimmune disease). Furthermore, SAR444245-related increases of plasma

monocyte chemoattractant protein-1 (MCP-1), IL-2, and IL-1RA were observed in NHP, indicating that SAR444245 administration may be associated with CRS.

No manifestations of VLS have been reported in pre-clinical toxicity studies with SAR444245. Although there is a theoretical risk of VLS occurring in an immunotherapy setting, it has not been observed for IL-2 variants with 'non-alpha' profiles. Being a "non-alpha" IL-2, SAR444245 is not anticipated to cause VLS.

No data pertaining to pregnancy and lactation exposure and outcomes are available for SAR444245. Due to the missing information for this important risk, detailed mitigation measures will be introduced. Conditions for eligibility of women of reproductive potential and male subjects with female partners of childbearing potential are detailed in Section 5.1. Also, since it is not known whether SAR444245 is excreted in human breast milk, nursing mothers cannot participate in this study.

2.3.1.2.2 Clinical studies

A Phase 1/2 first-in-human study (HAMMER) is currently ongoing in adult patients with advanced or metastatic solid tumors. This is an open-label, multicenter, dose escalation and expansion study of SAR444245 IV as a single agent and in combination with the checkpoint inhibitor pembrolizumab or cetuximab.

Available safety information from this study has informed the selection of the dose (see details in Section 4.3).

For the most up-to-date safety information from this study please refer to SAR444245 IB.

2.3.1.3 NKTR-214 (bempegaldesleukin) clinical data

Useful insight can also be obtained from NKTR-214 (bempegaldesleukin), another new generation IL-2 derivative, with activity biased towards the IL-2Rβγ receptor.

In the first-in-human Phase 1 study, NKTR-214 was administered as an outpatient regimen and was well tolerated. Twenty-eight patients with advanced or locally advanced solid tumor malignancies were enrolled in the study. Grade 3 treatment-related adverse events (TRAEs) were reported by 21.4% of patients; there were no Grade 4 TRAEs or any treatment related deaths. The most common TRAEs included fatigue (71%), flu-like symptoms (68%), pruritus (64%), hypotension (57%), rash (50%), decreased appetite (46%), arthralgia and cough (each 32%). The majority of these events coincided with the peak plasma concentrations of the active cytokine and resolved spontaneously or were mitigated by nonprescription oral or topical treatments. There was one reported immune-related adverse event (irAE) of hypothyroidism associated with NKTR-214, which was treated with replacement therapy. All Grade 3 hypotension events (18%) were rapidly reversed with IV fluid administration and did not require treatment discontinuation. NKTR 214 related hypotension was predictable, manageable, and reversible and the incidence of Grade 3 hypotension was reduced once hypotension risk mitigation strategies were implemented. The maximum tolerated dose (MTD) was determined to be 0.009 mg/kg Q3W. This new generation,

IL-2Rβγ-biased IL2 could be safely administered as outpatient basis, and there was no report of capillary leak syndrome (CLS) or VLS (23).

In PIVOT-02, a single-arm, Phase 1/2 study, NKTR-214 plus nivolumab was administered to 38 patients with selected immunotherapy-naïve advanced solid tumors (melanoma, RCC, and NSCLC). Several treatment regimens were explored. The dose of 0.009 mg/kg had excessive toxicity (2 of 3 patients with DLT: Grade 3 hypotension [n=1] & Grade 4 hyperglycemia + metabolic acidosis [n=1]) when combined with 360 mg of nivolumab. All 38 patients had TEAEs that were considered related to the study combination. The MTD of the combination was defined as NKTR 214 0.006 mg/kg + nivolumab 360 mg Q3W and this dose was selected as the recommended Phase 2 dose (RP2D). The most common TRAEs (≥30%) at the RP2D were flu-like symptoms (80%), rash (80%), fatigue (76%), pruritis (48%), arthralgia (44%), headache and diarrhea (40%), nausea (40%), decreased appetite (36%) and peripheral edema (36%), myalgia (32%), and nasal congestion (32%). Grade ≥3 TRAEs occurred in 16% of patients at the RP2D (hyperglycemia, lipase increase, rash, cerebrovascular accident, hyponatremia, infectious pleural effusion, syncope). Immune-mediated AEs were observed in 31.6% overall: hypothyroidism (11), hyperthyroidism (2), hyperglycemia (2). Cytokine-related symptoms were observed primarily in Cycles 1 & 2 and significantly reduced thereafter. There were no treatment related deaths and generally, Grade ≥3 TRAEs were manageable using standard guidelines. Tumor responses were observed regardless of baseline PD-L1 status and baseline levels of tumor-infiltrating lymphocytes, suggesting therapeutic potential for patients with poor prognostic risk factors for response to PD-1/PD-L1 blockade. These data demonstrated that NKTR-214 can be safely combined with a checkpoint inhibitor as dual immunotherapy for the treatment of a range of advanced solid tumors (24).

2.3.2 Benefit assessment

The ability of IL-2 to expand T cells with maintenance of functional activity has been translated into the first reproducible effective human cancer immunotherapies. The first-generation IL-2 (aldesleukin) was the first immunotherapy effective for human cancer. Aldesleukin is approved in metastatic RCC and metastatic melanoma and its use has resulted in durable, complete responses in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, clinical benefit of aldesleukin requires high dose as the enhancement of the CD8+ T-cell population is mediated through the intermediate-affinity by IL-2Rβγ, the suppressor CD4+ Treg cells are preferentially enhanced at lower dose through the high-affinity IL-2Rαβγ which is probably responsible for the limited proportion of responding patients (ORR 16% in metastatic melanoma patients - US Label), and at the price of significant toxicities.

SAR444245, as a “non-alpha” new generation IL-2 is expected to result in greater anti-tumor activity than aldesleukin that has already demonstrated clinical benefit.

2.3.3 Overall benefit: risk conclusion

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the IL-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. These design features are anticipated to minimize safety liability

associated with Proleukin® by avoiding expansion of immunosuppressive immune cell populations (regulatory T cells) and off-target complications such as VLS, while still promoting expansion of immune populations that can support anti-tumor immune responses.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with this new generation IL-2 SAR444245 with or without other anticancer therapies are justified by the anticipated benefits that may be afforded to participants with relapsed or refractory B cell lymphoma.

2.3.4 Benefits and risks assessment in the context of COVID-19 pandemic

2.3.4.1 Risks in the context of COVID-19

2.3.4.1.1 Risks related to the patient population

Patients potentially eligible for this study have relapsed or refractory B cell lymphoma. In general, patients with hematologic malignancies are at increased risk for bacterial, fungal, or viral infection, however data on the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Corona Virus Disease 2019 [COVID-19]) in patients with lymphoma are limited. The first cohort study of the incidence of COVID-19 in patients with hematologic malignancies, hospitalized in Wuhan, China during the COVID-19 pandemic, indicate that the case rate was not significantly higher than for that of health care providers in Wuhan (10% vs 7%, p=0.322), however the case fatality rates were significantly higher for patients with hematologic cancers than for health care providers (62% vs 32%, p=0.002) (25). A recent study indicates that reduced therapy intensity during the COVID-19 pandemic is associated with increased anxiety levels and impaired health-related quality of life for patients with lymphoma (26). Furthermore, guidelines have been developed to limit the spread of SARS-CoV-2 infection to lymphoma patients, even while these patients continue to receive treatment and participate in clinical trials, given the potentially serious consequences that may result from delaying treatment and the high degree of unmet need for effective therapies for patients with relapsed or refractory disease (27, 28, 29). To that end, trial participation will proceed during the COVID-19 pandemic, however measures will be taken to mitigate the potential risk of SARS-CoV-2 infection to trial participants.

Testing for SARS-CoV-2 infection during the screening phase should be at Investigator's discretion and should also follow local/international guidelines (eg, asymptomatic but high risk of infection patients, patients with symptoms that could be associated with SARS-CoV-2 infection). To be eligible for trial participation, participants with a history of SARS-CoV-2 infection must have completed clinical recovery from SARS-CoV-2 infection at least 1 month prior to enrollment and no longer have a positive polymerase chain reaction (PCR) test for SARS-CoV-2 at the time of enrollment (E 17).

During the study, if a participant is diagnosed with SARS-CoV-2 infection, dose modification of study intervention should be based on the recommendations provided in Section 6.5. In addition, all Investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as:

- American society of clinical oncology (ASCO) (30).
- European Society for Medical Oncology (ESMO) (31).

2.3.4.1.2 Risks related to study treatment

SAR444245 has the potential to induce CRS which could exacerbate the manifestations of COVID-19 infection. It is, however, worth noting that pegylated IL-2 bempegaldesleukin is currently being evaluated for the treatment of patients with mild COVID-19 in a Phase 1b study (NCT04646044).

2.3.4.1.3 Risks related to study related activity

It is important to minimize the risk of exposure of patients to COVID-19. In addition to the contingency measures described in Section 10.9, the following prevention and mitigation plans could be implemented at clinical sites:

- All participating sites should have implemented measures according to regional/local Health Authorities, European Medicines Agency (EMA), ESMO, ASCO guidelines including but not limited to restrictions of access to the hospitals for visitors, physical distancing and personal protective equipment (PPE).
- Study participants should be treated in a dedicated area that is separated from patients with COVID-19 infection.

2.3.4.1.4 Conclusion on the benefit-risk assessment pertaining to COVID-19

Overall, the benefit-risk ratio is deemed acceptable in patients with relapsed or refractory B cell lymphoma during COVID-19 pandemic. The Sponsor will continue to evaluate the benefit-risk ratio during the study period.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 with or without other anticancer therapies.	• Refer to individual substudy.
Secondary	
• To confirm the dose and to assess the safety profile of SAR444245 when combined with or without other anticancer therapies.	• Incidence of treatment emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus gradings (1).
• To assess other indicators of antitumor activity.	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first documented evidence of PR or CR determined by Investigator per Lugano response criteria 2014 (2). • Duration of response (DoR) defined as the time from first documented evidence of PR or CR until progressive disease (PD) determined by Investigator per Lugano response criteria 2014 (2), or death from any cause, whichever occurs first. • Clinical benefit rate (CBR) including CR or PR at any time or stable disease (SD) of at least 6 months (determined by Investigator per Lugano response criteria 2014) (2). • Progression free survival (PFS) defined as the time from the date of first IMP administration to the date of the first documented disease progression determined by Investigator per Lugano response criteria 2014 (2) or death due to any cause, whichever occurs first.
• To assess the plasma concentrations of SAR444245 when given with or without other anticancer therapies.	• Plasma concentrations of SAR444245.
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245.
Exploratory	
[redacted]	

[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in an oncology study setting.

In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 with or without other anticancer therapies in adults and adolescents with relapsed or refractory B cell lymphoma.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 with or without other anticancer therapies by identifying early signals. This design is with the flexibility to open new treatment cohorts as new treatment become available and close existing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity.

The information that is introductory and common to all cohorts is included in the present document ("Master Protocol"), and cohort-specific elements are included in separate substudies. This study is designed with the flexibility to open new treatment arms or add new indications as permitted by scientific rationale.

A graphical presentation of the study schema is shown in Figure 1.

A safety run-in will confirm the dose of SAR444245 in each substudy. Participants who fulfill the eligibility criteria of any cohort may be enrolled to the safety run-in of that cohort. After a maximum of 10 participants have been enrolled into a specific cohort, enrollment will be paused for that cohort.

Once a total of at least 6 participants are evaluable for DLT in a specific cohort, safety data for these participants will be reviewed by the Study Board. DLT-evaluable participants include all treated participants in the safety run-in part who have been observed for the DLT observation period (defined in the individual substudy). Any participant who experienced a DLT at any time during the DLT observation period will also be DLT-evaluable.

If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from SB. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants for that specific cohort (for example, if 10 Cohort A participants are enrolled in the safety run-in, and treated at the confirmed safe dose, approximately 15 additional participants will be enrolled into Cohort A to have the total number of 25 participants).

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an IV infusion over 30 minutes during each cycle (see Section 1.1 Study interventions for details). Overall safety monitoring will be performed throughout the study. If recommended by the Study Board, SAR444245 dose may be reduced to [redacted] µg/kg or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

The Modified Toxicity Probability Interval 2 (mTPI2) design will be used in the safety run-in part. The mTPI2 design is a Bayesian interval design that can be implemented in a simple fashion as the traditional 3+3 design, but it is more flexible and possesses superior operating characteristics. The target toxicity rate for the MTD is 0.3, with the acceptable toxicity probability interval of (0.25,0.35). The dose decision (stay at 24 µg/kg dose or reduce the dose) will be made by the Study Board and will be guided by the decision rules from the mTPI2 design. The mTPI2 decision rules are based on calculating the unit probability mass (UPM) of intervals as following: (0, 0.05), (0.05, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45) …… (0.85, 0.95), (0.95, 1). In mTPI2 method, intervals that are lower than 0.25 indicate dose escalation, equivalence interval (0.25,0.35) indicates staying at the current dose level, and intervals that are higher than 0.35 indicate dose de-escalation. The interval with the largest UPM is the winning interval and implies the corresponding dose escalation/de-escalation decision. For the safety run-in part of the study, mTPI2 rules (see Table 2) will be applied as follows, unless decided otherwise by the Study Board:

- If the dose recommendation from mTPI2 is “E” (Escalate to the next higher dose) or “S” (Stay at the same dose), all cohorts treated at the current regimen will continue with the SAR444245 24 µg/kg dose
- If the dose recommendation from mTPI2 is to de-escalate to a lower dose (either “D” [De-escalate to the previous lower dose] or “DU” [De-escalate to the previous lower dose and the current dose will never be used again in the trial]), a dose lower than 24 µg/kg will be tested and assessed with the same methodology.

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

Number of dose limiting toxicities	Number of DLT-evaluable participants									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E
2		DU	D	D	D	S	S	S	E	E
3			DU	DU	D	D	D	D	S	S
4				DU	DU	DU	D	D	D	D
5					DU	DU	DU	DU	DU	D
6						DU	DU	DU	DU	DU
7							DU	DU	DU	DU
8								DU	DU	DU
9									DU	DU
10										DU

E: Escalate to the next higher dose, S: Stay at the current dose, D: De-escalate to the previous lower dose, DU: De-escalate to the previous lower dose and the current dose will never be used again because of unacceptable high toxicity.
Note: a total of at least 6 participants are evaluable for DLT in a specific cohort, safety data for these participants will be reviewed by the Study Board to determine if the dose needs to be reduced.

Dose limiting toxicity: Selected events occurring during the DLT observation period (defined in the individual substudy) are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245. Please refer to the full list of events as below. Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the Study Board will determine if the dose of SAR444245 needs to be reduced to [redacted]µg/kg or another lower dose level, in agreement with the Sponsor.

Hematologic abnormalities:

- Grade 4 neutropenic fever (temperature ≥38.5°C on more than 1 occasion).
- Grade 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention.

Non-hematologic abnormalities:

- Grade 3 or above alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with a bilirubin > 2 × upper limit of normal (ULN) with no evidence of cholestasis or another cause, such as viral infection or other drugs.
- Grade 3 or above vascular leak syndrome (VLS)
- Grade 3 or above hypotension

- Grade 3 or above cytokine release syndrome
- Grade 3 or above AE that does not resolve to grade ≤ 2 within 7 days of starting accepted standard of care medical management.
- The following non-hematologic AEs are exceptions that are not considered DLTs:
  - Grade 3 or 4 laboratory abnormalities that are not clinically significant per recruiting Investigator and Sponsor will not be considered a DLT.

Study Board

The study Investigators (or designee) participating in the safety run-in of applicable cohorts and the Sponsor clinical team members will constitute the Study Board (SB). The SB will review clinical data on a regular basis. In order to decide dose confirmation or dose reduction on the basis of their knowledge of the safety data. Minutes of each meeting will be written by the Sponsor and distributed to all sites participating in the safety run-in. Decisions regarding final dose selection will be made during one of the SB meetings and documented in the meeting minutes.

After safety run-in dose confirmation, occurrence of any treatment related G3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants per regimen will trigger an ad hoc Data Monitoring Committee (DMC) to rapidly convene to assess safety or need to pause enrollment to allow for a safety review. The SB (during safety run-in), independent DMC (during core phase and expansion) and Sponsor can decide to stop any cohort in the event excessive toxicity (for example but not limited to excessive irAE or excessive number of G4/5 events) is observed.

Special considerations pertaining to methodology

Interactive Response Technology will be used to control recruitment, assignment per site and facilitate the handling, management, and accountability of drug supply.

The duration of the study for a participant will include:

- **Screening period**: Up to 28 days.
- **Treatment Period**: Enrolled participants will receive continuous treatment until PD, unacceptable adverse event (AE), or other full permanent discontinuation criteria as described in Section 7, or completion of the maximum cycles allowed in the substudies. However, treatment beyond PD may be allowed for up to 9 weeks if the participant appears to be benefiting clinically after discussion with the Sponsor.
- **End of Treatment and Follow-up**: End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **End of Treatment (EOT)**:
  1. Participants who discontinue study treatment **without PD** or who **complete** the maximum cycles allowed in the substudies **without PD** (per Lugano response criteria 2014[2]), will be followed every 3 months ±7 days from last IMP administration, for

safety (as per Schedule of Activities [SoA] in the individual substudy) and tumor imaging assessments, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.

2. Participants who discontinue study treatment **with PD** (per Lugano response criteria 2014[2]) will be followed for safety in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the study. Survival Phone Call Follow up will continue until death, participant request to discontinue from follow-up, or cut-off date for final analysis has been reached, or upon cancellation of Survival follow-up at the discretion of the Sponsor at any prior timepoint.

After the cohort cut-off date for the primary analysis, participants can continue to receive IMP, if clinical benefit is observed, until full permanent discontinuation criteria described in Section 7 are met and will continue to undergo all assessments as per the study schedule of activities in the individual substudy.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of the primary objective) will be 3 years from cohort last participant in (LPI).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with other anticancer therapies, or as monotherapy, in trial participants with relapsed or refractory B cell lymphoma.

The design of the study is a non-randomized study where the experimental combination or monotherapy will be assessed in a single cohort for each indication, using historical data for single agent as a benchmark to show outstanding objective response rate. The primary endpoint will be assessed using Lugano response criteria 2014 for participants with relapsed or refractory B cell lymphoma. It will be assessed per Investigator. Central imaging reading may be done retrospectively if significant activity is observed.

A safety run-in on the first 6-10 participants being enrolled in the individual substudy has been embedded in the study to confirm the absence of safety issues before launching enrollment of the remaining participants in a specific cohort.

4.2.1 Participant input into design

Teenagers with a history of lymphoma and their parents participated in an advisory panel, reviewed the study design, and provided input.

4.3 JUSTIFICATION FOR DOSE

Dose escalation for SAR444245 monotherapy and in combination with pembrolizumab or cetuximab is ongoing in the first-in-human HAMMER study. Data from a total of 68 patients who have received SAR444245 Q2W or Q3W in monotherapy, in a Q3W regimen in combination with pembrolizumab 200 mg Q3W, or with cetuximab 400/250 mg/m² QW is available as of 18 June 2021. HAMMER Safety Review Committee have cleared SAR444245 24 µg/kg Q3W pembrolizumab combination dose level based on this data cut-off.

The dose levels tested to date for SAR444245 monotherapy administered using a Q3W schedule are 8 µg/kg (n=4), 16 µg/kg (n=6), 24 µg/kg (n=11), 32 µg/kg (n=6) and 40 µg/kg (n=2).

In combination with pembrolizumab, SAR444245 has been administered Q3W at the doses of 8 µg/kg (n=4), 16 µg/kg (n=9), 24 µg/kg (n=6), 32 µg/kg (n=1). In combination with cetuximab, SAR444245 has been administered Q3W at 16 µg/kg (n=5) or 24 µg/kg (n=5).

For monotherapy cohort, the only DLT observed to date is a Grade 3 infusion reaction (occurred on C2D1 which resolved on the same day with supportive care) reported in a patient on 32 µg/kg Q3W monotherapy.

For SAR444245 in combination with pembrolizumab 200 mg Q3W, 1 DLT (Grade 3 liver enzyme elevation with Grade 2 bilirubin elevation meeting drug-induced liver injury [DILI] criteria occurred on C1D1 which resolved after 7 days with steroids) was observed in a participant with SAR444245 24 µg/kg Q3W with pembrolizumab.

No DLTs were reported by SAR444245 cetuximab combination cohort (SAR444245 24 µg/kg Q3W).

Grade 3/4 TEAEs commonly reported by participants who received SAR444245 24 µg/kg monotherapy (n=11) include in particular Grade 4 lymphocyte count decreased/lymphopenia (7 participants, 63.6%) and Grade 3 anemia (3 participants, 27.3%) and Grade 3 dyspnea (2 participants, 18.2%). Of note, transient lymphocyte count decrease in the peripheral blood is an expected effect, consequence of T cell activation and temporary compartmental redistribution after IL-2 treatment. Nevertheless, this phenomenon is reported as an adverse event (AE) in HAMMER study.

