STATISTICAL ANALYSIS PLAN

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**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Study phase:	**Phase 2**
Short 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 (Pegathor Lymphoma 205)**
Statistician:	[redacted] **(contractor, IT&M Stats)**
Statistical project leader:	[redacted]
Date of issue:	**07-Dec-2022**
Regulatory agency identifier number(s):	
IND:	156112
EudraCT:	2021-002150-91
NCT:	NCT05179603
WHO:	U1111-1251-5834

Date: 07-Dec-2022 Total number of pages: 42

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan (SAP) for study ACT16941 is the first version and based on the amended protocol 01 dated 28-Apr-2022. This section summarizes the major changes to the statistical analysis features in the SAP

The first participant was enrolled on 20-Dec-2021. This SAP is approved before the first interim analysis is conducted.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale	Change from
1	Current version	Estimand framework has been added for the primary and main secondary efficacy endpoints.	To further characterize the antitumor activity effect that will be estimated.	Protocol amendment 02

1 INTRODUCTION

Major changes to the protocol-planned analyses are described in Section 3.9.

1.1 STUDY 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.

After a screening period of up to 28 days, participants who fulfill eligibility criteria of any cohort will be enrolled to the safety run-in of that cohort depending on the type of lymphoma and the number of prior lines therapy:

- **Cohort A (3L/4L cHL)** will include 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.
- Cohort C1 (3L DLBCL post-CAR-T) will include 25 participants with diffuse large B cell lymphoma (DLBCL) who have received at least 2 lines of systemic therapy and are post-CAR-T and will assess SAR444245 monotherapy regimen as at least 3rd line of therapy.

A safety run-in will confirm the dose of SAR444245 in each cohort. The dose confirmation will proceed using Modified Toxicity Probability Interval Design (mTPI-2 design, Guo et al 2017 (1)) 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 at least 6 participants are evaluable for dose limited toxicity (DLT)in a specific cohort, safety data for these participants will be reviewed by the Study Board. DLT-evaluable participants include all participants in the safety run-in part who have been observed for the DLT observation period (defined in the individual cohort). 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. 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.

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 with or without other anticancer therapies	• **Cohort A**: 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) • **Cohort C1:** 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
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), DLTs, serious adverse events (SAEs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0.
• To assess other indicators of antitumor activity	• **Cohort A**: ORR defined as the proportion of participants who have CR or partial response (PR) determined by Investigator per Lugano response criteria 2014 • **Cohort C1:** CRR defined as the proportion of participants who have a CR determined by Investigator per Lugano response criteria 2014 • Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR determined by Investigator per Lugano response criteria 2014. • Duration of response (DoR) defined as the time from first tumor assessment at which the overall response was recorded as PR or CR until progressive disease (PD) determined by Investigator per Lugano response criteria 2014, 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. • 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 or death due to any cause, whichever occurs first.
• To assess the plasma concentrations of SAR444245 when given with or without other anticancer therapies.	• Concentration of SAR444245
• To assess the immunogenicity of SAR444245.	• Incidence of anti-drug antibodies (ADAs) against SAR444245
Tertiary/exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 3. More details are provided in Section 3.