Grade 3/4 TEAEs reported by participants who received SAR444245 24 µg/kg in combination with pembrolizumab (n=6) include Grade 4 lymphocyte count decreased (3 participants, 50.0%), Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) & gamma-glutamyl transferase (GGT) increased (2 participants each for AST & ALT increased, 33.3%; 1 participant for GGT increased, 16.7%), Grade 3 blood phosphorus decreased & hypophosphatemia (1 participant each, 16.7%) and Grade 3 dyspnea (1 participant, 16.7%).

Grade 3/4 TEAEs reported by participants who received SAR444245 24 µg/kg in combination with cetuximab (n=5) include Grade 3 chills (1 participant, 20.0%) and Grade 3 abdominal pain and vomiting (1 participant for each, 20.0%).

Only 1 high grade CRS with Grade 3 hypertension, Grade 2 fever, and Grade 2/3 neurological symptoms (with 24 µg/kg Q3W, 2.6%) is reported among participants who received SAR444245

monotherapy (n=38). From participants who received SAR444245 pembrolizumab combination (n=20), Grade 3 CRS (with 16 µg/kg Q3W) is observed in 1 participant (5.0%) with Grade 3 hypotension and Grade 2 fever.

According to literature, prophylactic hydration on the dosing days could mitigate incidence and severity of hypotension as part of CRS. As HAMMER study was not mandating prophylactic hydration before January 2021, the participants who experienced CRS in HAMMER study did not receive peri-infusion hydration. Based on this learning, hydration and CRS management guidelines have been included in the Phase 2 study protocols.

With respect to PK, SAR444245 exposure increased in an approximately dose-proportional manner in the monotherapy cohorts, and no impact of anti-drug antibody (ADA) on SAR444245 PK could be identified. Also, in the combination cohort, there was no apparent impact of pembrolizumab on the PK of SAR444245.

Differently from native IL-2 and aldesleukin, SAR444245 does not have high potency at the IL-2Rα/β/γ receptor subunit expressed on T regulatory (Treg) cells because the site-specific pegylation blocks IL-2Rα engagement and demonstrates high potency at the IL2Rβ/γ receptor subunit expressed on CD8+ T and natural killer cells (NK). Due to this re-programmed receptor bias, SAR444245 induces proliferation of peripheral CD8+ T and NK cells and less impact on immunosuppressive Treg cells. Therefore, we closely monitored the PD change of CD8+ T, NK and Treg cells in HAMMER study as supportive information for R2PD selection.

In the SAR444245 monotherapy dose levels (8 µg/kg, 16 µg/kg, 24 µg/kg, and 32 µg/kg Q3W), the PD data suggest that a trend for dose-dependent expansion of CD8+ T cells and NK cells has been achieved. In the 8 µg/kg dose levels, the average increase in peripheral blood CD8+ T cells over baseline at 72 hours post-dose was 1.75-fold. For dose levels 16 µg/kg and 24 µg/kg, the peripheral blood CD8+ T cell expansion was 2.47 and 4.47-fold at the day 8 post-dose peak of expansion. The day 8 sample timepoint was added after the first 3 participants in the 8 µg/kg cohort were dosed.

In addition, the average increase in peripheral blood NK cells was 4.22-fold at 72 hours for 8 µg/kg. The 16 µg/kg and 24 µg/kg dose levels resulted in 5.9 and 7.67-fold NK expansion, compared to baseline at the day 8 peak expansion. Among the dose levels tested to date for SAR444245 in combination with pembrolizumab administered using Q3W schedule, we have collected available PD data for the 8 µg/kg (n=4) and 16 µg/kg cohort (n=6), in which the average increase in CD8+ T cells, compared to baseline, is 2.06-fold and 3.71-fold, respectively; and the average increase in NK cells, compared to baseline, is 6.73-fold and 13.43-fold, respectively at the peak expansion day 8. In addition, the comparison of T and NK cell expansion between [redacted] µg/kg and [redacted]µg/kg cohorts indicated that the anticipated maximum CD8+ T and NK cells expansion PD effect may have been achieved at [redacted] µg/kg cohort. Based on these data, additional quantitative systems pharmacology (QSP) and popPK/PD models were developed and indicated that the increase of CD8+ T and NK cells was less than proportional with increasing dose, suggesting a flattening of the dose-response curve.

In addition, preclinical studies using human whole blood to assess the induction of cytokines showed no change in cytokine profiles when administering SAR444245 with and without

pembrolizumab. This study used SAR444245 concentration ranges that went significantly higher than current clinical dosages (0.2-4.5 µg/mL) and showed that SAR444245-induced cytokine release in human whole blood was not affected in the presence of pembrolizumab at Q3W schedule.

Considering below, Sponsor proposes to evaluate the clinical benefit of SAR444245 24 µg/kg in this Phase 2 study.

1. SAR444245 monotherapy up to 32 µg/kg Q3W, pembrolizumab combination up to 24 µg/kg Q3W and cetuximab combination 16 µg/kg Q3W are all cleared in HAMMER study.
2. Sustained relevant PD effect in blood, higher at higher dose, was documented in participants; and
3. Overlapping toxicities not expected for SAR444245 in combination with pembrolizumab or cetuximab, as suggested by safety data observed.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities in individual substudies for the last participant in the trial globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

The inclusion criteria listed in the master protocol are only those applicable to all the participants common to all substudies. For additional substudy specific criteria, refer to the particular substudy.

Participants are eligible to be included in the study only if all of the following criteria apply for a given cohort:

Age

I 01. Participant must be ≥12 years of age, at the time of signing the informed consent.

See requirement specific to France in Appendix 7 (Section 10.7).

Type of participant and disease characteristics

I 02. Provision of tumor tissue:

- Disease location amenable to mandatory tumor biopsy (optional for participants ≥ 12 and <18 years of age) at baseline unless clinically unfeasible (minimum 10 slides with 4-5 micron thickness for the participants who have signed ICF [excluding screen failure participants]) and possibly at Cycle 2 Day 1. Fine needle aspirates are not acceptable. Availability of a tissue specimen from core needle or excisional biopsies, or resected tissue are required. Provision of archival tumor tissue sample obtained within 6 months (there should be no systemic anti-cancer therapy between collection of biopsy and enrollment) is allowed to replace mandatory baseline biopsy.

  Note: Clinically unfeasible biopsy should be documented by a written communication from the Investigator to the Sponsor that performing a biopsy will put the wellbeing of the subject at an excessive risk.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - Location of the tumor not amenable to biopsy due to significant risk, OR
  - Less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening.

I 03. Measurable disease:

The participant must have relapsed or refractory disease. Measurable disease defined as at least one measurable node that must have an LDi (longest diameter) >1.5 cm and/or measurable extranodal lesion that must have a LDi >1 cm according to Lugano response criteria 2014. Tumor sites that are considered measurable must not have received prior radiotherapy, unless among them at least one is FDG-avid.

Weight (not applicable)

Sex, contraceptive/barrier method and pregnancy testing requirements

I 04. All (male and female)

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 3 days [corresponding to time needed to eliminate SAR444245] after the last dose of SAR444245:

- Refrain from donating or cryopreserving sperm.

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below
- A male condom when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant, or during homosexual intercourse. The participant should also be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Appendix 4 Contraceptive and barrier requirements [Section 10.4]) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP).

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 (Section 10.4) during the intervention period (to be effective before starting the

intervention) and for at least 120 days (or refer to the individual substudy protocol) [corresponding to the time needed to eliminate any study intervention(s)] after the last dose of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.

- A WOCBP must have a negative highly sensitive pregnancy test (as required by local regulations) within 72 hours before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4 (Section 10.4).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 05. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. For participant below legal age to provide ICF, a specific ICF must be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply. For additional individual substudy specific criteria, refer to the particular substudy.

Medical conditions

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2 (≥ 16 years old). Lansky Scale (< 16 years old) ≤ 60%.

E 02. Lymphomatous involvement of the central nervous system.

E 03. Predicted life expectancy ≤3 months.

E 04. History of solid organ transplant.

E 05. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents and anti-cytotoxic T lymphocyte associated protein 4 monoclonal antibodies) that caused permanent discontinuation of the agent, or that were Grade 4 in severity.

E 06. Prior IV or subcutaneous anticancer therapy, investigational agent, major surgery within 21 days prior to initiation of IMP; oral anticancer therapy within 5 half-lives or completed palliative radiotherapy within 21 days prior to initiation of IMP.

E 07. Uncontrolled pleural/peritoneal effusion, pericardial effusion or ascites requiring recurrent drainage procedures (once monthly or more frequently).

E 08. Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of IMP initiation. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder. Participants who require a brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents or as premedication for erythrocyte or platelet transfusions) are not excluded.

E 09. Antibiotic use (excluding topical antibiotics) ≤14 days prior to the first dose of IMP, or any serious systemic fungal, bacterial, viral (excluding viral infection settings as described in E 16), or other infection that is not controlled. Participants who require prophylactic antibiotics because of chronic immunodeficiency will be allowed.

E 10. Severe or unstable cardiac condition within 6 months prior to starting study treatment, such as congestive heart failure (New York Heart Association Class III or IV), cardiac bypass surgery or coronary artery stent placement, angioplasty, left ventricular ejection fraction (LVEF) below 50%, unstable angina, medically uncontrolled hypertension (eg, ≥160 mmHg systolic or ≥100 mmHg diastolic), uncontrolled cardiac arrhythmia requiring medication (≥Grade 2, according to NCI-CTCAE v5.0), or myocardial infarction.

E 11. Ongoing AEs caused by any prior anticancer therapy ≥Grade 2 (NCI-CTCAE Version 5.0). Participants with Grade 2 peripheral neuropathy, or Grade 2 alopecia are permitted. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

Note: please refer to the individual substudy protocol for cohort specific requirement.

E 12. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). The following are not exclusionary: vitiligo, childhood asthma that has resolved, psoriasis that does not require systemic treatment.

E 13. History of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.

E 14. History of thoracic radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

E 15. Receipt of a live or live attenuated virus vaccine within 28 days of planned treatment start. Seasonal flu vaccines or SARS-CoV-2 vaccines that do not contain live virus are permitted.

E 16. Human immunodeficiency virus (HIV)-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease or known uncontrolled infection with HIV. HIV-infected participants must be on anti-retroviral therapy (ART) and have a well-controlled HIV infection/disease defined as:

- Participants on ART must have a CD4+ T-cell count >350 cells/mm^3 at time of screening.
- Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening.
- Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1).
- Combination ART regimen must not contain any antiretroviral medications other than: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenofovir.

HIV serology will be tested at screening for participants in France (see details and specific instructions in Section 10.2 and Section 10.7).

E 17. Known uncontrolled hepatitis B infection, known untreated current hepatitis C infection, active tuberculosis, SARS-CoV-2 infection, or severe infection requiring parenteral antibiotic treatment.

- To control HBV infection, participants with positive HBsAg should have started anti-HBV therapy before initiation of IMP. Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.
- Participants who are positive for anti-hepatitis B core antibody HBc, negative for hepatitis B surface antigen (HBsAg), and negative or positive for anti-hepatitis B surface antibody (HBs), and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.
- Participants with past or ongoing hepatitis C virus (HCV) infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention. Participants with positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.
- Participants with a history of SARS-CoV-2 infection must have completed clinical recovery at least 1 month prior to enrollment and no longer have a positive PCR test for SARS-CoV-2 at the time of enrollment.

E 18. Known second malignancy either progressing or requiring active treatment within the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the

skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

E 19. Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and *E. coli*-derived protein.

E 20. Participants with baseline oxygen saturation (SpO_2) ≤92% (without oxygen therapy).

Prior/concomitant therapy

E 21. Has received prior IL2-based anticancer treatment.

E 22. Is unable or unwilling to take premedication.

E 23. Deleted by protocol amendment 01.

E 24. Deleted by protocol amendment 01.

Prior/concurrent clinical study experience

E 25. Current enrollment or past participation in a study of an investigational treatment or has used an investigational device within 28 days prior to the first dose of study treatment.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational treatment.

Organ and bone marrow function

E 26. Absolute neutrophil count <1000/uL (1×10^9/L) (after at least one week off G-CSF).

E 27. Platelets <50 × 10^3 /uL (after at least 3 days without platelet transfusion).

E 28. Hemoglobin <9 g/dL or <5.6 mmol/L (after at least 1 week without packed red blood cell [pRBC] transfusion. Participants can be on stable dose of erythropoietin (≥ approximately 3 months)).

E 29. Total bilirubin >1.5 × upper limit of normal (ULN) unless direct bilirubin ≤ ULN (participants with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled).

E 30. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2.5 × ULN (or >5 × ULN for participants with lymphoma involving the liver).

E 31. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD] Formula, see Section 10.2 Appendix 2).

E 32. International Normalized Ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT]) >1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

Other exclusions

E 33. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 34. Any country-related specific regulation that would prevent the participant from entering the study - see Section 10.7 Appendix 7 (country-specific requirements).

E 35. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 36. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).

E 37. Any specific situation during study implementation/course that may raise ethics considerations.

E 38. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No food or drink restrictions are required. Guidelines on fluid intake are presented in Section 6.1.3.

5.3.2 Caffeine, alcohol, and tobacco

No restrictions are required.

5.3.3 Activity

Participants are advised to abstain from strenuous exercise and avoid long hot showers and saunas on Days 1 to 4 of every treatment cycle.

5.3.4 Hydration

Since SAR444245 may induce episodes of hypotension, participants should be informed of the importance of being well hydrated and provided hydration instructions. Guidelines pertaining to fluid intake on the day of SAR444245 dosing and for the 3 days after administration are detailed in Section 6.1.3.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) and for whom resolution of the screen failure reason may not be expected within a reasonable time frame, will be recorded as screen failures. In case the participant is a temporary screen failure (ie prolonged screening), there is no need to have participant (or the participant's legally authorized representative) re-consent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered to the additional pages.

A participant who screen failed may be rescreened; in this situation, the rescreened participant (or the participant's legally authorized representative) should sign a new ICF. A participant may be rescreened only once. Rescreened participants should be assigned a different participant number as for the initial screening.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 10.9.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants will receive study treatment until PD, unacceptable toxicity, other permanent discontinuation criteria as described in Section 7, or completion of the maximum cycles allowed in the substudies. However, treatment beyond PD may be allowed for up to 9 weeks if the participant appears to be benefiting clinically after discussion with the Sponsor.

6.1.1 Investigational medicinal product

Details of SAR444245 are shown in Table 3.

Preparation and administration of investigational medicinal product (IMP) are detailed in the pharmacy manual.

Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3.

Table 3 - Overview of IMP administered

Intervention name	**SAR444245**
Type	Biologic
Dose formulation	Concentrate for solution for infusion
Unit dose strength(s)	2.0 mg/mL
Dosage level(s)[a]	24 µg/kg (or reduced to ■ µg/kg or another lower dose level recommended by Study Board)
Route of administration	IV infusion
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Supplied in a single-dose vial in a treatment box. Each vial contains 2 mg/mL with an extractable volume of 1 mL. Each vial and treatment box will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	NA

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the e-CRF. Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted.

6.1.2 Non-investigational medicinal products

Non-investigational medicinal products (NIMP) include the premedication administered for SAR444245.

6.1.2.1 Premedication for SAR444245

All participants will receive the following premedication to prevent or reduce the acute effect of infusion-related reactions (IRR) or flu-like symptoms, 30 to 60 minutes prior to SAR444245 infusion (no longer than 60 minutes) for the first 4 cycles:

- Acetaminophen (paracetamol) 650 to 1000 mg (IV or PO) (or equivalent), and then optionally thereafter as needed.
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent eg, cetirizine, promethazine, dexchlorpheniramine, according to local approval and availability), and then optionally thereafter as needed.

SAR444245 premedication may be optional after 4 cycles:

- For a participant who has no IRR for the first 4 cycles, premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent infusions.
- If a participant develops an IRR Grade <2 during their first cycle only and then experiences no further IRRs during their next 3 cycles the Investigator may consider omitting premedication for Cycle 5. If no IRR is observed during Cycle 5 without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during Cycle 5 without premedication the participant experiences an IRR (any grade), premedication must be restarted for all subsequent cycles.

6.1.3 Hydration guidelines for SAR444245 administration

[redacted]

6.1.4 Readiness for treatment of severe cytokine release syndrome

Doses of tocilizumab or alternative therapies per site practice in CRS management should be available at site at all times in the event that a participant requires rapid intervention for the treatment of severe CRS. Please refer to the individual substudies for detailed guidelines for the management of CRS.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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 8.3.9).

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 the 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.

Treatment preparation and administration (including compatible materials) will be further detailed in the pharmacy manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Participants must be dosed at the site and will receive IMP directly from the Investigator or designee, under medical supervision. The person responsible for drug dispensing is required to maintain adequate records of the IMP administration. These records include the date the IMP components are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number and the treatment number on the vial must be recorded on the drug accountability form. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the e-CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 DOSE MODIFICATION

Refer to individual substudy for details.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

There will be no intervention beyond the end of the study.

6.7 TREATMENT OF OVERDOSE

There is no specific antidote for overdose with SAR444245.

If overdose occurs (see Section 8.3.8 for definitions), symptomatic management is indicated.

Treatment of overdose should consist of general supportive care with aggressive fluid management, if clinically indicated.

Procedures for treating symptoms and complications of immune-related adverse events (irAEs) are provided in the individual substudies.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 3 months).
3. Obtain a plasma sample for PK analysis right after the overdose event is identified (only if an overdose is identified within 5 days from start of overdose infusion).
4. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study intervention may be required. The Investigator is to discuss prohibited medication/vaccination with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy schedule requires the mutual agreement of the Investigator, the Sponsor, and the participant.

6.8.1 Acceptable concomitant medications

All treatments that the Investigator considers necessary for a participant’s welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (e-CRF) including all prescription, OTC, herbal supplements, and IV medications and fluids. If

changes occur during the trial period, documentation of route, and date will also be included on the e-CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed after discussion with and approval by the Sponsor.

All concomitant medications received within 28 days before the first dose of trial treatment through the Follow-up Visit should be recorded.

Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed (32).

6.8.2 Prohibited concomitant medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Period of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Investigational agents other than specified in this protocol.
- Radiotherapy for tumor control (please refer to Section 6.8.1 for allowed radiotherapy).
- Live or live attenuated virus vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live-virus vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, seasonal flu (seasonal flu vaccines that do not contain live virus are permitted), nasal H1N1 flu, rabies, Bacillus Calmette–Guérin (BCG), and typhoid.
- Systemic glucocorticoids and other immunosuppressive therapies such as anti-TNF, anti-IL6, etc, except for:
  - Use in premedication defined in the study protocol,
  - Treatment of immune-mediated AEs when indicated (irAE, CRS, ICANS, IRR, see details in the substudies),
  - Treatment of any life-threatening emergency,
  - Physiologic replacement as long as they are not being administered for immunosuppressive intent, and
  - A brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions caused by contact allergen).

Participants who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Participants may receive other medications that the Investigator deems to be medically necessary.

The exclusion criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the Observation and Survival Follow-up Period.

For withholding antihypertensive medications as part of hydration guidelines, please refer to Section 6.1.3.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Study intervention should be permanently discontinued in any of the following cases:

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative. "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 participant to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Unacceptable AE.
  - Documented disease progression
  -
  - Poor compliance to the study protocol.
  - Other, such as concurrent illness, that prevents further administration of study intervention, or that in the Investigator's opinion, in the best interest of the participant.
- In case of pregnancy occurrence.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for serial tumor assessment if permanent discontinuation is not due to PD, for safety assessment as per SoA in the individual substudy and until resolution or stabilization of AE, and any other assessment as per SoA. Data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed are reported in the SoA.

7.1.1.1 Unacceptable adverse events leading to permanent intervention discontinuation

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in the dose modification and toxicity management guidelines (see individual substudy protocols), or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Any potentially clinically significant abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation and repeated after 24 hours to document evolution before making a decision of permanent intervention discontinuation for the concerned participant.

Decision criteria for discontinuation following immune-mediated AEs are described in the individual substudy (Guidelines for the management of IRR, CRS, ICANS, VLS).

If participants are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, they will be maintained on treatment.

See the SoA in the individual substudy for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent intervention discontinuation

Participants 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, and after the permanent intervention discontinuation, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate. Tumor assessment should be repeated if not done at the last cycle.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.9). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.3 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met.

Recommendations for rechallenge in the context of an epidemic/pandemic (eg, COVID-19) are included in Appendix 9 Contingency Measures for a regional or national emergency (Section 10.9) that is declared by a governmental agency.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request (or at their legally authorized representative's request), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, or their legally authorized representative(s) no longer wish the participant to take it, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. 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.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant (or their legally authorized representative) may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be re-included in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (refer to individual substudy). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- During the screening period, demography, medical/surgical, and disease history will be evaluated. Demography includes age, gender, race, and ethnicity. Medical/surgical history includes relevant history of previous pathologies and smoking status. Disease history includes stage at diagnosis and at study entry, and previous anti-tumor therapy (type, duration, reason for discontinuation and response to the therapy). In addition, results of driver gene mutation are also to be collected.
- A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiography and troponin level.
- Regular blood samples will be collected from each participant throughout the duration of the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Details on blood sampling, including the estimated volume collected for each analysis are provided in the laboratory manual.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9.

8.1 EFFICACY ASSESSMENTS

The assessment of anti-tumor activity documented by objective response or complete response to the IMP is the primary endpoint for this study and is conducted as per schedule provided in the SoA (refer to individual substudy). All participants treated must have relapsed or refractory disease.

Decision to pursue treatment will be based on the response evaluation made by the Investigator, however, measures of lesions will be collected in the e-CRF for a determination of response by the Sponsor. Tumor assessment using Lugano response criteria 2014 may be done at the discretion of the Investigator when clinically indicated. Please refer to Section 7.1.1 for details.

Investigators will obtain copies of the images and will provide them to repository facility identified by the Sponsor for potential central review. Study sites must retain tumor assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

Assessment of tumor response will be conducted using Lugano response criteria 2014 (see Section 10.8) according to the nature of the measurable lesions, as described below.

8.1.1 Assessment of objective response using the most appropriate modality according to the nature of the measurable lesion(s)

For participants with disease that is measured radiologically according to Lugano response criteria 2014 (2) (Section 10.8), a PET-CT-based or CT-based criteria for tumor assessment will be performed as detailed in the individual substudy SOA.

Baseline imaging should include all known target lesions. Baseline and follow-up scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis and any other locations with suspicion or evidence of disease involvement. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium.

The initial tumor imaging FDG-PET CT and/or MRI will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP and if clinically indicated. FDG-PET must be performed for the 9-week and 18-week on-treatment assessments. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days) until progressive disease (PD). Brain CT/MRI will be performed if clinically indicated.

PET imaging is always required to confirm the first documented complete response (CR). If the first documented radiological CR is seen on CT scan only, a confirmatory PET scan (either FDG PET or PET-CT) should be obtained within 14 days to confirm that timepoint's response of CR. If the PET scan is not obtained within 14 days, the timepoint must be assessed as a PR, and the next scan should be done by one of the 3 methods above as soon as possible to confirm the CR. Once CR has been established by PET imaging, subsequent CR and/or PD may be followed by CT imaging only. The CT component of the PET-CT may be used in lieu of a standalone CT/MRI, only if the CT component is of similar diagnostic quality as a contrast enhanced CT performed without PET. If contrast enhanced PET-CT with diagnostic CT is not available, a standard FDG-PET must be performed, and a standalone diagnostic CT/MRI should be performed in addition to the FDG-PET scan. If independent CT and PET scanners are used, and the participant is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast so as to not compromise PET results. The PET-CT acquisition methodology (eg, administration of intravenous contrast) should remain consistent at all imaging visits for any given patient.

Bone marrow sample is mandated to confirm CR if bone marrow was involved by lymphoma or involvement is unknown prior to study treatment and as “clinically indicated” and “If bone marrow biopsy is not negative, a radiographic timepoint response (TPR) of CR at that time point would be downgraded to an overall PR”.

Progressive disease (PD) by CT scan, with complete metabolic response (CMR) or partial metabolic response (PMR) by PET, should be reported as PD. Although the results of PET/CT are generally prioritized over CT, CT evidence of progressive disease cannot be discounted in the overall response assessment. Additionally, the Lugano PET/CT criteria for CMR and PMR require absence of new lesions. CT may, for example, reveal progressive disease in non-measurable or non-FDG avid sites (eg, ascites, bony lesions, effusions, bowel lesions). Such cases should be reported as PD. Likewise, a CT finding of progressive disease, in the context of no metabolic response on PET, is to be considered overall disease progression, rather than stable disease.

The findings of clinical (non-radiographic) progressive disease (PD) per Investigator should be considered PD:

- Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.
- If skin lesions are identified as a result of a physical exam, these are to be documented via the Lugano classification 2014 assessment as a physical exam, skin lesion.

Skin lesions must be histologically confirmed for lymphoma involvement and photographed including a ruler (color photography using digital camera). Response assessment of skin lesions should be performed at baseline and at the time of each radiological assessment.

Table 4 - Imaging or disease assessment collection plan

Procedure	Screening	Post-administration assessment
Bone marrow biopsy	-	As clinically indicated during the treatment period, EOT, and Follow-visit 1[a]
Spleen measurement by PET-CT	Mandated	As clinically indicated during the treatment period, at EOT visit and Follow-up visit 1
CT/MRI (chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement)	Mandated	Every 9 weeks and if clinically indicated until Week 45, and every 12 weeks from Week 45 until progressive disease
Brain imaging	If clinically indicated	-
FDG-PET	Mandated	As clinically indicated during the treatment period, at EOT visit and Follow-up visit 1, and must be performed for the 9-week and 18-week on-treatment assessments.

a A reported response of CR by CT, or CMR by FDG-PET, must be confirmed by a bone marrow assessment performed within 14 days of the assessment.

Response assessment is detailed in Table 7.

8.2 SAFETY ASSESSMENTS

The main anticipated adverse effect for the monotherapy of SAR444245 or combination of SAR444245 with other anticancer therapies includes manifestations of cytokine release that can range from fever to hypoxia to hypotension, with or without manifestations that may include any of the organ systems. These mild events occur between around 12 to 18 hours after the first administration and a more intensive monitoring of vital signs is planned during that period. Targeted physical exams and standard laboratory tests will be conducted to monitor potential changes in the main body functions. Measurement of cytokines in plasma are planned at relevant timepoints. White blood cell differential count will be measured to monitor for transient lymphopenia which is commonly observed in the first few days following SAR444245 infusion. Eosinophilia that is surrogate to VLS will also be monitored. IL-5, which is also a marker of VLS, will be included in the PDy cytokine panel. Combining SAR444245 with other anticancer therapies may increase the frequency and severity of immune-related adverse events related to other anticancer therapies. Immune-mediated endocrinopathies involving the thyroid being the most frequent, T3, T4, TSH, and cortisol level will be monitored. When clinically indicated, on-treatment ECG, LVEF, and troponin will be assessed and compared to baseline. More details on the safety assessment are provided below. Planned time points for all safety assessments are provided in the individual substudy SoA.

8.2.1 Physical examinations

- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological, and skin systems. Height and weight will also be measured and recorded.
- A directed physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Investigators should also pay attention to clinical signs suggestive of VLS, such as peripheral edema, pericardial effusion, and pleural effusion, as well as clinical signs suggestive of immune-related adverse events, such as pneumonitis, colitis, endocrinopathies, to name a few. Complementary assessments should be performed to establish the diagnosis when clinically indicated. Early signs of cytokine release syndrome should also prompt a thorough clinical assessment to identify the involvement of a specific organ system, including neurological system.

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.

- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively:
  - **For the safety run-in participants** vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting.
  - **For other participants**, vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose. At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring (to be measured at Pre-dose, 0.5 [±0.25], 1 [±0.25], 2 [±0.5], 4 [±0.5], 8 [±0.5], 12 [±1], 16 [±1], 20 [±1], 24 [±1] hours after start of SAR444245 dose in an in-patient setting).

8.2.3 Electrocardiograms and LVEF

- Includes single 12-lead ECG, LVEF, and troponin that will be performed at screening and troponin at Cycle 4 Day 1, then, as clinically indicated.
- LVEF evaluation will be done by echocardiography or multigated acquisition (MUGA), and any repeated assessment should be done with the same technology used at screening.
- Additional evaluations such as unscheduled ECG, LVEF, Holter monitoring, cardiac enzymes (such as troponin) and consultation with a cardiologist should be done when clinically indicated.
- During treatment, or post treatment follow-up: Troponin will be performed at Cycle 4 Day 1. In case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, troponin elevation, etc.), Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (refer to individual substudy) for the timing and frequency.
- The clinical safety laboratory assessments will be done in the local laboratory.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within Follow-Up Visit 1 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the individual substudy SoA.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria 05 for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
- Women of childbearing potential must have a negative urine pregnancy test result within 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 120 days (or refer to the individual substudy protocol) after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of adverse event of special interest (AESI) is provided in Section 8.3.8

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, including adverse events of new onset, as well as worsening of baseline signs and symptoms will be collected throughout study period, from the signing of the informed consent form (ICF) until **30 days** following cessation of study treatment.

All SAEs and AESIs will be collected throughout the study period, from the signing of the informed consent form (ICF) until **3 months** following last administration of study treatment.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESIs (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Stabilization is defined as an AE ongoing without any change for at least 3 months. Participants with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or starting of a new antineoplastic therapy, whichever occurs first.

Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- Serious adverse events (SAEs) that are considered expected will be specified in the reference safety information (IB for SAR444245).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, should be expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 120 days (or refer to the individual substudy protocol) following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates another anticancer therapy
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants /pregnant female partner, 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 intervention.

8.3.6 Cardiovascular and death events

Cardiovascular events that meet AESI criteria should be reported as such (see Section 8.3.8 for details).

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or 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. The following events need to be reported as AESIs:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose of IMP is defined as: 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.
  - An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
- An elevated AST or ALT lab value that is greater than or equal to 3X the ULN and an elevated total bilirubin lab value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted

above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor.

- Other project-specific AESIs
  - IRR Grade ≥2
  - CRS Grade ≥2
  - ICANS of any grade
  - VLS of any grade
  - Any immune-related AE Grade ≥3
  - Arrhythmia Grade ≥3

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP/NIMP 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 like 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.

8.4 PHARMACOKINETICS

The sampling time-points for PK and ADA for/against SAR444245 and/or other IMPs may be updated during the course of the study based on the updated knowledge of drug behavior upon notification from the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded while for samples to be collected at time of biomarker sampling, no specific time on the given day is necessary.

Instructions on the collection, processing, storage, and shipment of samples will be provided in the laboratory manual. Sample analysis will be performed at a laboratory designated by the Sponsor.

Samples collected for analyses of SAR444245 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study and any remaining plasma/serum volume may also be used for further exploratory analysis if deemed relevant.

8.5 GENETICS AND/OR PHARMACOGENOMICS

[redacted]

[redacted]

8.6 BIOMARKERS

[redacted]

[redacted]

8.7 IMMUNOGENICITY ASSESSMENTS

The sampling time points for ADAs may be reduced or increased during the course of the study based on the updated knowledge of drug behavior and its immunogenicity, upon notification from the Sponsor.

Samples for the immunogenicity assessment of SAR444245 will be collected according to the PK flowcharts in the individual substudy. Instructions for the collection and handling of biological samples will be provided by the Sponsor. Sample analysis will be performed at a laboratory designated by the Sponsor.

Samples will be screened and then confirmed for anti-drug antibodies and the titer of confirmed positive samples will be reported. Additional analyses may be performed to further characterize the immunogenicity of SAR444245.

Anti-drug antibody (ADA) samples remaining after determination of immunogenicity may be kept for possible exploratory analysis of biomarkers. The exploratory data will not be included in the study report but will be kept on file.

8.8 HEALTH ECONOMICS

No health economics data will be collected.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

[redacted]

9 STATISTICAL CONSIDERATIONS

Please refer to the individual substudy protocols for additional statistical considerations.

9.1 STATISTICAL HYPOTHESES

All cohorts of the study are designed to obtain antitumor activity, safety, PK, pharmacodynamic (PDy), and immunogenicity data on SAR444245 administered either in monotherapy or in combination.

The study is designed to assess clinical benefit of SAR444245 with or without other anticancer therapies in adults and adolescents with relapsed or refractory B cell lymphoma. As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. No formal testing procedure is going to be considered.

9.2 SAMPLE SIZE DETERMINATION

The study will start with a safety run-in with 6-10 participants from each cohort. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants from their given cohort.

Sample size:

Number of participants to be enrolled in each cohort is described in the substudies.

9.3 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 5 - Populations for analyses

Population	Description
Exposed	Exposed population will include all participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or other anticancer therapies).
Efficacy	Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.
DLT-evaluable	DLT-evaluable population will include all participants in safety run-in part who have been treated and observed for DLT observation period (defined in the individual substudy). Any participants who have experienced a DLT during DLT observation period will also be DLT-evaluable.
Pharmacokinetic (PK)	The PK population will include all participants from the exposed population with at least 1 PK concentration available after the first dose of study intervention.
PDy	The PDy population will include all participants from the exposed population with at least 1 PDy (biomarker) parameter assessed after the first dose of study intervention.

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

This study is not intended to explicitly test a hypothesis, and 90% confidence interval (CI) will be provided for primary and secondary efficacy endpoints for descriptive purpose only.

All efficacy analyses will be performed on the efficacy population and analyzed by cohort. Objective response rate (ORR), CRR as well as all other efficacy variables will be derived using local radiologist's/Investigator's assessment for all cohorts according to Lugano response criteria 2014.

All safety analyses will be performed on the exposed population by cohort, by dose (if applicable) and overall (if applicable). A baseline value will be defined as the latest value or measurement taken up to the first administration of the IMP.

The analysis period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The **on-treatment period** (ie, treatment-emergent period) is defined as the time from the first administration of IMP up to 30 days after the last administration of IMP.
- The **post-treatment period** is defined as the time from the 31 days after the last administration of IMP.

9.4.2 Primary endpoint(s)

Refer to individual substudy for details.

9.4.3 Secondary endpoint(s)

The secondary endpoints include efficacy (TTR, DoR, CBR, PFS), safety, immunogenicity, and PK.

9.4.3.1 Time to Response (TTR)

The TTR will be assessed on the subgroup of participants who have achieved objective response. Time to Response will be defined as the time from the first administration of IMP to the first documented evidence of PR or CR determined by Investigator per Lugano response criteria 2014.

9.4.3.2 Duration of response (DoR)

The DoR will only be analyzed on the subgroup of participants who have achieved objective response. The DoR will be defined as the time from the date of first initial occurrence of the PR or CR to the date of first documentation of objective PD before the initiation of any post-treatment anticancer therapy or death due to any cause, whichever occurs first.

Duration of response will be summarized with descriptive statistics using Kaplan-Meier methods. The median DoR and associated 90% CI will be provided.

9.4.3.3 Clinical benefit rate (CBR)

The CBR is defined as the proportion of participants with clinical benefit (CR or PR as BOR, or SD lasting at least 6 months (ie, 26 weeks or later from first IMP intake, allowing for the ±7 days visit window for tumor assessment scheduled at 27 weeks) determined by Investigator per Lugano response criteria 2014.

9.4.3.4 Progression-free survival (PFS)

For all cohorts, progression -free survival is defined as the time from the date of first IMP to the date of the first documentation of objective progressive disease, or death due to any cause, whichever occurs first.

The analysis of PFS will be based on the following censoring rules:

- If progression or death is not observed before the cohort cut-off date for final analysis and prior to the initiation of a further anticancer therapy, then PFS will be censored at the date of the last valid tumor assessment performed before the cohort cut-off date for final analysis or date of initiation of a further anticancer therapy, whichever is earlier.
- A participant without event (death or disease progression) and without any valid post-baseline tumor assessment will be censored at the day of first IMP (Day 1).

Progression-free survival will be summarized using Kaplan-Meier methods. The median PFS times and associated 90% CI will be provided.

9.4.3.5 Adverse events

All AEs will be categorized according to NCI-CTCAE V5.0 and classified by SOC and Preferred Term (PT) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Immune cell-associated neurotoxicity syndrome and CRS events will be graded using ASTCT Consensus Grading and will be summarized separately.

- Pre-treatment AEs are defined as any AEs occurring during the pre-treatment period.
- Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator’s opinion), or become serious during the on-treatment period.
- Post-treatment AEs are defined as AEs that are reported during the post-treatment period.

For participants with multiple occurrences of the same PT, the maximum grade will be used.

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

Treatment-emergent adverse events:

An overall summary of TEAEs will be provided. The number and percentage of participants experiencing any of the following will be provided:

- TEAEs.
- TEAEs of Grade ≥3.
- Grade 5 TEAE (any TEAE with a fatal outcome during the treatment-emergent period).
- Serious TEAEs.
- Serious treatment-related TEAEs.
- TEAE leading to full intervention discontinuation.
- TEAE leading to partial intervention discontinuation (for each individual drug, if applicable).
- Treatment-related TEAEs.
- Treatment-related TEAEs of Grade ≥3.

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v 5.0 grade (all grades and Grade ≥3). Missing grades, if any, will be included in "all grades" category. Similar summaries will be prepared for TEAEs related to SAR444245 and those related to each individual drug (if applicable), TEAEs leading to partial intervention discontinuation (if applicable), TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

The following deaths summaries will be generated:

- Number and percentage of participants who died by study period (treatment-emergent period, post-treatment period) and reasons for death (disease progression, AE, or other reason).
- All TEAEs leading to death by primary SOC and PT showing number and percentage (%) of participants.

9.4.3.6 Clinical Laboratory evaluations

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v 5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided for the exposed population.

When the NCI-CTCAE v 5.0 grading scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

For laboratory variables graded by NCI-CTCAE:

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

9.4.3.7 Other Secondary endpoints

Immunogenicity analyses will be described in the SAP finalized before database lock. The PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

Plasma concentrations of SAR444245 will be summarized with descriptive statistics.

9.4.4 Tertiary/exploratory endpoint(s)

9.4.4.1 Biomarker endpoints

9.4.5 Other safety analysis

The summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs (raw data and changes from baseline) will be calculated for baseline, last on-treatment value and/or worst value.

9.4.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 .

9.5 INTERIM ANALYSES

No formal interim analyses are planned. However, at the end of the safety run-in of each cohort, the occurrence of DLTs and other safety data will be reviewed by the Study Board to decide about continuation of the dose of SAR444245 24 µg/kg or reduced to ■ µg/kg or another lower dose level.

For each cohort, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the study (eg, after half of the planned number of participants have undergone two post-baseline tumor assessment or have discontinued study treatment, whichever is earlier).

In addition, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the independent DMC. The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. DMC will review safety data periodically. An ad hoc DMC meeting may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other SAR444245 studies. Occurrence of any treatment related Grade 3 or higher AE (excluding lymphocyte count decrease) not resolving within 72 hours in >25% of participants will trigger an ad hoc DMC. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

The cohort cut-off for the primary endpoint analysis is in the individual substudy.

After the cohort cut-off date for the primary analysis, participants can continue to receive IMP, if clinical benefit is observed, until full permanent discontinuation criteria described in Section 7 are met and will continue to undergo all assessments as per the study schedule of activities in the individual substudy.

For each cohort, the cut-off date for the final analysis will be 3 years from cohort LPI.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9 (Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Data Monitoring Committee

Independent from the Sponsor and Investigators, the DMC role will be to monitor the safety of the participants enrolled in the study (ie, exposed to study treatment and/or to study procedures) and to provide the Sponsor with appropriate recommendations in due time to ensure the safety of the participants.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites for each completed substudy and final study results. This is based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments

established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF (e-CRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided in the relevant sponsor data management study document.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study

report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the e-CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study or one or more cohorts at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study or cohort termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For cohort termination
  - Early evidence of lack of benefit

- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study or cohort is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. He/she should also stop all screening activities pertaining to the study or the relevant cohort(s). Should the Sponsor decide to pause recruitment in a cohort to allow decision making, the Investigator should pause all screening activities until further notice.

If the study is early terminated the patients who are receiving and benefitting from study treatment as per Investigator judgment may continue study treatment provided by the Sponsor until protocol defined treatment discontinuation criteria are met. The patients who continue study treatment after early study termination should be followed for safety (ie, study treatment administrations, ongoing SAE/related AE, new related AE, AESI or SAE and their associated concomitant medications and lab if any) and end of treatment reason during this time period.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 6 - Protocol-required laboratory assessments

Laboratory tests	Parameters
Hematology[a]	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Urea or blood urea nitrogen (BUN)
	Creatinine and eGFR (MDRD formula[b])
	Glucose
	Potassium
	Sodium
	Corrected Calcium
	Phosphate
	Chloride
	Magnesium
	Bicarbonate[c]
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
	Lactate dehydrogenase (LDH)
	Albumin
	Amylase
	Lipase
Endocrine function tests[d]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Routine urinalysis	• Specific gravity, pH, glucose, protein, blood, ketones, and leukocytes by dipstick
	• Microscopic examination (if blood or protein is abnormal)
Other screening tests	• Follicle-stimulating hormone and estradiol may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT)
	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) [e]
	• Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus antibody), Hepatitis

	B viral load, HCV RNA level, CD4 counts & HIV viral Load[f]
	• Troponin
	• The results of each test must be entered into the e-CRF

NOTES:

a Blood Chemistry/hematology should be done with an overnight fasting if possible (should not interfere with hydration requirements). It will be performed weekly on D1 pre-dose, D8 and D15 (D15 for participants who receive Q3W only) during Cycle 1, then on Day 1 of every cycle up to Cycle 12, then every other cycle during Treatment Phase. Visits and assessments on C1D2-D3 will be performed for participants in the safety run-in or participants who are hospitalized because of high tumor burden or at Investigator's discretion. During the Observation Period, it will be performed at Follow-Up Visit 1. It can also be performed as clinically indicated. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

b Modification of Diet in Renal Disease (MDRD) equation: Glomerular filtration rate (mL/min/1.73 m^2) = 175 × (Serum Creatinine)-1.154 × (Age)-0.203 × (0.742 if Female) × (1.212 if African American)

c Bicarbonate or carbon dioxide (venous) (if bicarbonate or carbon dioxide are assessed only on arterial blood at site level, to be done only if clinically indicated)

d Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

e Pregnancy Test: Women of childbearing potential must have a negative urine pregnancy test result within 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 120 days (or refer to the individual substudy protocol) after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

f Participants with known HIV infection under antiretroviral treatment should have HIV viral load & CD4+ count done at screening to confirm controlled infection. Participants with known HBV hepatitis under treatment must have viral load determined at baseline to document controlled infection. Participants with positive serology against HCV must have determination of HCV RNA levels. The need for additional testing due to positive test results will be at the discretion of the Investigator. HIV serology at screening will be tested in any countries where mandatory as per local requirements (see Section 10.7).