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To determine the antitumor activity of SAR444245 with or without other anticancer therapies				
Cohort A				
Primary endpoint (estimand 1)	Complete Response (CR)	Efficacy	• While not initiating new anti-cancer therapy (NAT) • Regardless of intervention discontinuation (treatment policy)	CRR is defined as the percentage of participants with complete response (CR) as the best overall response. The CI will be calculated using Clopper-Pearson methods.
Cohort C1				
[Secondary endpoint (estimand 1)	Objective Response (OR) (confirmed CR or PR)	Efficacy	• While not initiating new anti-cancer therapy (NAT) • Regardless of intervention discontinuation (treatment policy)	ORR is defined as the percentage of the participants with complete response (CR) or partial response (PR) as the best overall response. The CI will be calculated using Clopper-Pearson methods.
Secondary objective: To assess other indicators of antitumor activity				
Cohort A				
Primary endpoint (estimand 2)	Objective Response (OR) (confirmed CR or PR)	Efficacy	• While not initiating new anti-cancer therapy (NAT) • Regardless of intervention discontinuation (treatment policy)	ORR is defined as the percentage of the participants with complete response (CR) or partial response (PR) as the best overall response. The CI will be calculated using Clopper-Pearson methods.
Cohort C1				
[Secondary endpoint (estimand 2)	Complete Response (CR)	Efficacy	• While not initiating new anti-cancer therapy (NAT) • Regardless of intervention discontinuation (treatment policy)	CRR is defined as the percentage of the participants with complete response (CR) as the best overall response. The CI will be calculated using Clopper-Pearson methods.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
All 2 cohorts				
Primary endpoint (estimand 3)	Duration of response (DoR)	Efficacy	- While not initiating new anti-cancer therapy (NAT) - Regardless of intervention discontinuation (treatment policy) - Had two or more consecutive tumor assessments not been missed/unevaluable immediately before documented progression or death (hypothetical strategy)	The Kaplan Meier estimate and corresponding confidence interval of DOR at specified time points. The quantiles of DOR and corresponding confidence interval will be calculated from Kaplan Meier method.
[Secondary endpoint (estimand 4)	Progression free survival (PFS)	Efficacy	- While not initiating new anti-cancer therapy (NAT) - Regardless of intervention discontinuation (treatment policy) - Had two or more consecutive tumor assessments not been missed/unevaluable immediately before documented progression or death (hypothetical strategy)	The Kaplan Meier estimate and corresponding confidence interval of PFS at specified time points. The quantiles of PFS and corresponding confidence interval will be calculated from Kaplan Meier method.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined. Unless otherwise specified, these populations will be applicable for both safety run-in and core phase parts. The participants included in the safety run-in part, if fulfilling the inclusion criteria of the core phase part and if the planned dose and dosing schedule are the same as in core phase will be included in the analyses of core phase.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who have been given the informed consent form.
Enrolled	All participants who have given their informed consent and have been allocated to an intervention (by IRT) regardless of whether the intervention was received or not.
Exposed	All participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or pembrolizumab).
Population without trial impact (disruption) due to COVID-19	All exposed participants: • without any critical or major deviation related to COVID-19 • and who did not permanently discontinue treatment due to COVID-19 • and who did not permanently discontinue study due to COVID-19.
Efficacy	All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.
DLT-evaluable [a]	All exposed 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.
Response evaluable	All participants from the efficacy population with at least one baseline and one evaluable post-baseline tumor assessments. Participants who died from disease progression before any TA will also be response-evaluable.
Pharmacokinetic (PK)	All participants from the exposed population with at least 1 PK concentration available after the first dose of study intervention.
ADA	All participants from exposed population with at least 1 ADA result (positive, negative or inconclusive) after the first dose of study intervention.
Pharmacodynamics (PDy)	All participants from the exposed population with at least 1 PDy (biomarker) parameter assessed after the first dose of study intervention.

a The dose-limiting toxicity (DLT) observation period is 21 days for Cohort A, and 28 days for Cohort C1.

Participants exposed to study intervention before or without being enrolled will not be considered enrolled and will not be included in any analysis population. The safety experience of these participants will be reported separately.

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

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

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

The baseline value is defined as the last available value before the first administration of any of the two IMPs (SAR444245 or pembrolizumab). For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

Unless otherwise specified, analyses will be performed by cohort, by dose level (if applicable) and overall. Participants enrolled in the safety run-in part and treated at the RP2D will be included in the analyses of the core part.

All efficacy analyses will be performed on the efficacy population. Complete response rate (CRR, for cohort A) and objective response rate (ORR, for cohort C1), as well as all other response-related efficacy endpoints will be derived using the Investigator's assessment per Lugano response criteria 2014 for all cohorts.

All safety analyses will be performed on the exposed population.

Central imaging may be done retrospectively if significant activity is observed (See Section 3.2.3 for sensitivity analysis).

Confidence intervals will be two-sided 90% CI for efficacy analyses. CI will be used for descriptive purposes only, without inference.

The BOR is defined as the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of subsequent anti-cancer therapy, whichever occurs first.

Analysis period

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** (i.e., treatment-emergent (TE) 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 end of the on-treatment, ie. 31 days after the last administration of IMP.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

The primary endpoint is:

- **Cohort A,** complete response rate (CRR)
- **Cohort C1,** objective response rate (ORR)

The complete response rate (CRR) is defined as the proportion of participants who have a complete response (CR) as the best overall response per Investigator assessment (Lugano response criteria 2014).

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

3.2.2 Main analytical approach

The primary endpoints, CRR and ORR, will be analyzed with estimand 1 introduced in Section 1.2.1. These endpoints are defined according to the following attributes:

- The endpoint complete response (CR) for cohort A
- The endpoint objective response (CR or PR) for cohort C1
- The treatment condition is SAR444245
  - in combination with pembrolizumab for Cohort A
  - in monotherapy for Cohort C1
- The analysis population is the efficacy population
- Intercurrent events (IE):
  - The new anticancer therapy IE will be handled with the “while not initiating new anti-cancer therapy” strategy; the primary endpoints will be assessed based on tumor assessments up to the time of new anticancer therapy.
  - The early IMP discontinuation IE will be handled with the “treatment policy” strategy; the primary endpoints will be assessed based on tumor assessments irrespective of the IMP discontinuation.