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or

- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
        - Intensive treatment in an emergency room or at home for:
            - Allergic bronchospasm
            - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
            - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
        - Development of drug dependence or drug abuse
        - Suicide attempt or any event suggestive of suicidality
        - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
        - Bullous cutaneous eruptions

The purpose of the seriousness criteria listed above is to guide regulatory reporting obligations by the Sponsor. The Sponsor is required to expedite serious unexpected adverse reactions to regulatory health authorities and Investigators.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the e-CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories as per NCI CTCAE V5.0 definitions (except for ICANS and CRS that will be graded using ASTCT criteria):

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, if available the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below). A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive 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 hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.

Permanent sterilization methods include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova and sperm for up to the number of days specified respectively for each cohort in the inclusion criteria (see inclusion criteria I 04).

CONTRACEPTION GUIDANCE:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia 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.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]

- Oral
- Intravaginal
- Transdermal
- Injectable

Progestogen-only hormone contraception associated with inhibition of ovulation[c]

- Oral
- Injectable

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 intervention. 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.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

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 intervention.
- 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 the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial 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 the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) 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 intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. 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 intervention.

10.5 APPENDIX 5: GENETICS

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

France

Section 5.1 **Inclusion Criteria** (Section 5.1):

I 01. Participants must be ≥18 years of age, at the time of signing the informed consent.

Section 5.2 **Exclusion Criteria** (Section 5.2) and Section 10.2 **Clinical Laboratory tests** (Section 10.2):

In France, serology for HIV will be tested at screening.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Table 7 - Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node >5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by>50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration	Not applicable

Response and Site	PET-CT–Based Response	CT-Based Response
	should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions≤2 cm 1.0 cm for lesions>2 cm In the setting of splenomegaly, the splenic length must increase by>50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to>16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site>1.0 cm in any axis; if<1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple

Response and Site	PET-CT–Based Response	CT-Based Response

lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake>mediastinum but ≤ liver; 4, uptake moderately liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Lugano Classification (2).

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, screening and enrollment of participants and administration of study intervention may be temporarily delayed (see also Section 7.1.2).

10.9.1 Informed consent

The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension, use of local labs).

10.9.2 Study procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. If onsite visits are possible and there is a need to reduce the time spent on site to a minimum, the focus should be on IMP infusion/administration, collection of safety information (vital signs, adverse events) and safety blood collection (mainly biochemistry, hematology and ADA, if planned for the visit). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints, namely CT/MRI scan and tumor tissue collection for this study.

If onsite visits are not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

- Remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data.
- Visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.

10.9.3 Statistical analysis

The impact of any regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

10.9.4 Temporary discontinuation

Study intervention must be administered intravenously and at study site under the responsibility of the Investigator. Consequently, for participants who have started treatment but are unable to come to the site, administration of study intervention must be paused until regular study visits can be safely resumed at the study site.

In the event of disruption of the clinical trial due to an epidemic/pandemic (eg COVID-19), reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg. COVID-19) was unlikely.

Contingencies implemented due to emergency will be documented.

10.10 APPENDIX 10: RISK ASSESSMENT

The information shown in Table 8 reflects the clinical safety data available at the time of Edition 4 of the SAR444245 IB. Please always refer to the latest version of the IB for the most up-to-date safety data.

Table 8 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the THOR-707-101/HAMMER study have reported such AE as detailed in the IB.	SAR444245 Standard pre-medication Dose modification and treatment guidelines for SAR444245 infusion-related reactions are provided in the individual substudy.
Hypersensitivity, including anaphylaxis	SAR444245 Not observed in non-clinical toxicology studies. No reports of anaphylaxis in the HAMMER study to date.	Exclusion of participants with known hypersensitivity to or contraindication any components of SAR444245, PEG, or pegylated drugs.
Infections	SAR444245 Nonclinical data do not indicate higher risk for infections. Adverse events of infections have been reported in the HAMMER study and are presented in the SAR444245 IB.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Signs and symptoms of infection are monitored as part of TEAE.
Cytokine release syndrome	SAR444245 No major increases in cytokines have been reported in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Study to be conducted at sites experienced with CRS management, with bed available in ICU. Premedication with paracetamol, diphenhydramine (or equivalent medications). Hydration guidelines, including management of anti-hypertensive treatment around the time of infusion, are provided. Extensive post-dosing monitoring will be performed. Dose modification and treatment guidelines are provided in the individual substudy.
Capillary leak syndrome (CLS) / Vascular leak syndrome (VLS)	SAR444245 Not observed in non-clinical toxicology studies. None reported in the HAMMER study.	Intensive monitoring in C1D1 and beyond in the first cycle. Participants are monitored for signs and symptoms of VLS. Dose modification and treatment guidelines are provided in the individual substudy.
Hematological/bone marrow toxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, SAR444245-related changes in clinical	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	pathology parameters were observed at all doses and were generally most prominent 3 days following each dose. Changes in hematology parameters included decreased or attenuated reticulocytes followed by decreases in red blood cell (RBC) mass at [redacted] mg/kg/dose, and increased WBCs (lymphocytes and monocytes) and transiently mildly decreased platelets at [redacted] mg/kg/dose. The increases in lymphocytes were attributed to the expected pharmacology of SAR444245 and correlated with the gross and microscopic findings of splenic and lymph node enlargement and increased lymphoid cellularity; there were no microscopic or clinical correlates for the decreases in platelets. Adverse events of bone marrow toxicity have been reported in the HAMMER study and are presented in the SAR444245 IB. Transient lymphopenia has also been observed.	During treatment, regular hematology and biochemistry is examined. Dose modification/discontinuation of IMP for Grade 3/4 anemia, thrombocytopenia and/or neutropenia as per general guidelines for the management of TRAEs (see Section 6.5.3 in the individual substudy).
Hepatotoxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in mice, males at [redacted] mg/kg/dose and females at [redacted] and [redacted] mg/kg/dose also had mild increases in AST and ALT activity that corresponded to a spectrum of microscopic findings in the liver including mononuclear cell infiltration, apoptosis, necrosis, mixed leukocyte inflammation, oval cell hyperplasia, and Kupffer cell hypertrophy. No such data are reported in 28-day Repeat-Dose Study of IV SAR444245 in non-human primates. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Patients with significant impaired liver functions are excluded. Monitor clinical signs and symptoms of hepatic impairment as part of TEAE. Monitor liver function parameters (AST, ALT, bilirubin & ALP) regularly from screening and throughout the study. Dose modification and treatment guidelines for liver enzyme increase are provide under immune-related reactions in the individual substudy.
Nephrotoxicity	SAR444245 There are no non-clinical data indicating a potential for nephrotoxicity. One relevant serious adverse event (SAE) considered related to SAR444245 (Acute Kidney Injury) has been reported in the HAMMER study within a monotherapy cohort. Investigator's assessment is that it is related to the CRS occurring in the same patient. Sponsor's assessment was that the kidney injury was related to increased fluid losses from persistent fever.	Participants must have appropriate eGFR to be included. Monitor renal function parameters (BUN/urea & creatinine) regularly from screening and throughout the study. Dose modification and treatment guidelines for nephrotoxicity are provide under immune-related reactions in the individual substudy.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Neurological AEs, including ICANS	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the IB. One SAE of CRS (Grade 4 with 24 ug/kg monotherapy) associated with neurological manifestations [hypertension, chills/rigors, flushing, fever (maximum temperature: 102.8°F), as well as neurological symptomatology (loss of ability to follow commands, confusion, aphasia, and involuntary fist clinching)] was reported in the HAMMER study. The event resolved completely within 30 to 60 minutes after treatment with tocilizumab and steroid. This patient later discontinued the study.	Exclusion of participants with lymphomatous involvement of the central nervous system. Guidelines for the management of ICANS are provided in individual substudies.
Cardiovascular effects, including QT interval prolongation	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, there were no SAR444245-related changes to the PR or QRS intervals or the heart rate (HR) corrected QTca interval. There was a SAR444245-related, dose dependent, non-adverse higher HR at doses of ≥[redacted] mg/kg/dose beginning on Day 1 compared to the control dose group and persisting through each respective dose following applicable telemetry recording sessions, with recovery. There was also an expected physiologic inverse relationship in the respiration rate (RR) intervals as well as the raw QT intervals, which correlated to the changes in HR, and were also considered to be non-adverse. There were increases in individual females of troponin I minimal post first dose. There were marked decreases in females and males. These changes correlated with findings of mononuclear cell infiltrates and/or myocardial degeneration. All changes however, recovered by the end of a 28 day or 42/44 day treatment free period. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Routine mitigation: Selection of qualified investigative centers with availability of intensive critical care/equipment. Exclusion of patients with severe or unstable cardiac condition within 6 months prior to starting study treatment, see E10 for details. ECG, LVEF, and vital sign monitoring and coagulation tests performed at screening and thereafter as clinically indicated. Blood pressure and vital signs monitored closely during hospitalization in safety run-in. For subsequent cycles, monitoring will depend on site assessment of participant's symptoms.
Immune-mediated Adverse Events	SAR444245 A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Exclusion of participants with: Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents,

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). Close monitoring for endocrine abnormalities and other potentially autoimmune phenomena will be performed. Dose modification and treatment guidelines for under immune-related reactions are provided in the individual substudy.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	SAR444245 No studies have been conducted with SAR444245 on fertility or general reproductive performance.	Exclusion of participants who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial as per inclusion criterion I05. Guidance on highly effective contraceptive methods is provided in the protocol. Pregnancy tests are to be performed regularly as described in Section 8.2.5.
Use in children	The safety and efficacy of the study interventions in children below 18 years of age have not yet been established.	
Participants over 75 years of age	SAR444245 At this stage of development, no safety data are available for this population.	No specific mitigation strategy for this population.
Clinically significant medication errors	With the increased complexity of the design of oncology clinical trials, medication errors need to be considered. Although their occurrence is estimated to be low (eg, chemotherapy errors occur at a rate of about one to four per 1000 orders), their impact may be high. According to the report on medication safety in cancer clinical trials, the processes in which the errors originated were prescribing (47%), administering (10%), dispensing (6%), and monitoring (5%). Prescribing errors typically arise from not following an institutional procedure or the protocol (39%, most likely due to the protocol procedures differing from existing standards of care), followed by the written order (30%), and poor communication involving both the healthcare team and the patient (26%)	Strict adherence to the protocol. Adequate and verified training of staff at investigational sites.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	(33,34,35).	
Overdose and its treatment	There is no specific antidote for overdose with SAR444245.	Strict adherence to the protocol; Adequate and verified training of staff at investigational sites. See Section 6.7
Study procedures		
Biopsies of tumor tissue are expected during the trial.		Strict adherence to the guidance in the protocol

10.11 APPENDIX 11: ASTCT ASSESSMENT FOR ICANS AND CRS

Table 9 - Encephalopathy assessment ICE tool for ICANS Grading

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment	Number of points
Orientation: Orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points
Following commands: ability to follow simple commands (eg, “Show me 2 fingers” or “Close your eyes and stick out your tongue”)	1 point
Writing: ability to write a standard sentence (eg, “Our national bird is the bald eagle”)	1 point
Attention: ability to count backwards from 100 by 10	1 point

Source: (1).

Table 10 - ASTCT ICANS consensus grading for adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (participant is unrousable and unable to perform ICE).
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Elevated ICP cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

a A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unrousable.

b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medications).

c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE V5.0, but they do not influence ICANS grading.

d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE V5.0.

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; EEG = Electroencephalogram; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = Intracranial pressure;
N/A = Not applicable.
Source: (1).

Table 11 - ASTCT ICANS consensus grading for children

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for children age > 12 years[a]	7-9	3-6	0-2	0 (participant is unrousable and unable to perform ICE).
CAPD score for children age < 12 years	1-8	1-8	≥9	Unable to perform CAPD
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
Seizure (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention.	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor weakness (any age)[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis.
Elevated ICP/ cerebral edema (any age)	N/A	N/A	Focal/local edema on neuroimaging[d]	Decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, Cushing's triad, or signs of diffuse cerebral edema on neuroimaging

ICANS grade is determined by the most severe event (ICE or CAPD score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. Baseline CAPD score should be considered before attributing to ICANS.

a A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unrousable.

b Depressed level of consciousness should be attributable to no other cause (eg, no sedating medications).

c Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE V5.0, but they do not influence ICANS grading.

d Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE V5.0.

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; EEG = Electroencephalogram; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = Intracranial pressure;
N/A = Not applicable.
Source: (1).

Table 12 - ASTCT CRS consensus grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
			With	
Hypotension[b]	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or[b]	
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=Bi-level positive airway pressure CPAP= Continuous Positive Airway Pressure; CRS=Cytokine release syndrome.
Source: (1)

10.12 APPENDIX 12 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 participants prior to start of SAR444245 infusions and is left to Investigator judgment for further cycles.

The participants 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 Table 13.

Table 13 - 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.

For participants in the safety run-in or participants who are hospitalized because of high tumor burden or at Investigator's discretion, tumor lysis laboratory tests (corrected calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase [LDH] levels) will be obtained per details provided in the individual substudy).

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 Table 14.

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 SAR444245 treatment in patients at high risk for TLS, include the following:

-

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 Table 15.

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 Table 15. Redosing must be individualized.

Recommendations regarding the selection of allopurinol and/or rasburicase are summarized in Table 16.

Table 14 - 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 Table 15 and Table 16 regarding selection and dose of hypouricemic agents: Allopurinol Rasburicase (recombinant urate oxidase).

Table 15 - 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.

Table 16 - 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	≤50 · 109/L	>50 · 109/L
LDH	≤ 2· normal	>2 · normal
Cytoreductive intensity	Mild	Aggressive
Kidney tumor infiltration	Absent	Present

10.13 APPENDIX 13: ECOG PERFORMANCE STATUS AND LANSKY SCALE

Table 17 - ECOG PERFORMANCE STATUS

Grade	ECOG
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, e.g., 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

Source: (36).

Table 18 - Lansky Play/Performance Status

A.	Normal range of play Able to carry on usual play activities both active and quiet; child initiates play; no special adult assistance or direction needed; participation in interactive play • 100 Fully active • 90 Minor restrictions in physically strenuous play • 80 Restricted in physically strenuous play (eg. chasing games); may tire more easily, otherwise active
B.	Mild to moderate restriction of play Able to engage in some active play, but spends greater than usual time in quiet play; requires varying degree of assistance in setting up and completing play; restricted in interactive play • 70 Both greater restriction of, and less time spent in, active play • 60 Ambulatory 50% of time; limited active play with adult assistance, supervision • 50 Considerable adult assistance required for any active play; fully able to engage in quiet play (set up games, turn on TV, etc.)

A.	Normal range of play Able to carry on usual play activities both active and quiet; child initiates play; no special adult assistance or direction needed; participation in interactive play • 100 Fully active • 90 Minor restrictions in physically strenuous play • 80 Restricted in physically strenuous play (eg. chasing games); may tire more easily, otherwise active
C.	Moderate to severe restriction of play No active play; play limited to quiet activities; requires varying degree of assistance for quiet play • 40 Able to initiate most quiet activities • 30 Needs considerable assistance even for quiet activities • 20 Play entirely limited to very passive activities initiated by other (eg. TV) • 10 Completely disabled, no play • 0 Unresponsive

Source: (37).
For participants < 16 years old.

10.14 APPENDIX 14: DEFINITION OF LINE OF THERAPY

One line of therapeutic regimen is defined as a composite of one or several treatment modalities (may include transplantation, radiotherapy and/or drug[s]) instituted based on the results of a restaging exam.

If a regimen is composed of several drugs and one of the drugs is stopped for any reason, the regimen must be considered as ongoing until the entire regimen is stopped due to any reason.

If a new line of therapy is instituted based on the results of a restaging exam, it is usually considered a distinct line of therapy (38).

10.15 APPENDIX 15: ABBREVIATIONS

ADA:	anti-drug antibody
ADL:	activities of daily living
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
aPTT:	activated Partial Thromboplastin Time
AST:	aspartate aminotranferase
ASTCT:	American Society for Transplantation and Cellular Therapy
CBR:	clinical benefit rate
cHL:	classic Hodgkin lymphoma
CI:	confidence interval
CLS:	capillary leak syndrome

COVID-19:	Corona Virus Disease 2019
CR:	complete response
CRS:	cytokine release syndrome
DLBCL:	diffuse large B cell lymphoma
DLT:	dose-limiting toxicity
DMC:	Data Monitoring Committee
DoR:	duration of response
ECOG:	Eastern Cooperative Oncology Group
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
IB:	Investigator's brochure
ICANS:	immune cell-associated neurotoxicity syndrome
ICF:	informed consent form
IHC:	immunohistochemistry
IL-2:	interleukin 2
IMP:	investigational medicinal product
INR:	International Normalized Ratio
irAE:	immune-related adverse event
IRR:	infusion-related reaction
IV:	intravenous
MCP-1:	monocyte chemoattractant protein-1
MTD:	maximum tolerated dose
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP:	non-human primate
NIMP:	non-investigational medicinal product
NK:	natural killer
NSCLC:	non-small cell lung cancer
PD:	progressive disease
PD-L1:	programmed death-ligand 1
PFS:	progression free survival
PK:	pharmacokinetic
PMBCL:	primary mediastinal large B cell lymphoma
PO:	oral route
PR:	partial response
pRBC:	packed red blood cell
Q2W:	every 2 weeks
Q3W:	every 3 weeks
RCC:	renal cell carcinoma
RP2D:	recommended Phase 2 dose
SAE:	serious adverse event
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SB:	Study Board
SUSAR:	suspected unexpected serious adverse reaction
TLS:	tumor lysis syndrome
TRAE:	treatment-related adverse event
TRR:	time to response

ULN: upper limit of normal
VLS: vascular leak syndrome
WOCBP: woman of childbearing potential

10.16 APPENDIX 16: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

11 REFERENCES

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Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 01 (SUBSTUDY 01)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of adults and adolescents with relapsed or refractory classic Hodgkin lymphoma**
Protocol number:	**ACT16941-S01**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of adults and adolescents with cHL**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin,** **France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	156112
EudraCT:	2021-002150-91
NCT:	NCT05179603
WHO:	U1111-1251-5834

Date: 28-Apr-2022 Total number of pages: 67

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01 (Substudy 01)	All	28 April 2022, version 1 (electronic 1.0)
Clinical Trial Protocol (Substudy 01)		16 July 2021, version 1 (electronic 1.0)

Amended protocol 01 (28 April 2022)

This amended protocol (Amendment 01) 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

In response to the requests from the French Health Authority (National Agency for the Safety of Medicines and Health Products [ANSM]) after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	The NCT number has been added.	This study has been registered on clinicaltrials.gov, the NCT number is applicable.
1.2 Schema	The Graphical study design for Cohort A has been updated with the instruction for FDG-PET.	For clarity and consistency.
1.3 Schedule of activities (SOA)	The assessment of troponin level has been added.	To allow assessment of any potential cardiotoxicity.
	For footnote “d”, the following sentence “Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected.” has been deleted.	Reduction in protocol complexity and patient/site burden.

Section # and Name	Description of Change	Brief Rationale
	Footnote “e” has been newly added for clarification on C1D2, D3 visits. The subsequent footnotes are re-numbered accordingly.	For clarity.
	Footnote “f” for blood draws and/or tumor biopsy for biomarker assessment has been removed and changed to “Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, if safety data justifies it.” The reference to the footnote “f” has been deleted at C1D8 in the SOA.	To make operational procedures easier.
	For footnote “i” (previous footnote h), tumor lysis laboratory tests on C1D1 have been changed from “for all participants” to “for safety run-in participants or participants who are hospitalized”.	For clarity.
1.3 Schedule of Activities (SOA), 10.7 Appendix 7: Country-Specific Requirements	Requirement of human immunodeficiency virus (HIV) has been added at screening for participants in France and specified in SOA newly added footnote “m” and country-specific requirements sections.	Regulatory Authority (ANSM) request.
1.4 Biomarker flowcharts	[redacted]	[redacted]
1.5 Pharmacokinetic flowcharts	PK sample collection on Cycle 1 D15 has been changed to “D8”.	To align with participants’ visit.
5.1 Exclusion criteria	E02 “Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease [GVHD]).” has been added from the master protocol (E24).	For clarity.
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS); 6.5.4.5 Immune cell-associated neurotoxicity syndrome (ICANS)	The following statement “alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following tocilizumab availability.
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 5, the following sentence has been deleted [redacted].	For consistency with instructions given in Section 6.5.1 General rules. Regulatory Authority (ANSM) request.

Section # and Name	Description of Change	Brief Rationale
6.5.4.7 Tumor Lysis Syndrome (TLS)	Tumor lysis laboratory tests on C1D1 have been changed from “for all participants” to “for safety run-in participants or participants who are hospitalized”.	For clarity and consistency.
10.1.6 Dissemination of clinical study data	The following texts has been added “Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study”.	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials.
Throughout	“Study Committee” has been changed to “Study Board”.	Harmonization per Sanofi standard terminology.
Throughout	Minor editorial updates.	For clarity and consistency.

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of adults and adolescents with relapsed or refractory classic Hodgkin lymphoma

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of adults and adolescents with cHL

Rationale:

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and non-human primate (NHP) models while anti programmed cell death-1 (anti-PD1) antibody prevents T cell suppression through the programmed cell death-1/programmed cell death-ligand 1 (PD1/PD-L1) pathway. The combination of anti-PD1 treatment with SAR444245 was tested in the syngeneic murine colon cancer CT-26 model and induced enhanced anti-tumor activity as demonstrated by an increased number of complete responses (CR) and tumor-free surviving animals compared to each agent in monotherapy. These data support evaluation of SAR444245 in combination with an anti-PD1 antibody.

The proposed study aims to establish proof-of-concept that non-alpha interleukin 2 (IL-2) SAR444245 combined with the anti-PD1 antibody, pembrolizumab in trial participants with classic Hodgkin lymphoma (cHL) who are anti-PD-(L)1-naïve and have received at least 2 or 3 lines of systemic therapy .

Objectives and endpoints

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 with or without other anticancer therapies.	• Complete response rate (CRR) defined as the proportion of participants who have a complete response (CR) determined by Investigator per Lugano response criteria 2014 (1).
Secondary	
• To assess other indicators of antitumor activity.	• Objective response rate (ORR) defined as the proportion of participants who have CR or partial response (PR) determined by Investigator per Lugano response criteria 2014 (1).

Overall design:

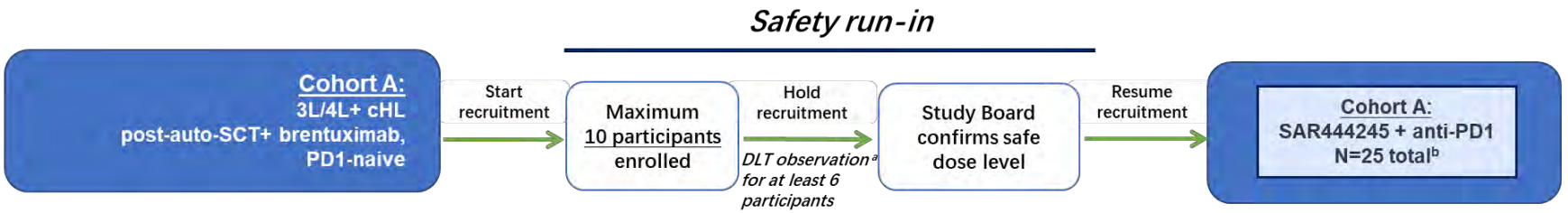
Please refer to the master protocol.

Brief summary:

Cohort A: This substudy will include approximately 25 participants with cHL who have received at least 2 or 3 lines of systemic therapy and will assess SAR444245 combined with pembrolizumab as at least 3rd or 4th line of therapy.

A graphical presentation of the substudy schema is shown in Figure 1.

Figure 1 - Overall study schema



a The DLT observation period is 21 days for Cohort A.
b Including participants enrolled in the safety run-in at the confirmed safe dose.

Abbreviations: 3L/4L: third-line or fourth-line; auto-SCT: autologous stem-cell transplantation; cHL: classic Hodgkin lymphoma; DLT: dose limiting toxicity; N: number; PD1: programmed cell death 1.

Number of participants:

Overall, approximately 25 participants will be treated in Cohort A

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration. For Cohort A, the maximum cycles allowed are 35 cycles.

Study interventions

Cohort A: cHL participants, SAR444245 + pembrolizumab as at least 3L/4L therapy

Dosing sequence: [redacted]

Investigational medicinal product(s)

Pembrolizumab

- Formulation: Keytruda® (pembrolizumab) as 100 mg/4 mL (25 mg/mL) solution in single-dose vials.
- Route of administration: intravenous (IV) infusion.
- Dose regimen: Pembrolizumab will be administered at a dose of 200 mg (for pediatric participants: 2 mg/kg, up to maximum 200 mg) using a 30-minute IV infusion on Day 1 of each 3-week treatment cycle for **up to 35 cycles.**

Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

SAR444245

SAR444245 formulation and route of administration as described in the master protocol.

- Dose regimen: 24 µg/kg (or reduced to [redacted] µg/kg or another lower dose level recommended by Study Board) administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles.**

Non-investigational medicinal products

Please refer to the master protocol.

After 4 cycles, in case of permanent SAR444245 discontinuation and continuation of pembrolizumab treatment as part of AE management, premedication for SAR444245 no longer needs to be administered.

Statistical considerations:

Please refer to the master protocol for description of common statistical considerations. Substudy-specific analyses are summarized below.

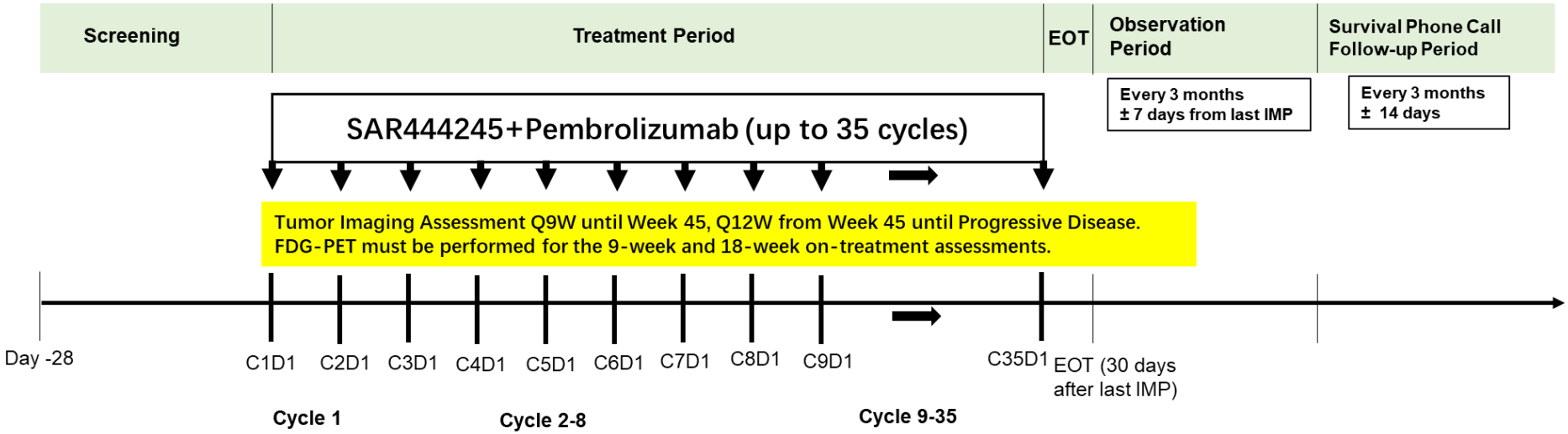
- **Analysis of primary endpoint:**
  - The complete response rate (CRR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for CRR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The objective response rate (ORR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for ORR will be computed using the Clopper-Pearson method.

Data Monitoring/Other Committee: Yes

1.2 SCHEMA

1.2.1 Study design for Cohort A

Figure 2 - Graphical study design-Cohort A



C=Study cycle (1 cycle = 21 days); D=Study day; EOT=end of treatment; IMP=Investigational medicinal product; FDG-PET=fluorodeoxyglucose-positron emission tomography.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D1	D2[e]	D3[e]	D8	D14/ D15[f]	D1(±3 days)	D8	D1(±3 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ± 14 days	
Informed consent	X														
Inclusion/ Exclusion criteria	X														
IRT contact	X	X					X		X	X					
Demography, medical/surgical and disease history	X														See Section 8 in the master protocol
Performance status (ECOG or Lansky Scale)	X	X					X	X	X	X	X				See Appendix 13 in the master protocol
Body weight/Height[g]	X	X					X		X						

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	**D-28 to D-1**	**D1**	**D2[e]**	**D3[e]**	**D8**	**D14/ D15[f]**	**D1(±3 days)**	**D8**	**D1(±3 days)**	**30 (±7) days after last IMP admin or prior to initiation of further therapy**	**3 months (±7 days) after last IMP admin**	**6 months (±7 days) after last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ± 14 days**	
Full physical examination	X									X					
Directed physical examination		X			X	X	X		X		X				See Section 8.2.1 in the master protocol
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X				See Section 8.2.2 in the master protocol
SpO_2[h]	X	As clinically indicated													
Bone marrow biopsy		As clinically indicated to confirm complete response													See Section 8.1 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]							End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8	Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	**D-28 to D-1**	**D1**	**D2[e]**	**D3[e]**	**D8**	**D14/ D15[f]**	**D1(±3 days)**	**D8**	**D1(±3 days)**	**30 (±7) days after last IMP admin or prior to initiation of further therapy**	**3 months (±7 days) after last IMP admin**	**6 months (±7 days) after last IMP admin**	**Every 3 months ±7 days**	**Every 3 months ± 14 days**	
Spleen measurement	X	As clinically indicated to evaluate response												See Section 8.1 in the master protocol
12-Lead ECG	X	As clinically indicated												See Section 8.2.3 in the master protocol
LVEF	X	As clinically indicated												See Section 8.2.3 in the master protocol
Troponin	X	As clinically indicated					X (Cycle 4 Day 1)	As clinically indicated						See Section 8.2.3 and Section 10.2 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D1	D2[e]	D3[e]	D8	D14/ D15[f]	D1(±3 days)	D8	D1(±3 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ± 14 days	
Pregnancy test	X	X					X		X	X	X	X			See Section 8.2.5 and Section 10.2 in the master protocol
Blood chemistry[h]	X	X	X	X	X	X	X		X	X	X				See Section 10.2 in the master protocol
Tumor Lysis Laboratory Tests[i]		X	X	X											
Hematology[h]	X	X	X	X	X	X	X		X	X	X				
T3, FT4, TSH and cortisol[j]	X						X		X	X	X				See Section 10.2 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D1	D2[e]	D3[e]	D8	D14/ D15[f]	D1(±3 days)	D8	D1(±3 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ± 14 days	
Coagulation[k]	X	As clinically indicated									X				See Section 10.2 in the master protocol
Urinalysis[l]	X	On C1D1 and C2D1, then as clinically indicated									X				See Section 10.2 in the master protocol
Hepatitis serology, CD4+ counts and viral load	X[m]	As clinically indicated													See Section 10.2 in the master protocol
IMP		X					X		X						
Hospitalization[o]		X	X	X											

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D1	D2[e]	D3[e]	D8	D14/ D15[f]	D1(±3 days)	D8	D1(±3 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ± 14 days	
AE/SAE assessment[p]	X	Continuous throughout treatment period									X				See Section 8.3 in the master protocol
Prior/Concomitant Meds	X[n]	Continuous throughout treatment period													See Section 6.8 in the master protocol
First subsequent anti-cancer therapy										X	X	X	X		
Survival status														X	
Pharmacokinetic (PK) / Pharmacodynamic (PD) / Immunogenicity assessments															
PK	See PK Flow-Charts in Section 1.5														
ADA															

Evaluation[a]	Screening	Treatment Period[b]								End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-8		Cycle 9 – 35	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D1	D2[e]	D3[e]	D8	D14/ D15[f]	D1(±3 days)	D8	D1(±3 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ± 14 days	
PDy - Blood and tumor tissue collection[r]	See Biomarker Flow-Chart in Section 1.4														
Tumor assessment															
CT/MRI[q]	X						X		X	X	X	X	X		See Section 8.1.1 in the master protocol
Brain imaging[s]	If clinically indicated														See Section 8.1.1 in the master protocol
FDG-PET[q]	X	As clinically indicated, and must be performed for the 9-week and 18-week on-treatment assessments													See Section 8.1.1 in the master protocol

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. Baseline evaluations should be completed within 7 days prior to the first dose of IMP, except for tumor assessment that may be performed within 28 days prior to IMP administration, and unless specified otherwise. There is no need to perform Cycle 1 Day 1 laboratory assessments that have been performed as part of screening within 3 days prior to first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator **prior to IMP administration** at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 3 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: A treatment cycle is 21 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the Cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

c Observation Period: Participants who enter the Observation period will be followed differently depending on the reason leading to permanent study treatment discontinuation. See Section 4.1 of the master protocol. For participant's convenience, all Follow-up assessments may occur during the same visit as that when tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the study.

e Visits on C1D2, D3 are for safety-run in participants only.

f Study Board may decide to cancel safety assessment on C1D15, upon agreement with Sponsor, if safety data justify it.

g Weight/Height: Height is required at baseline only for patients > or =18 years old. For trial participants <18 years old, height should be assessed on day 1+/-1 of each cycle. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

h Blood chemistry/ hematology will be performed weekly on D1 pre-dose, D8 and D15 during Cycle 1, then on Day 1 of every cycle up to Cycle 12, then every other cycle during Treatment Phase. Visits and assessments on C1D2-D3 are only for participants in the safety run-in or participants who are hospitalized because of high tumor burden or at investigator's discretion. For these participants, vital signs, SpO_2 and complete blood counts (CBC) and differentials, chemistries (blood urea nitrogen (BUN), creatinine (Cr), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (Alk Phos), total bilirubin (TBil) will be obtained daily.

i Tumor lysis laboratory tests (corrected calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase [LDH] levels) will be obtained every 8 hours on C1D1 for safety run-in participants or participants who are hospitalized, and C1D2-D3 for safety run in or participants who are hospitalized because of high tumor burden or at investigator's discretion.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

k Coagulation includes international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT).

l Urinalysis will be performed on C1D1 and C2D1, then as clinically indicated during the treatment period, and will be performed at Follow-Up Visit 1.

m For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in France (see details and specific instructions in Section 10.2 and Section 10.7 in the master protocol, and Section 10.7 in this substudy 01).

n Prior medications that are received within 30 days before the first dose of IMP.

o Hospitalization for 48 h for safety run-in participants or for participants with a high tumor burden or at investigator's discretion.

p AE/SAE assessment: Severity will be graded according to NCI-CTCAE v 5. ICANS and CRS will be graded using ASTCT criteria integrated with central laboratory cytokine results (2).

q The initial tumor imaging FDG-PET CT and/or MRI will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP and if clinically indicated. FDG-PET must be performed for the 9-week and 18-week on-treatment assessments. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is required for the baseline and follow-up assessments.

r If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Tumor biopsy should be considered for new lesions if their pathologic etiology is ambiguous.

s Brain CT/MRI: To be performed if clinically indicated.

Abbreviations: ADA = Anti-drug antibodies; AE = Adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; C = Cycle; CT = Computed tomography; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; FDG-PET = fluorodeoxyglucose-positron emission tomography; FT4 = Free thyroxine; FU = Follow-up visit; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICF = Informed consent form; IMP = Investigational medicinal product; LVEF = Left ventricular ejection fraction; MRI = Magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = Progressive disease; PDy = Pharmacodynamic; PK = Pharmacokinetic; Q3W = Every 3 weeks; SAE = Serious adverse event; TSH = Thyroid stimulating hormone.

1.4 BIOMARKER FLOWCHARTS

1.5 PHARMACOKINETIC FLOWCHARTS

Cycle	Treatment Cycle 1						Treatment Cycle 2, 4, 7, 10 + every 5th cycle		EOT visit
Day	**D1**			**D2**	**D3**	**D8**	**D1**		**30 (±7) days after last IMP administration**
Time after start of SAR444245 dosing [h]	SOI	EOI	4h post EOI	At any time	At any time	At any time	SOI	EOI	At any time
SAR444245 PK sample		P00[b]	P01	P02[c]	P03[c]			P00[b]	
SAR444245 ADA sample	AB00[a]					AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI). ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.

b PK sample must be taken at the end of infusion (EOI) after flush.

c P02 and P03 to be collected during safety run-in and when participants are hospitalized.

In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at 4 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end resumed infusion and subsequent sample should be drawn at 0.5 h after end of resumed infusion. PK sampling may be discontinued by the Sponsor once sufficient data have been collected.

Abbreviations: ADA: anti-drug antibodies; D: day; EOT: end of treatment; PK: pharmacokinetic.

2 INTRODUCTION

Study ACT16941 is developed as a master protocol in order to accelerate the investigation of SAR444245 with or without various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort A (participants with cHL who are anti-PD-(L)1-naïve and have received at least 2 or 3 lines of systemic therapy) for the combination therapy with pembrolizumab.

Please refer to the master protocol for an introduction for ACT16941.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD1 antibody prevents T cell suppression through the PD1/PD-L1 pathway. The combination of anti-PD1 treatment with SAR444245 was tested in a syngeneic mouse CT-26 colon cancer model and demonstrated enhanced anti-tumor activity and prolonged survival compared to each monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death protein 1 (PD1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for many advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications, including as monotherapy for relapsed or refractory cHL or PMBCL. For more details on specific indications refer to the pembrolizumab Investigator's Brochure (IB).

Refer to the approved local labeling for detailed background information on pembrolizumab.

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decade (3). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long term

survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (4, 5).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)
(6, 7).

The structure of murine PD1 has been resolved (8). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3
T-cell signaling cascade (7, 9, 10, 11). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (12, 13). As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in cHL.

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (14, 15, 16, 17, 18, 19, 20). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (8, 17, 19, 20, 21). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (19). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the pembrolizumab Investigator's brochure [IB]).

A summary of clinical trial data and the justification of the choice of pembrolizumab dose is provided in Section 4.3.2.

2.2.2 Rationale for B cell lymphoma and selected participant population

Please refer to Section 2.2.1 of the master protocol.

2.2.3 Current standard of care in classic Hodgkin lymphoma

At diagnosis, patients usually receive multiagent chemotherapy (eg, adriamycin, bleomycin, vinblastine, and dacarbazine [ABVD]; adriamycin, vinblastine, and dacarbazine [AVD]; bleomycin, etoposide, adriamycin, cytoxan, vincristine, procarbazine, and prednisone [BEACOPP]) with or without brentuximab and/or radiotherapy. For refractory disease, or at first relapse, transplant-eligible patients are referred for autologous stem cell transplant with or without radiotherapy and/or brentuximab or allogeneic stem cell transplant (in select patients). Transplant-ineligible patients may be treated with brentuximab monotherapy or in combination with nivolumab (off-label). At second relapse and beyond, patients are offered currently approved therapy, such as pembrolizumab or nivolumab, or enrollment in a clinical trial (22). Pembrolizumab is approved to treat adults and children with relapsed/refractory cHL (USPI). The KN204 study compared pembrolizumab to brentuximab vedotin (BV) in patients who were ineligible for or relapsed following an autologous stem cell transplant (ASCT). With the KN204 approval, pembrolizumab is now a treatment option as 2nd line therapy in the US.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SAR444245 and other combinations may be found in the Investigator's Brochure.

2.3.1 Risk assessment

Please refer to the master protocol for risk assessment for SAR444245, the known safety profile of the structurally similar product aldesleukin (Proleukin®) and current knowledge of the new-generation, investigational IL-2 analog NKTR-214 (bempegaldesleukin).

Risk assessment of SAR444245 combined with pembrolizumab results from anticipated risks for SAR444245 and from the label information for pembrolizumab, taking into account potential overlapping risks. The available safety data for pembrolizumab, along with proposed mitigation strategies are summarized below and also provided in Table 10.

2.3.1.1 Pembrolizumab

Pembrolizumab potentiates T-cell responses, including antitumor responses, through blockade of PD1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumors or other cells in the tumor microenvironment.

The use of pembrolizumab may cause infusion-related reactions (IRRs) (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, and hypersensitivity). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia,

leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risks for pembrolizumab (23).

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Among the immune-related adverse events (irAEs) associated with pembrolizumab are: immune-related pneumonitis, immune related colitis, immune-related hepatitis, immune-related nephritis, immune-related endocrinopathies, immune-related skin adverse reactions and other additional clinically significant, immune-related adverse reactions (reported in clinical studies or in post marketing experience): uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, and myelitis.

Efficacy and safety data for pembrolizumab from patients ≥75 years are limited. In this population, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

Please refer to pembrolizumab country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for more detailed information.

2.3.1.2 SAR444245 combined with pembrolizumab

Due to synergistic action of SAR444245 and pembrolizumab, combining these two substances may lead to an increased frequency and/or severity of adverse events (AEs) related to immune activation for each substance individually or may cause occurrences of qualitatively different AEs. Serious adverse drug reactions reported with agents known to increase immune activation include pneumonitis, hepatitis, nephritis, colitis, and hormonal dysfunction (see Section 2.3.1.1).

The maximum tolerated dose of SAR444245 combined with the approved dosing of the anti-PD1 pembrolizumab is under assessment in the HAMMER study using a Q3W schedule. Safety data generated from the combination of SAR444245 and pembrolizumab have informed the selection of the combination dose in this study.

2.3.2 Benefit assessment

More detailed information about the expected benefits of SAR444245 may be found in the master protocol, and the combination of SAR444245 and pembrolizumab are provided below.

In a syngeneic mouse model CT-26, relatively resistant to immune checkpoint treatment, SAR444245 potentiated the activity of an anti-PD1 antibody. Combination treatment in animals, when compared to respective monotherapies, increased the number of complete responses and prolonged survival which was durable as demonstrated by the failure of the tumor to grow upon re-engraftment on the tumor free animals, indicating the establishment of a durable memory T-cell population in response to the initial treatment (see SAR444245 IB).

The regimen proposed to be evaluated in this substudy is anticipated to bring benefit to patients with cHL.

2.3.3 Overall benefit: risk conclusion

More detailed information about the expected benefits of SAR444245 may be found in the master protocol. Overall, the potential risks identified in association with this new generation IL-2 SAR444245 combined with the anti-PD1 inhibitor pembrolizumab are justified by the anticipated benefits that may be afforded to participants with cHL.

2.3.4 Benefits and risks assessment in the context of COVID-19 pandemic

Please refer to the master protocol for more details about risks related to the patient population, SAR444245 treatment, and study related activity.

In addition, the impact of PD-1 blockade therapy on Coronavirus Disease 2019 (COVID-19) severity was explored by 2 groups who did not find a clinically meaningful signal (24, 25).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 with or without other anticancer therapies.	• Complete response rate (CRR) defined as the proportion of participants who have a complete response (CR) determined by Investigator per Lugano response criteria 2014 (1).
Secondary	
• To assess other indicators of antitumor activity.	• Objective response rate (ORR) defined as the proportion of participants who have CR or partial response (PR) determined by Investigator per Lugano response criteria 2014 (1).

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include approximately 25 participants with classic Hodgkin lymphoma (cHL) who have received at least 2 or 3 lines of systemic therapy and will assess SAR444245 combined with pembrolizumab as at least 3rd or 4th line of therapy.

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the study schema is shown in Figure 1.

The dose-limiting toxicity (DLT) observation period is 21 days for Cohort A.

Please refer to the master protocol for the full list of common events and below for substudy specific events occurring during the DLT observation period (21 days) which are considered as DLT unless due to disease progression or to a cause obviously unrelated to SAR444245.

Hematologic abnormalities:

- Grade 3 neutropenic fever (ANC<1000/mm^3 with single temperature >38.3°C [101°F] or sustained temperature >38°C [100.4°F] for more than 1 hour) for Cohort A.

The maximum cycles allowed in this substudy for Cohort A are 35 cycles.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with the anti-PD1 antibody, pembrolizumab, in trial participants with cHL.

The design of the study is a non-randomized study where the experimental combination will be assessed in a single cohort, using historical data for single agent immune-checkpoint as a benchmark to show outstanding complete response rate. The CRR will be assessed using Lugano response criteria 2014 for participants with cHL.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

Please refer to the master protocol.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg (for pediatric participants: 2 mg/kg, up to maximum 200 mg), every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB)
- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications. And
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5- fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor

penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

To date, pembrolizumab (2 mg/kg Q3W) has been evaluated in 161 pediatric participants (aged 1 to 18 years) with advanced melanoma, PD-L1 positive advanced, relapsed, or refractory solid tumors, or lymphoma. The exposures in pediatric participants following the 2 mg/kg Q3W regimen were found to be similar to that observed in adult participants. Pediatric data has also been incorporated in an integrated population PK analysis, which confirmed that a pembrolizumab dose of 2 mg/kg Q3W (up to a maximum of 200 mg Q3W) in pediatric participants renders exposures similar to adults. Based on these results, the pediatric dose for evaluation in this trial is 2 mg/kg Q3W (up to a maximum of 200 mg Q3W).

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort A specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed in the master protocol):

Type of participant and disease characteristics

I 01. Cancer diagnosis at study entry:

Histologically or cytologically confirmed diagnosis of classic Hodgkin lymphoma (cHL), according to the WHO 2016 classification.

I 02. Prior anticancer therapy:

- Must have received at least two prior lines of systemic therapy for cHL, including at least one containing an anthracycline or brentuximab.
- Must have failed or declined autologous stem cell transplantation (ASCT), or not be a candidate for ASCT.
- May have received a prior autologous stem cell transplant but must be at least ≥100 days post-auto-transplant, and all transplant- related adverse events must have resolved to grade 1 or less and meet all other eligibility criteria.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply (in addition to the criteria listed in the master protocol):

Prior/concomitant therapy

E 01. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD-1/PD-L1 but have written confirmation they were on control arm [must not contain anti-PD1/PD-L1] are allowed).

E 02. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Participants who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease [GVHD]).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

The maximum cycles allowed in this substudy for Cohort A are 35 cycles.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245, and pembrolizumab administered as described in Section 4.1. Details of each IMP component to be administered are shown in Table 2.

Preparation and administration of IMP are detailed in the pharmacy manual. Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 2 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	100 mg/vial
Dosage level(s)[a]	24 µg/kg Q3W (or reduced to [redacted] µg/kg [redacted] or another lower dose level recommended by Study Board)	200 mg Q3W (for pediatric participants: 2 mg/kg, up to maximum 200 mg)
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	IMP	IMP
Packaging and labeling	See master protocol	Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	NA	Keytruda

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the electronic case report form (e-CRF). Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

6.1.2 Non-investigational medicinal products

Please refer to the master protocol.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modification for SAR444245 is permitted according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be withheld or discontinued due to toxicity.

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor, unless required for immediate participant safety.

Cycle delay (ie, Day 1 should be delayed for all IMPs) is permitted in case of treatment-emergent adverse event (TEAE). Dose modification will be made according to the worst grade of toxicity observed within a cycle. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other TEAE that, in the opinion of the Investigator, warrants discontinuation.

If any of the IMP components is permanently discontinued, the other IMP component can be continued until disease progression or other criteria as detailed in Section 7.1.1 of the master protocol are met. In this case it is partial permanent discontinuation and the end of treatment (EOT) assessment will be 30 days after the date of the last administration of the remaining IMP. When all IMP components are permanently discontinued it is full permanent discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 Cycle delay

The treatment window is ±3 days for each of the Q3W administrations. A cycle is deemed to have been delayed if the treatment is administrated ≥4 days beyond the theoretical day of Q3W IMP administration. The participant may receive the next dose after recovery from the toxicity as described in Section 6.5.3, and Section 6.5.4. After cycle is delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy.

Participants may have cycle delay, if toxicity occurs and the participant does not recover according to following rules:

- For Q3W IMP administration: If toxicity occurs and the participant does not recover on the day of planned administration, the cycle will be delayed: restart of study IMPs could occur only on the initiation of the subsequent cycle.
- In case of cycle delay for the recovery of toxicity, the following rules should be followed for restart or discontinuation of the treatment:
    - In case of a cycle delay up to 14 days, it is per Investigator's decision to restart the study treatment.
    - After a cycle delay of >14 days and ≤84 days, it is per Investigator's decision to restart the study treatment, if a clear benefit from treatment is observed and after consultation with the Sponsor.
    - The study treatment must be permanently discontinued if the cycle delay is longer than 84 days.
- Cycle may be delayed for situations other than TEAEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled delay, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for this delay should be documented in the participant's study record.

6.5.3 General guidelines for the management of treatment-related adverse events

Participants who experience Grade ≥3 treatment-related adverse events (TRAEs) at any time of the study (including clinically significant grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to cycle delay the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy. Treatment resumption is at the discretion of the Investigator and Sponsor, if thought to be in the best interest of the participant, except when specified otherwise in this protocol, or if the event has required the IMP temporary withheld for more than 84 days from the last scheduled dose.

The cycle delay of treatment for Grade 2 events is left at the discretion of the Investigator unless otherwise specified in this protocol.

No cycle delay of treatment or dose modification is required for Grade 1 events.

Dose reduction for SAR444245 from [redacted]µg/kg to [redacted] µg/kg (or another lower dose recommended by Study Board) may be decided when specified in the protocol or following discussions with the Sponsor.

The final decision on dose modification and/or corrective therapy will be based on the Investigator's judgment, in the best interest of the participant.

Recommended guidelines for the management of specific adverse events including irAE, CRS, vascular leak syndrome (VLS) and IRR are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interests (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the electronic case report form (e-CRF).

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol, prior to SAR444245 administration, to prevent or reduce the incidence or severity of IRRs.

An infusion-related reaction (IRR) in this study is defined as any signs or symptoms which develop during the infusion or up to 24 hours after the completion of the infusion. The term IRR indicates only a specific temporal relationship with the infusion and does not specify a particular mechanism underlying the signs or symptoms.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug

infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 3.

After an IRR due to pembrolizumab infusion (Grade 3 or Grade 4), the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 IRR events are provided in Table 4. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 3 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - IV fluids, - Antihistamines, - NSAIDs, - Acetaminophen, - Narcotics. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: - Epinephrine*, - IV fluids, - Antihistamines, - NSAIDs,	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	- Acetaminophen, - Narcotics, - Oxygen, - Pressors, - Corticosteroids. • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Table 4 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE definition. If IRR happens after completion of infusion, increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given at half the infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.

Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be prematurely permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be prematurely permanently discontinued. The participant can continue treatment with the other anti-cancer therapy in combination. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
b In cases of anaphylaxis, epinephrine should be used immediately
Abbreviations: CTCAE = Common terminology criteria for adverse events; IRR = Infusion related reaction; NCI = National Cancer Institute; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.5.4.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of both SAR444245 and pembrolizumab being administered.

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines) (26, 27, 28).

6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)

Fever can frequently happen with infusion of IL-2 and may possibly evolve into flu-like symptoms or could be an early manifestation of CRS. Fever or flu-like symptoms should be graded according to CTCAE V5.0 and managed according to institutional standards.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 5. If any grade of CRS is suspected, sites should make every effort to draw an additional blood sample for cytokines levels (by central laboratory), prior to the administration of tocilizumab, as well as for C-reactive protein (CRP) and ferritin (by local laboratory).

Sites should have at least 2 full doses of tocilizumab available, or alternative therapies per site practice in CRS management, and access to an intensive care unit (ICU), in case participants develop CRS.

Guidelines for management of CRS according to severity grading are provided in Table 5. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

Table 5 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a]. Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt of SAR444245, if event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. SAR444245 may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin)	If CRS grade 3, SAR444245 should be temporarily withheld, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated. If CRS Grade 4, SAR444245 should be permanently discontinued, as clinically indicated. If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management should be considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
• And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed. CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS. If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants weighing ≥30 kg), or alternative therapies per site practice in CRS management, should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension, fever and other manifestations is observed after the first dose of tocilizumab, or alternative therapies per site practice in CRS management, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab or alternative therapies per site practice in CRS management and steroids, alternative options should be discussed with clinical site specialists

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or alternative therapies per site practice in CRS management or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

d Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Abbreviations: AE = Adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP= Bilevel Positive Airway Pressure; CPAP= Continuous Positive Airway Pressure; CRS= cytokine release syndrome; ICU=intensive care unit; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune-related adverse events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Immune-related AEs are thought to be caused by unrestrained cellular immune responses directed at the normal host tissues. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing pembrolizumab clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. For suspected irAEs, adequate evaluation should be performed to confirm etiology or exclude neoplastic,

infectious, metabolic, toxin, or other etiologic causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 6. Of note, when study interventions are administered in combination, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

The CTCAE V5.0 must be used to grade the severity of AEs.

When SAR444245 or pembrolizumab can be restarted, they should be administered at the initial planned dose and schedule as no modification is allowed:

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the combination of SAR444245 and pembrolizumab may be restarted at the discretion of the Investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 6 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and SAR444245 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SAR444245 have been withheld, pembrolizumab and SAR444245 may be resumed after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		
AST or ALT elevation or Increased Bilirubin	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[af]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold[a]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold[a] or permanently discontinue[bf]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold[a] or permanently discontinue[bf]		

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold[a]	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue[b]		
Neurological Toxicities	Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue[b]		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold[a]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue[b]		
All Other irAEs	Persistent Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold[a] or discontinue based on the event[g]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		

a SAR444245 to be withheld plus pembrolizumab to be withheld corresponds to "cycle delay".
b Permanently discontinuation of full study treatment.
c AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal.
d AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal.
e AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.
f The decision to withhold or permanently discontinue pembrolizumab and SAR444245 is at the discretion of the Investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab and SAR444245 may be resumed.
g Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.11 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab, or alternative therapies per site practice in CRS management, should only be used in the context of CRS, as outlined in Table 7. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 7 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	SAR444245 [a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted]µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. If Grade 4 ICANS, SAR444245 should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab, or alternative therapies per site practice in CRS management, and should be handled as described in Table 5. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS If there is no clinical improvement within 24 to 72 hours, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab, or alternative therapies per site practice in CRS management, at 8 mg/kg (for participants weighing ≥30 kg, total dose should not exceed 800 mg) should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual
Abbreviations: AE = Adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; IV = Intravenous; NCI = National Cancer Institute.

6.5.4.6 Vascular Leak Syndrome (VLS)

Vascular leak syndrome (VLS) is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 8. These guidelines are not comprehensive and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (29).

Table 8 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted]µg/kg. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, SAR444245 should be permanently discontinued. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
	specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.5.4.7 Tumor Lysis Syndrome (TLS)

Tumor lysis laboratory tests (corrected calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase [LDH] levels) will be obtained every 8 hours on C1D1 for safety run-in participants and participants who are hospitalized, and C1D2-D3 for safety run in or participants who are hospitalized because of high tumor burden or at investigator's discretion (refer to Section 1.3 SOA for details). 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 12 of the master protocol (30).

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information.

Please refer to the master protocol for AEs and SAEs collection. For participants in Cohort A, irAEs will be collected until 3 months following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

For pembrolizumab, serious adverse events (SAEs) that are considered expected will be specified in the reference safety information (country-approved product labeling for pembrolizumab).

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse event of special interest

Please refer to the master protocol.

In addition, symptomatic or asymptomatic overdose with pembrolizumab are described as below:

- An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 PHARMACODYNAMICS

Please refer to the master protocol.

8.6 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.7 BIOMARKERS

Please refer to the master protocol.

8.8 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.9 HEALTH ECONOMICS

Please refer to the master protocol.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The study will start with a safety run-in with 6-10 participants from Cohort A. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in Cohort A.

Sample size:

The plan is to treat a total of 25 participants at the confirmed safe dose in Cohort A.

Table 9 lists estimated CRR and the corresponding 90% exact confidence interval (CI) by number of responders from a sample size of 25 participants in Cohort A.

Table 9 - Cohort A: Estimated complete response rate (CRR) depending on number of responders

Number of Responders (N=25)	Complete Response Rate in % (90% Clopper-Pearson CI)
1	4 % (0.2% - 17.6%)
3	12 % (3.4% - 28.2%)
4	16 % (5.7% - 33%)
5	20 % (8.2% - 37.5%)
6	24 % (11% - 42%)
8	32 % (17% - 50.4%)
9	36 % (20.2% - 54.4%)

With a sample size of 25 participants in Cohorts A, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2% or 5% is 22.2%, 39.7% or 72.3% respectively.

This provides reasonable assurance that events occurring at ≥ 5% frequency can be identified in this substudy.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

For Cohort A, the complete response rate (CRR) is defined as the proportion of participants who have a CR per Investigator assessment (Lugano response criteria 2014).

The BOR is the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anticancer therapy, whichever occurs first. The BOR will be summarized with descriptive statistics.

The CRR and the BOR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed for CRR from Clopper-Pearson exact method.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol for descriptions of common secondary endpoints. Substudy-specific analysis for secondary endpoints is summarized below.

9.4.3.1 Objective response rate

The ORR is defined as the proportion of participants who have a CR or partial response (PR) per Investigator assessment (Lugano response criteria 2014).

The ORR will be summarized with descriptive statistics and the corresponding two-sided 90% CIs calculated from Clopper Pearson exact method will be also presented.

9.5 INTERIM ANALYSES

Please refer to the master protocol.

The cohort cut-off for the primary endpoint analysis is estimated to be approximately 8 months from the date of the last participant's first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Please refer to the master protocol.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Please refer to the master protocol.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol, and in addition to the requirements listed in the master protocol:

France

Section 1.3 Schedule of Activities (SoA) (Section 1.3)

In France, serology for HIV will be tested at screening.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Please refer to the master protocol.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab is shown in Table 10.

Table 10 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion-related reactions are provided in Table 3.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported, but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Hepatotoxicity	Pembrolizumab Hepatitis occurred in 1.0% of patients, including Grade 2, 3 or 4 cases in 0.1%, 0.7% and 0.1% patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.8 months (range 8 days to 26.3 months). The median duration was 1.1 months (range 1 day to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 0.4% patients. Hepatitis resolved in 46 patients.	Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 6.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury.	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 6.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy. Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 6.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 6.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.
Drug-drug interactions	No data available.	

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.7

10.11 APPENDIX 11: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.12 APPENDIX 12: GUIDELINES FOR THE MANAGEMENT OF TUMOR LYSIS SYNDROME (TLS)

Please refer to the master protocol.

10.13 APPENDIX 13: ECOG PERFORMANCE STATUS AND LANSKY SCALE

Please refer to the master protocol.

10.14 APPENDIX 14: ABBREVIATIONS

AE:	adverse event
ASCT:	autologous stem cell transplantation
BOR:	best overall response
cHL:	classic Hodgkin lymphoma
COVID-19:	Corona Virus Disease 2019
CR:	complete response
CRF:	case report form
CRS:	cytokine-release syndrome
CTLA-4:	cytotoxic T-lymphocyte-associated protein 4
DLT:	dose-limiting toxicity
ICANS:	immune cell-associated neurotoxicity syndrome
IL-2:	interleukin 2
IMP:	investigational medicinal product
irAE:	immune-related adverse event
IRR:	infusion-related reaction
IV:	intravenous
NHP:	non-human primate
ORR:	objective response rate
PD1:	programmed cell death protein 1
PD-L1:	programmed cell death-ligand 1
PR:	partial response

Q3W: every 3 weeks
TIL: tumor-infiltrating lymphocyte
TRAE: treatment-related adverse event
VLS: vascular leak syndrome

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

11 REFERENCES

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Signature Page for VV-CLIN-0627903 v1.0
act16941-16-1-1-amended-protocol01-substudy-01

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 01 (SUBSTUDY 03)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) as monotherapy for the treatment of adults and adolescents with relapsed or refractory diffuse large B-cell lymphoma**
Protocol number:	**ACT16941-S03**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR444245** **(Not applicable)**
Brief title:	**A study of SAR444245 monotherapy for the treatment of adults and adolescents with DLBCL**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette,** **91380 Chilly-Mazarin,** **France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	156112
EudraCT:	2021-002150-91
NCT:	NCT05179603
WHO:	U1111-1251-5834

Date: 28-Apr-2022 Total number of pages: 58

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01 (Substudy 03)	All	28 April 2022, version 1 (electronic 1.0)
Clinical Trial Protocol (Substudy 03)		16 July 2021, version 1 (electronic 1.0)

Amended protocol 01 (28 April 2022)

This amended protocol (Amendment 01) 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 rationale for this amendment is to: (1) change the SAR444245 dosing schedule (from one injection every 21 days [21 days a cycle] to one injection every 14 days [14 days a cycle]) in order to [redacted]; and (2) in response to requests from the French Health Authority (National Agency for the Safety of Medicines and Health Products [ANSM]) after initial review.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	The NCT number has been added.	This study has been registered on clinicaltrials.gov, the NCT number is applicable.
1.1 Synopsis-Rationale, Brief summary; 2 Introduction; 4.1 Overall design	Trial participants in this study have been updated from “must have received at least 2 lines of systemic therapy and are post-CAR-T treatment” to “must have received at least 2 lines of systemic therapy and have either stable or progressive disease 1-3 months after receiving a Health	For clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
	Authority approved CAR-T therapy".	
1.1 Synopsis-Objectives and endpoints, Statistical considerations; 3 Objectives and endpoints; 9.4.3 Secondary endpoint (s)	For the secondary endpoints "[redacted] has been changed to [redacted] and [redacted] has been removed.	Program level alignment.
1.1 Synopsis-Brief summary; 4.1 Overall design	The DLT observation period for Cohort C1 has been changed from "21 days" to "28 days".	To align with the Cohort C1 Q2W dosing.
1.1 Synopsis-Study interventions	SAR444245 dosing schedule has been changed from "every 3 weeks on Day 1" to "every 2 weeks on Day 1".	[redacted]
1.2 Schema	The Graphical study design for Cohort C1 has been updated with the instruction for FDG-PET.	For clarity.
1.2 Schema, 1.3 Schedule of activities (SOA)	For the treatment period, the previous "Cycle 2-8" has been changed to "Cycle 2-16", and previous "Cycle 9-52" has been changed to "Cycle 17-52".	To align with the Cohort C1 Q2W dosing.
1.3 Schedule of activities (SOA)	D14/D15 visit has been removed for Cycle 1. The time window for D1 from Cycle 2 has been changed from 3 days to 2 days. For the treatment period, the previous "Cycle 2-8" has been changed to "Cycle 2-16".	To align with the Cohort C1 Q2W dosing.
	The assessment of troponin level has been added.	To allow assessment of any potential cardiotoxicity.
	For footnote "d", the following sentence "Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected" has been deleted.	Reduction in protocol complexity and patient/site burden.
	Footnote "e" has been newly added for clarification on C1D2, D3 visits. Other footnotes are re-numbered accordingly.	For clarity.
	For footnote "f" (previous footnote e) and footnote "h" (previous footnote g), C1D15 visit has been removed.	To align with the Cohort C1 Q2W dosing.
	For footnote "h" (previous footnote g), data collection for blood chemistry/ hematology on Day	To align with the Cohort C1 Q2W dosing.

Section # and Name	Description of Change	Brief Rationale
	1 of every cycle up to Cycle 12 has been change to “up to Cycle 24”. For footnote “i” (previous footnote h), tumor lysis laboratory tests on C1D1 have been changed from “for all participants” to “for safety run-in participants or participants who are hospitalized”.	For clarity.
1.3 Schedule of Activities (SOA), and 10.7 Appendix 7: Country-Specific Requirements	Requirement of human immunodeficiency virus (HIV) has been added at screening for participants in France and specified in SOA newly added footnote “m” and country-specific requirements sections.	Regulatory Authority (ANSM) request.
[redacted]		
1.5 Pharmacokinetic flowcharts	ADA sampling on C1D15 has been changed to C1D8.	To align with the Cohort C1 Q2W dosing.
2.2.1 Pre-clinical trials	Rationale behind changing the dosing schedule from every 21 days to every 14 days for Cohort C1 has been added. A new reference (Reference 4) has been added and the subsequent references have been renumbered.	To update [redacted] and rationale of dose changing.
5.1 Inclusion criteria	For I01 cancer diagnosis at study entry, “cytologically” has been removed from confirmed diagnosis of DLBCL.	Typographical error corrected.
5.1 Inclusion criteria	For I02 Prior anticancer therapy, “patients must have BOR of stable disease (SD) or progressive disease (PD) after a Health Authority approved CD19-directed CAR-T therapy” has been added. “If more than 3 months have passed since the CAR-T therapy the Investigator can discuss the patient on a case by case basis with the Sanofi Medical Monitor.” Has been added to the second bullet. “No other systemic anti-lymphoma therapy may have been administered between the completion of CAR-T therapy” has been changed to “… between the infusion of CAR-T therapy”.	For clarity.
5.1 Inclusion criteria	The following sentence has been added "For I04 in the master protocol, the contraception period for female participant who is a WOCBP can be during the intervention period (to be effective before	Shorten the minimum contraception period to 1 week for female participants with SAR444245 monotherapy.

Section # and Name	Description of Change	Brief Rationale
	starting the intervention) and for at least 7 days [corresponding to the time needed to eliminate any study intervention(s)] after the last dose of study intervention" to specify the contraception requirement for women who is a WOCBP for Cohort C1.	
5.2 Exclusion criteria	Specific requirement for Cohort C1 has been added for E11 related criteria in the master protocol.	To allow a participant with Grade 2 cytopenia or Grade 2 hypogammaglobinemia to be included in substudy 03.
6.1.1 Investigational medicinal product	The table for overview of IMP administered has been added without referring to the master protocol.	To align with the Cohort C1 Q2W dosing.
6.5.2 Dose delay and dose omission	The section has been updated to clarify the treatment windows within a cycle, and the dose delay and omission rules. The title of the section has been renamed as “Dose delay and dose omission” accordingly.	To align with the Cohort C1 Q2W dosing.
1.4 Biomarker flowchart, 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS); 6.5.4.4 Immune cell-associated neurotoxicity syndrome (ICANS)	The following statement “alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following tocilizumab availability.
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 4, the following sentence has been deleted [redacted]	For consistency with instructions given in Section 6.5.1 General rules. Regulatory Authority (ANSM) request.
6.5.4.6 Tumor Lysis Syndrome (TLS)	Tumor lysis laboratory tests on C1D1 have been changed from “for all participants” to “for safety run-in participants or participants who are hospitalized”.	For clarity and consistency.
9.4.4 Exploratory endpoint(s)	Section has been newly added with subsection of [redacted].	For consistency.
10.1.6 Dissemination of clinical study data	The following sentence has been added “Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study”.	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials.
10.8 Appendix 8: Criteria for response	Reference to master protocol has been deleted and Table 8 - Overall disease response has been	For clarity.

Section # and Name	Description of Change	Brief Rationale
assessment response was added	added.	
Throughout	The duration for each cycle has been changed from “21 days” to “14 days”. The total number of cycles has been changed from “35 cycles” to “52 cycles”.	To align with the Cohort C1 Q2W dosing.
Throughout	“Study Committee” has been changed to “Study Board”.	Harmonization per Sanofi standard terminology.
Throughout	Minor editorial updates.	For clarity and consistency.

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) as monotherapy for the treatment of adults and adolescents with relapsed or refractory diffuse large B-cell lymphoma

Brief title: A study of SAR444245 monotherapy for the treatment of adults and adolescents with DLBCL

Rationale:

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 as monotherapy in trial participants with diffuse large B-cell lymphoma (DLBCL). Trial participants in this study must have received at least 2 lines of systemic therapy and have either stable or progressive disease 1-3 months after receiving a Health Authority approved CAR-T therapy.

Objectives and endpoints

Please refer to the master protocol for descriptions of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245.	• Objective response rate (ORR) defined as the proportion of participants who have complete response (CR) or partial response (PR) determined by Investigator per Lugano response criteria 2014 (1).
Secondary	
• To assess other indicators of antitumor activity.	• Complete response rate (CRR) defined as the proportion of participants who have a CR determined by Investigator per Lugano response criteria 2014 (1).

Overall design:

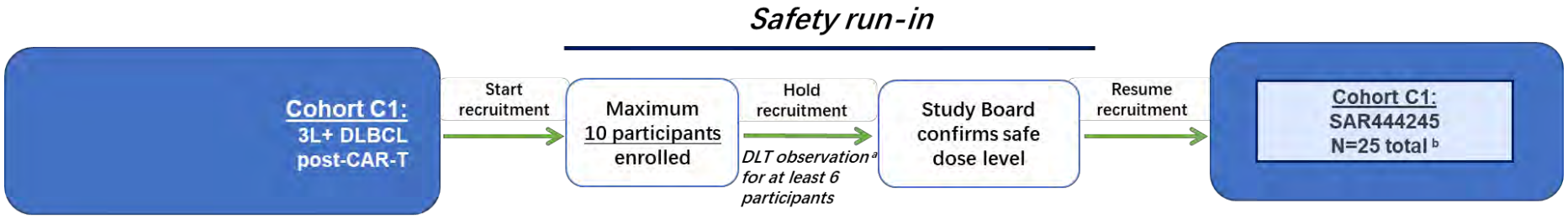
Please refer to the master protocol.

Brief summary:

Cohort C1: This substudy will include approximately 25 participants with DLBCL who have received at least 2 lines of systemic therapy and have either stable or progressive disease 1-3 months after receiving a Health Authority approved CAR-T therapy. The substudy will assess SAR444245 monotherapy as at least 3rd line of therapy.

A graphical presentation of the substudy schema is shown in Figure 1.

Figure 1 - Overall study schema



a The DLT observation period is 28 days for Cohort C1.
b Including participants enrolled in the safety run-in at the confirmed safe dose.

Abbreviations: 3L: third-line; CAR-T: chimeric antigen receptor T-cell immunotherapy; DLBCL: diffuse large B cell lymphoma; DLT: dose-limiting toxicities; N: number.

Number of participants:

Overall, 25 participants will be treated in Cohort C1.

Intervention groups and duration:

Please refer to the master protocol for common descriptions of the study duration. For Cohort C1, the maximum cycles allowed are 52 cycles.

Study interventions

Cohort C1: DLBCL participants with stable disease or progressive disease 1-3 months after receiving a Health Authority approved CAR-T as at least 3L therapy

Dosing sequence: premedication for SAR444245 (30 to 60 minutes prior to start of SAR444245 infusion), and SAR444245.

Investigational medicinal products

SAR444245

SAR444245 formulation and route of administration as described in the master protocol.

- Dose regimen: 24 µg/kg administered (or reduced to ■ µg/kg or another lower dose level recommended by Study Board) as an IV infusion over 30 minutes every 2 weeks on Day 1 of each cycle (14 days per cycle) for **up to 52 cycles**.

Non-investigational medicinal products

Please refer to the master protocol.

Statistical considerations:

Please refer to the master protocol for descriptions of common statistical considerations. Substudy-specific analyses are summarized below.

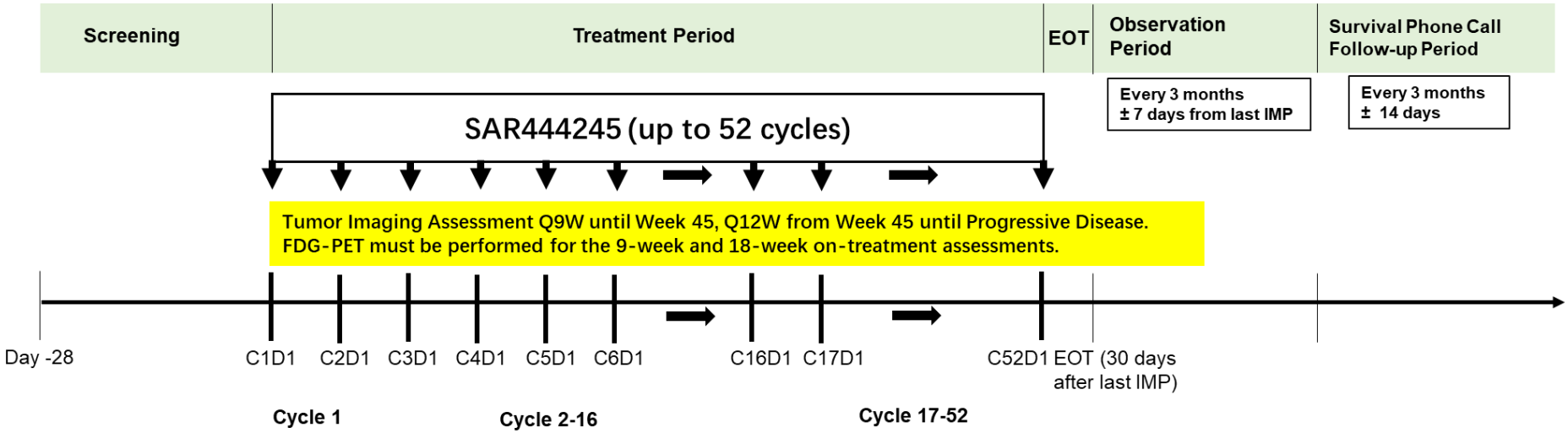
- **Analysis of primary endpoint:**
  - The objective response rate (ORR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for ORR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The complete response rate (CRR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% CIs for CRR will be computed using the Clopper-Pearson method.

Data Monitoring/Other Committee: Yes

1.2 SCHEMA

1.2.1 Study design for Cohort C1

Figure 2 - Graphical study design-Cohort C1



C=Study cycle (1 cycle = 14 days); D=Study Day; EOT=end of treatment; IMP=Investigational medicinal product; FDG-PET=fluorodeoxyglucose-positron emission tomography; Q9W=every 9 weeks; Q12W=every 12 weeks.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16				Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)		30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Informed consent	X																
Inclusion/ Exclusion criteria	X																
IRT contact	X	X					X			X		X					
Demography, medical/surgical and disease history	X																See Section 8 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Performance status (ECOG or Lansky Scale)	X	X					X	X		X	X	X				See Appendix 13 in the master protocol
Body weight/Height[g]	X	X					X			X						
Full physical examination	X										X					
Directed physical examination		X			X		X			X		X				See Section 8.2.1 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16				Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8			D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Vital signs[h]	X	X	X	X	X		X	X			X	X	X				See Section 8.2.2 in the master protocol
SpO_2[h]	X	As clinically indicated															
Bone marrow biopsy		As clinically indicated to confirm complete response															See Section 8.1 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Spleen measurement	X	As clinically indicated to evaluate response														See Section 8.1 in the master protocol
12-Lead ECG	X	As clinically indicated														See Section 8.2.3 in the master protocol
LVEF	X	As clinically indicated														See Section 8.2.3 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)		30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Troponin	X	As clinically indicated					X (Cycle 4 Day 1)			As clinically indicated						See Section 8.2.3 and Section 10.2 in the master protocol
Pregnancy test	X	X					X			X	X	X	X			See Section 8.2.5 and Section 10.2 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16				Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)		30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Blood chemistry[h]	X	X	X	X	X		X			X		X	X				See Section 10.2 in the master protocol
Tumor Lysis Laboratory Tests[i]		X	X	X													
Hematology[h]	X	X	X	X	X		X			X		X	X				
T3, FT4, TSH and cortisol[j]	X						X			X		X	X				See Section 10.2 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Coagulation[k]	X	As clinically indicated										X				See Section 10.2 in the master protocol
Urinalysis[l]	X	On C1D1 and C2D1, then as clinically indicated										X				See Section 10.2 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Hepatitis serology, CD4+ counts and viral load	X[m]	As clinically indicated														See Section 10.2 in the master protocol
IMP		X					X			X						
Hospitalization[o]		X	X	X												
AE/SAE assessment[p]	X	Continuous throughout treatment period										X				See Section 8.3 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Prior/Concomitant Meds	X[n]	Continuous throughout treatment period														See Section 6.8 in the master protocol
First subsequent anti-cancer therapy											X	X	X	X		
Survival status															X	
Pharmacokinetic (PK) / Pharmacodynamic (PD) / Immunogenicity assessments																
PK	See PK Flow-Charts in Section 1.5															
ADA																

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
PDy - Blood and tumor tissue collection[r]	See Biomarker Flow-Chart in Section 1.4															
Tumor assessment																
CT/MRI[q]	X						X			X	X	X	X	X	X	See Section 8.1.1 in the master protocol

Evaluation[a]	Screening	Treatment Period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Cycle 1					Cycle 2-16			Cycle 17 – 52	EOT visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3 and beyond	Phone call Follow-up	
Cycle day	D-28 to D-1	D 1	D 2[e]	D 3[e]	D 8[f]		D1(± 2 days)	D 8		D1(± 2 days)	30 (±7) days after last IMP admin or prior to initiation of further therapy	3 months (±7 days) after last IMP admin	6 months (±7 days) after last IMP admin	Every 3 months ±7 days	Every 3 months ±14 days	
Brain imaging[s]	If clinically indicated															See Section 8.1.1 in the master protocol
FDG-PET[q]	X	As clinically indicated, and must be performed for the 9-week and 18-week on-treatment assessments														See Section 8.1.1 in the master protocol

a Evaluation: Screening assessments to be performed prior to first IMP administration unless otherwise indicated. Baseline evaluations should be completed within 7 days prior to the first dose of IMP, except for tumor assessment that may be performed within 28 days prior to IMP administration, and unless specified otherwise. There is no need to perform Cycle 1 Day 1 laboratory assessments that have been performed as part of screening within 3 days prior to first IMP administration. During the study treatment period, all assessments must be performed, and results should be reviewed by the investigator **prior to IMP administration** at that visit. After Cycle 1, samples for laboratory assessments (excluding PK & biomarker) can be collected up to 2 days prior to IMP administration. ICF must be signed before any study-specific procedures are performed and can be signed more than 28 days prior to first IMP administration. Screening time indicates the maximum time frame relative to the first IMP administration in which study procedures used to support eligibility are done.

b Cycle: A treatment cycle is 14 days. See details in Section 6.1 for IMP administration. If treatment cycles are adjusted, all procedures except tumor assessment imaging will be completed according to the Cycle number. Tumor assessment imaging will be performed at fixed time points from C1D1 regardless of any treatment delays.

c Observation Period: Participants who enter the Observation period will be followed differently depending on the reason leading to permanent study treatment discontinuation. See Section 4.1 of the master protocol. For participant's convenience, all Follow-up assessments may occur during the same visit as that when tumor assessment is performed.

d Survival Phone Call Follow-Up Period: Once the participant stops the tumor assessments due to PD or starts a new antineoplastic therapy, the participant moves into the Survival Follow-up Period and should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the study.

e Visits on C1D2, D3 are for safety-run in participants only.

f C1D8 visit must be performed on site only for participants enrolled in the Safety run-in and participants scheduled to have blood draws for biomarker assessment on Day 8. For all other participants, this on-site visit may be done remotely as appropriate based on Investigator's discretion per institutional standard and local regulations. If this is the case, this must be documented in the source document. Study Board may decide to cancel safety assessment on C1D8, upon agreement with Sponsor, if safety data justify it.

g Weight/Height: Height is required at baseline only for patients > or =18 years old. For trial participants <18 years old, height should be assessed on day 1+/-1 of each cycle. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

h Blood chemistry/ hematology will be performed weekly on D1 pre-dose and D8 during Cycle 1, then on Day 1 of every cycle up to Cycle 24, then every other cycle during Treatment Phase. Visits and assessments on C1D2-D3 are only for participants in the safety run-in or participants who are hospitalized because of high tumor burden or at investigator's discretion. For these participants, vital signs, SpO_2 and complete blood counts (CBC) and differentials, chemistries (blood urea nitrogen (BUN), creatinine (Cr), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (Alk Phos), total bilirubin (TBil) will be obtained daily.

i Tumor lysis laboratory tests (corrected calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase [LDH] levels) will be obtained every 8 hours on C1D1 for safety run-in participants or participants who are hospitalized, and C1D2-D3 for safety run in or participants who are hospitalized because of high tumor burden or at Investigator's discretion.

j Endocrine function tests will be performed every 2 cycles throughout the entire treatment period and at EOT. During the Observation Period, they will be performed at Follow-Up Visit 1. They can also be performed as clinically indicated.

k Coagulation includes international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT).

l Urinalysis will be performed on C1D1 and C2D1, then as clinically indicated during the treatment period, and will be performed at Follow-Up Visit 1.

m For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in France (see details and specific instructions in Section 10.2 and Section 10.7 in the master protocol, and Section 10.6 in this substudy 03).

n Prior medications that are received within 30 days before the first dose of IMP.

o Hospitalization for 48 h for safety run-in participants or for participants with a high tumor burden or at investigator's discretion.

p AE/SAE assessment: Severity will be graded according to NCI-CTCAE v 5. ICANS and CRS will be graded using ASTCT criteria integrated with central laboratory cytokine results (2).

q The initial tumor imaging FDG-PET CT and/or MRI will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP and if clinically indicated. FDG-PET must be performed for the 9-week and 18-week on-treatment assessments. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the chest, abdomen, pelvis and any other locations with suspicion or evidence of disease involvement is required for the baseline and follow-up assessments.

r If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Tumor biopsy should be considered for new lesions if their pathologic etiology is ambiguous.

s Brain CT/MRI: To be performed if clinically indicated.

Abbreviations: ADA = Anti-drug antibodies; AE = Adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; C = Cycle; CT = Computed tomography; D = Day; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End-of-treatment; FDG-PET = fluorodeoxyglucose-positron emission tomography; FT4 = Free thyroxine; FU = Follow-up visit; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICF = Informed consent form; IMP = Investigational medicinal product; LVEF = Left ventricular ejection fraction; MRI = Magnetic resonance imaging; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = Progressive disease; PDy = Pharmacodynamic; PK = Pharmacokinetic; Q2W = Every 2 weeks; SAE = Serious adverse event; TSH = Thyroid stimulating hormone.

1.5 PHARMACOKINETIC FLOWCHARTS

Cycle	Treatment Cycle 1						Treatment Cycle 2, 4, 7, 10 + every 5th cycle		EOT visit
Day	**D1**			**D2**	**D3**	**D8**	**D1**		**30 (±7) days after last IMP administration**
Time after start of SAR444245 dosing [h]	SOI	EOI	4h post EOI	At any time	At any time	At any time	SOI	EOI	At any time
SAR444245 PK sample		P00[b]	P01	P02[c]	P03[c]			P00[b]	
SAR444245 ADA sample	AB00[a]					AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI). ADA sampling may be discontinued by the Sponsor once sufficient data have been collected.
b PK sample must be taken at the end of infusion (EOI) after flush.
c P02 and P03 to be collected during safety run-in and when participants are hospitalized.
In the event the infusion is interrupted, a PK sample should be drawn immediately after interruption. If infusion is not likely to be resumed by clinical assessment, subsequent samples should be drawn at 4 h after interruption. If infusion is resumed, a (further) PK sample should be drawn at end of resumed infusion and subsequent sample should be drawn at 0.5 h after end of resumed infusion. PK sampling may be discontinued by the Sponsor once sufficient data have been collected.

Abbreviations: ADA: anti-drug antibodies; D: day; EOT: end of treatment; PK: pharmacokinetic.

2 INTRODUCTION

Study ACT16941 is developed as a master protocol in order to accelerate the investigation of SAR444245 with or without various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort C1 (participants with DLBCL who have received at least 2 lines of systemic therapy and have either stable or progressive disease 1-3 months after receiving a Health Authority approved CAR-T therapy) for SAR444245 monotherapy.

Please refer to the master protocol for an introduction for ACT16941.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models. Furthermore, recombinant IL-2 has been shown to enhance T cell activation and proliferation. For these reasons, [redacted].

2.2 BACKGROUND

2.2.1 Pre-clinical trials

Additional preclinical studies support the role of IL-2 in promoting engineered T cells to eliminate tumors and demonstrate enhancement of antibody drug-dependent cellular cytotoxicity (ADCC). Studies in mouse models demonstrate that recombinant IL-2 (NKTR-214), given as a single agent, expands adoptively transferred T cells (engineered with TCR targeting murine melanoma antigen, p100) leading to a reduction in melanoma tumor burden in a mouse model (3).

[redacted]Based on these observations in vitro, as well on the previously reported results from pembrolizumab for B-cell lymphomas refractory or relapsed (BCL R/R) to CD19-directed CAR-T therapy (4),[redacted]

2.2.2 Rationale for B cell lymphoma and selected participant population

Please refer to Section 2.2.1 of the master protocol.

2.2.3 Current standard of care in DLBCL

At diagnosis, patients usually receive multiagent chemoimmunotherapy including an anthracycline, rituximab, and prednisone (eg, R-CHOP, dose adjusted R-EPOCH, or R-ICE) with or without radiotherapy. For refractory disease, or at first relapse, transplant-eligible patients are referred for autologous stem cell transplant. Transplant-ineligible patients will be offered rituximab containing combinations, such as RGemOx or the recently approved combinations: polatuzumab vedotin (Polivy)+bendamustine+rituximab or rituximab+tafasitamab (Monjuvi), or are offered participation in a clinical trial. Eligible patients with relapsed or refractory disease, following two or more lines of therapy, are offered CD19-directed CAR-T cell therapy, (eg. tisagenlecleucel [Yescarta], axicatbtagene ciloleucel [Kymriah], or lisocabtagene maraleucel [Breyanzi]), selinexor (Xpovio), or autologous or allogeneic stem cell transplantation, or enrollment in a clinical trial (5).

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SAR444245 may be found in the Investigator's Brochure.

2.3.1 Risk assessment

Please refer to the master protocol.

2.3.2 Benefit assessment

Please refer to the master protocol.

The regimen proposed to be evaluated in this substudy is anticipated to bring benefit to patients with DLBCL post CAR-T.

2.3.3 Overall benefit: risk conclusion

Please refer to the master protocol.

2.3.4 Benefits and risks assessment in the context of COVID-19 pandemic

Please refer to the master protocol.

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for descriptions of common objectives and endpoints. Substudy-specific objectives and endpoints are summarized below.

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245.	• Objective response rate (ORR) defined as the proportion of participants who have complete response (CR) or partial response (PR) determined by Investigator per Lugano response criteria 2014 (1).
Secondary	
• To assess other indicators of antitumor activity.	• Complete response rate (CRR) defined as the proportion of participants who have a CR determined by Investigator per Lugano response criteria 2014 (1).
Exploratory	
[redacted]	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include approximately 25 participants with diffuse large B cell lymphoma (DLBCL) who have received at least 2 lines of systemic therapy and have either stable or progressive disease 1-3 months after receiving a Health Authority approved CAR-T therapy. The substudy will assess SAR444245 monotherapy as at least 3rd line of therapy.

Please refer to the master protocol for a full description of the study design, and for details applicable to all therapy cohorts.

A graphical presentation of the study schema is shown in Figure 1.

The dose-limiting toxicity (DLT) observation period is 28 days for Cohort C1. The maximum cycles allowed in this substudy for Cohort C1 are 52 cycles.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 as monotherapy in trial participants with DLBCL.

The design of the study is a non-randomized study where the monotherapy will be assessed in a single cohort, using historical data for single agent as a benchmark to show outstanding objective response rate. The ORR will be assessed using Lugano response criteria 2014 for participants with DLBCL.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

Please refer to the master protocol.

4.3 JUSTIFICATION FOR DOSE

Please refer to the master protocol.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort C1 specific criteria.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply (in addition to the criteria listed in the master protocol):

Type of participant and disease characteristics

I 01. Cancer diagnosis at study entry:

Histologically confirmed diagnosis of diffuse large B Cell lymphoma (DLBCL), according to the WHO 2016 classification.

I 02. Prior anticancer therapy:

- Must have received at least two prior lines of systemic therapy for DLBCL, including one containing a combination of anthracycline and rituximab (or another anti-CD20 agent), with the last line of therapy a Health Authority approved CD19-directed CAR-T therapy.
    - Patients must have BOR of stable disease (SD) or progressive disease (PD) after a Health Authority approved CD19-directed CAR-T therapy.
    - 1 to 3 months must have passed between the administration of the Health Authority approved CAR-T therapy and start of treatment in this trial. If more than 3 months have passed since the CAR-T therapy the Investigator can discuss the patient on a case by case basis with the Sanofi Medical Monitor.
    - No other systemic anti-lymphoma therapy may have been administered between the infusion of CAR-T therapy and enrollment in the trial.
    - All CAR-T related adverse events must have resolved to grade 1 or less, and participant must meet all other eligibility criteria.
- May have received a prior autologous or allogeneic stem cell transplant but must be at least ≥100 days post-auto-transplant, and all transplant- related adverse events must have resolved to grade 1 or less, and meet all other eligibility criteria.

Sex, contraceptive/barrier method and pregnancy testing requirements

For I04 in the master protocol, the contraception period for female participant who is a WOCBP can be during the intervention period (to be effective before starting the intervention) and for at least 7 days [corresponding to the time needed to eliminate any study intervention(s)] after the last dose of study intervention.

5.2 EXCLUSION CRITERIA

Please refer to the master protocol.

Due to the nature of the disease and prior treatment, a participant with Grade 2 cytopenia or Grade 2 hypogammaglobinemia, who should be excluded per E11 in the master protocol, will be allowed to be included.

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/ADMINISTRATION OF STUDY INTERVENTION

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

The maximum cycles allowed in this substudy for Cohort C1 are 52 cycles.

Dosing sequence: premedication for SAR444245 (30 to 60 minutes prior to start of SAR444245 infusion), and SAR444245.

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245 administered as described in Section 4.1 of the master protocol. Details of are shown in Table 2.

Preparation and administration of IMP are detailed in the pharmacy manual. Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 2 - Overview of IMP administered

Intervention name	**SAR444245**
Type	Biologic
Dose formulation	Concentrate for solution for infusion
Unit dose strength(s)	2.0 mg/mL
Dosage level(s)[a]	24 µg/kg (or reduced to ■ µg/kg or another lower dose level recommended by Study Board) Q2W
Route of administration	IV infusion
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Supplied in a single-dose vial in a treatment box. Each vial contains 2 mg/mL with an extractable volume of 1 mL. Each vial and treatment box will be labeled as required per country requirement.
Current/Former name(s) or alias(es)	NA

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the e-CRF. Study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted.

6.1.2 Non-investigational medicinal products

Please refer to the master protocol.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modification for SAR444245 is permitted according to the guidelines described in this section.

Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor, unless required for immediate participant safety.

Cycle delay (ie, Day 1 should be delayed for the IMP) is permitted in case of treatment-emergent adverse event (TEAE). Dose modification will be made according to the worst grade of toxicity observed within a cycle. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment should be followed. Once a dose has been decreased, intra-patient re-escalation back to the previous dose level is not permitted.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other TEAE that, in the opinion of the Investigator, warrants discontinuation.

All changes to study treatment administration must be recorded in the electronic case report form (e-CRF).

6.5.2 Dose delay and dose omission

Within a cycle, the treatment windows are:

- For the Q2W administration, the C_{n+1} (±2 days), dose is deemed to have been delayed if the treatment is ≥3 days beyond the theoretical day of treatment.
- The reason for the dose delay will be captured. If the reason for the dose delay is an adverse event, the participant will receive the next infusion after recovery of the AE as described in Section 6.5.2 and Section 6.5.3

Participants may have dose omission if an AE occurs and does not recover according to following rules:

- If an AE occurs and the participant does not recover on the day of planned infusion or within the following 2 days, infusion of SAR444245 may be omitted for participants.
- In case of consecutive dose omissions/delay for the recovery of AE, the following rules should be followed for restart or discontinuation of the treatment:
  - Dose delay (cycle delay) up to 9 days, it is per Investigator's decision to restart the study treatment.
  - After dose delay of >9 days and ≤84 days, it is per Investigator's decision to restart the study treatment, if a clear benefit from treatment is observed and after consultation with the Sponsor.
  - Treatment must be permanently discontinued if the delay is longer than 84 days.

Cycle may be delayed for situations other than TEAEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 14 days of the scheduled delay, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for this delay should be documented in the participant's study record.

6.5.3 General guidelines for the management of treatment-related adverse events

Participants who experience Grade ≥3 treatment-related adverse events (TRAEs) at any time of the study (including clinically significant Grade 3 laboratory abnormalities as defined in Section 10.3.1 of the master protocol) will be required to cycle delay the IMP, unless specified otherwise in the protocol, and with the exception of the TRAEs resolving within 5 days. After cycle delay, such participants may be considered for treatment resumption once the TRAE resolves or improves to Grade 1 or baseline or is stable and manageable through supportive/medical therapy.

Treatment resumption is at the discretion of the Investigator and Sponsor, if thought to be in the best interest of the participant, except when specified otherwise in this protocol, or if the event has required the IMP temporary withheld for more than 84 days from the last scheduled dose.

The cycle delay of treatment for Grade 2 events is left at the discretion of the Investigator unless otherwise specified in this protocol.

No cycle delay of treatment or dose modification is required for Grade 1 events.

Dose reduction for SAR444245 from [redacted] µg/kg to [redacted] µg/kg (or another lower dose level recommended by Study Board) may be decided when specified in the protocol or following discussions with the Sponsor.

The final decision on dose modification and/or corrective therapy will be based on the Investigator's judgment, in the best interest of the participant.

Recommended guidelines for the management of specific adverse events including irAE, CRS, vascular leak syndrome (VLS) and IRR are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

Specific adverse events described in sections below may classify as adverse events of special interests (AESIs), depending on grading according to National Cancer Institute- Common Terminology Criteria for Adverse Event (NCI-CTCAE) V5.0 (see Section 8.3.8 of the master protocol). In case a specific adverse event meets the AESI definition it must be documented in the electronic case report form (e-CRF).

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol, prior to SAR444245 administration, to prevent or reduce the incidence or severity of IRRs.

An infusion-related reaction (IRR) in this study is defined as any signs or symptoms which develop during the infusion or up to 24 hours after the completion of the infusion. The term IRR indicates only a specific temporal relationship with the infusion and does not specify a particular mechanism underlying the signs or symptoms.

Guidelines for the management of SAR444245 IRR events are provided in Table 3. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 3 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE definition. If IRR happens after completion of infusion, increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	SAR444245 infusion should be interrupted if applicable. If symptoms resolve within 1 hour of interrupting drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. The next infusion should be given at half the infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be prematurely permanently discontinued. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; pressor or ventilator support indicated	SAR444245 infusion should be interrupted if applicable. If IRR is clearly attributable to SAR444245, SAR444245 should be prematurely permanently discontinued. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b In cases of anaphylaxis, epinephrine should be used immediately

Abbreviations: CTCAE = Common terminology criteria for adverse events; IRR = Infusion-related reaction; NCI = National Cancer Institute; NSAIDs: nonsteroidal anti-inflammatory drugs.

6.5.4.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of SAR444245 being administered.

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines) (6, 7, 8).

6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)

Fever can frequently happen with infusion of IL-2 and may possibly evolve into flu-like symptoms or could be an early manifestation of CRS. Fever or flu-like symptoms should be graded according to CTCAE V5.0 and managed according to institutional standards.

Cytokine-release syndrome (CRS) should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 4. If any grade of CRS is suspected, sites should make every efforts to draw an additional blood sample for cytokines levels (by central laboratory), prior to the administration of tocilizumab, as well as for C-reactive protein (CRP) and ferritin (by local laboratory).

Sites should have at least 2 full doses of tocilizumab available, or alternative therapies per site practice in CRS management, and access to an intensive care unit (ICU), in case participants develop CRS.

Guidelines for management of CRS according to severity grading are provided in Table 4. ASTCT CRS consensus grading scale is provided in Section 10.11 of the master protocol.

Table 4 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a]. Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interruption of SAR444245, if event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
	For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. SAR444245 may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 3, SAR444245 should be temporarily withheld, and subsequent treatment should be resumed only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated. If CRS Grade 4, SAR444245 should be permanently discontinued, as clinically indicated. If CRS Grade 3 or Grade 4, IV corticosteroids should be initiated (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management should be considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed. CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS. If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants weighing ≥30 kg), or alternative therapies per site practice in CRS management, should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension, fever and other manifestations is observed after the first dose of tocilizumab, or alternative therapies per site practice in CRS management, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab or alternative therapies per site practice in CRS management and steroids, alternative options should be discussed with clinical site specialists

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

b Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or alternative therapies per site practice in CRS management or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

d Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Abbreviations: AE = Adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP= Bilevel Positive Airway Pressure; CPAP= Continuous Positive Airway Pressure; CRS= cytokine release syndrome; ICU=intensive care unit; IL = Interleukin; IMP=investigational medicinal product; IV = Intravenous; NSAIDs=Non-steroidal anti-inflammatory drugs.

6.5.4.4 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.11 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab, or alternative therapies per site practice in CRS management, should only be used in the context of CRS, as outlined in Table 5. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 5 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	SAR444245[a] should be delayed. Treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention. Grade 4	If Grade 3 ICANS, SAR444245 should be delayed. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. If Grade 4 ICANS, SAR444245 should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	may require tocilizumab, or alternative therapies per site practice in CRS management, and should be handled as described in Table 4. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS If there is no clinical improvement within 24 to 72 hours, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants weighing ≥30 kg, total dose should not exceed 800 mg) or alternative therapies per site practice in CRS management, should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant clinical specialists should be involved whenever indicated.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual
Abbreviations: AE = Adverse event; ASTCT=American Society for Transplantation and Cellular Therapy; CRS= cytokine release syndrome; IV = Intravenous; NCI = National Cancer Institute.

6.5.4.5 Vascular Leak Syndrome (VLS)

Vascular leak syndrome (VLS) is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 6. These guidelines are not comprehensive, and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (9).

Table 6 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	SAR444245 should be delayed. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, SAR444245 should be permanently discontinued. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.

Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.5.4.6 Tumor Lysis Syndrome (TLS)

Tumor lysis laboratory tests (corrected calcium, magnesium, phosphate, uric acid, and lactate dehydrogenase [LDH] levels) will be obtained every 8 hours on C1D1 for safety run-in participants and participants who are hospitalized, and C1D2-D3 for safety run in or participants who are hospitalized because of high tumor burden or at Investigator's discretion (refer to Section 1.3 SOA for details). 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 12 of the master protocol (10).

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for definition and treatment of SAR444245 overdose.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

Please refer to the master protocol.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 PHARMACODYNAMICS

Please refer to the master protocol.

8.6 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.7 BIOMARKERS

[redacted]

[redacted]

8.8 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.9 HEALTH ECONOMICS

Please refer to the master protocol.

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

The study will start with a safety run-in with 6-10 participants from Cohort C1. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants in Cohort C1.

Sample size:

The plan is to treat a total of 25 participants at the confirmed safe dose in Cohort C1.

Table 7 lists estimated ORR and the corresponding 90% exact confidence interval (CI) by number of responders from a sample size of 25 participants in Cohort C1.

Table 7 - Cohort C1: Estimated objective response rate (ORR) depending on number of responders

Number of Responders (N=25)	Objective Response Rate in % (90% Clopper-Pearson CI)
1	4 % (0.2% - 17.6%)
3	12 % (3.4% - 28.2%)
4	16 % (5.7% - 33%)
5	20 % (8.2% - 37.5%)
6	24 % (11% - 42%)
8	32 % (17% - 50.4%)
9	36 % (20.2% - 54.4%)

With a sample size of 25 participants in Cohort C1, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2% or 5% is 22.2%, 39.7% or 72.3% respectively.

This provides reasonable assurance that events occurring at ≥ 5% frequency can be identified in this substudy.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

For Cohort C1**,** objective response rate (ORR) is defined as the proportion of participants who have a CR or PR per Investigator assessment (Lugano response criteria 2014).

The BOR is the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anticancer therapy, whichever occurs first. The BOR will be summarized with descriptive statistics.

The ORR and BOR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed for ORR from Clopper-Pearson exact method.

9.4.3 Secondary endpoint(s)

Please refer to the master protocol for descriptions of common secondary endpoints. Substudy-specific analyses for secondary endpoints are summarized below.

9.4.3.1 Complete response rate (CRR)

The CRR is defined as the proportion of participants who have a CR per Investigator assessment (Lugano response criteria 2014).

The CRR will be summarized with descriptive statistics. In addition, two-sided 90% CIs will be computed for CRR from Clopper Pearson exact method.

9.4.4 Exploratory endpoint(s)

[redacted]

[redacted]

9.5 INTERIM ANALYSES

Please refer to the master protocol.

The cohort cut-off for the primary endpoint analysis is estimated to be approximately 8 months from the date of the last participant's first infusion. This would allow the possibility to observe the response of the last participant for 6 months, assuming there is a response at first treatment assessment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

Please refer to the master protocol.

10.1.2 Financial disclosure

Please refer to the master protocol.

10.1.3 Informed consent process

Please refer to the master protocol.

10.1.4 Data protection

Please refer to the master protocol.

10.1.5 Committees structure

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

Please refer to the master protocol.

Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study.

10.1.7 Data quality assurance

Please refer to the master protocol.

10.1.8 Source documents

Please refer to the master protocol.

10.1.9 Study and site start and closure

Please refer to the master protocol.

10.1.10 Publication policy

Please refer to the master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Please refer to the master protocol.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Please refer to the master protocol.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol, and in addition to the requirements listed in the master protocol:

France

Section 1.3 **Schedule of Activities (SoA)** (Section 1.3)

In France, serology for HIV will be tested at screening.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Overall disease response for Cohort C1 is provided in Table 8.

Table 8 – Overall disease response

Overall raiological response	Bone marrow biopsy/aspirate	Clinical findings	Overall disease response
CR/PR/SD	Negative at baseline or negative ± 28 days from assessment	Any except new or recurrent lymphoma involvement	CR/PR/SD
CR	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR
PR/SD	Positive at baseline and either positive (without new or recurrent involvement) or not done ± 28 days from assessment	Any except new or recurrent lymphoma involvement	PR/SD
PD	Any	Any	PD
Any	New or recurrent involvement	Any	PD
Any	Any	New or recurrent lymphoma involvement	PD

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

Please refer to the master protocol.

10.11 APPENDIX 11: ASTCT ASSESSMENT FOR ICANS AND CRS

Please refer to the master protocol.

10.12 APPENDIX 12: GUIDELINES FOR THE MANAGEMENT OF TUMOR LYSIS SYNDROME (TLS)

Please refer to the master protocol.

10.13 APPENDIX 13: ECOG PERFORMANCE STATUS AND LANSKY SCALE

Please refer to the master protocol.

10.14 APPENDIX 14: ABBREVIATIONS

ADCC:	antibody drug-dependent cellular cytotoxicity
BOR:	best overall response
CAR-T:	chimeric antigen receptor T-cell immunotherapy
CRF:	case report form
CRR:	complete response rate
CRS:	cytokine-release syndrome
DLBCL:	diffuse large B-cell lymphoma
DLT:	dose-limiting toxicity
ICANS:	immune cell-associated neurotoxicity syndrome
IMP:	investigational medicinal product
IRR:	infusion-related reaction
ORR:	objective response rate
PR:	partial response
TRAE:	treatment-related adverse event
VLS:	vascular leak syndrome

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

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Approve & eSign	[redacted] Clinical [redacted]

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