Population-level summary: Will include the - CRR (cohort A) and ORR (cohort C) and corresponding confidence interval using the Clopper Pearson exact method.

3.2.3 Sensitivity analysis

Central imaging reading may be done retrospectively if significant activity is observed. CRR (cohort A) and ORR (cohort C1) may be presented based on central imaging assessment, using the same estimand as for the primary analysis.

3.2.4 Supplementary analyses

ORR will be presented for the response-evaluable population.

This supplementary analysis will be provided using an estimand defined according to the following attributes:

- The endpoint is ORR.
- The treatment condition is SAR444245 in combination with/without pembrolizumab.
- The analysis population is the response-evaluable population.
- Intercurrent events and their handling strategy will be the same as for ORR estimand defined in Section 3.2.2.
- Population-level summary will be the same as for ORR estimand defined in Section 3.2.2.

The BOR will also be summarized with descriptive statistics.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are efficacy endpoints. Other secondary endpoints analyses are defined in Section 3.6 (safety), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Efficacy secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

The secondary efficacy endpoints are:

- The ORR is defined as the proportion of participants who have a CR or PR as BOR, for cohort A.
- The CRR is defined as the proportion of participants who have a CR as BOR, for cohort C1.
- The TTR is defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR determined by Investigator.

- The duration of response (DoR) is defined as the time from the first tumor assessment at which the overall response was recorded as PR or CR until progressive disease (PD) determined by Investigator, or death from any cause, whichever occurs first.
- The clinical benefit rate (CBR) is defined as the proportion of participants with clinical benefit (CR or PR as BOR, or SD lasting at least 6 months (i.e., 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.
- 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 or death due to any cause, whichever occurs first.

3.3.1.2 Main analytical approach

The ORR and CRR will be summarized using the same estimand as for primary endpoint (Section 3.2.2).

The time to response will be assessed on the subgroup of participants who have achieved objective response (CR or PR) and will be summarized using descriptive statistics.

The analyses of DoR and PFS are based on estimand 3 and 4 in Section 1.2.1, These endpoints are defined according to the following attributes:

- DoR and PFS
- The treatment condition is SAR444245
  - in combination with pembrolizumab for Cohort A
  - in monotherapy for Cohort C1
- The analysis population for DoR corresponds to the subgroup of participants of efficacy population who have achieved objective response
- The analysis population for PFS is the efficacy population
- Intercurrent events (IE):
  - The new anticancer therapy IE will be handled with the “while not initiating new anti-cancer therapy” strategy; the primary endpoints will be assessed based on tumor assessments up to the time of new anticancer therapy.
  - The early IMP discontinuation IE will be handled with the “treatment policy” strategy; the primary endpoints will be assessed based on tumor assessments irrespective of the IMP discontinuation.
  - Two or more consecutive missing/unevaluable tumor assessments immediately before documented progression or death will be handled with the hypothetical strategy: DoR and PFS will be assessed based on tumor assessments had two consecutive tumor assessments not been missed immediately before documented progression or death.

- Population-level summary:
  - CRR and ORR will be summarized with descriptive statistics. In addition, two-sided 90% CIs calculated for CRR and ORR from Clopper Pearson exact method will be also provided.
  - Population-level summary will include the Kaplan Meier estimate of DOR and PFS at specified time points and corresponding CI. CIs for KM estimates will be estimated for each treatment group using the Kaplan Meier method and log-log approach based on a normal approximation following the Greenwood's formula. The quantiles of DOR and PFS and corresponding CI from Kaplan Meier method will also be provided; CI will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley. In the absence of disease progression or death before the cut-off date, DOR and PFS will be censored as indicated in Table 5.

Table 5 - Censoring rules for DOR and PFS

Situation	Date of progression or censoring	Outcome	Category
No baseline tumor assessments[a]	Date of first treatment intake	Censored	No baseline tumor assessments
No evaluable[b] post-baseline tumor assessments[a]	Date of first treatment intake	Censored	No evaluable post-baseline tumor assessments
Progression documented at or between scheduled visits	Date of the first tumor assessment documenting progression	Event	Documented progression
New anticancer treatment before documented progression	Date of the last evaluable tumor assessment before new treatment	Censored	New anticancer treatment
Death prior to the first planned post-baseline tumor assessment[a]	Date of death	Event	Death
Death at or between scheduled visits	Date of death	Event	Death
Death or documented progression immediately after two[c] or more missed or non-evaluable tumor assessments	Date of the last evaluable tumor assessment documenting no progression	Censored	Death or progression after two or more missed/unevaluable tumor assessments
Alive and no documented progression	Date of the last evaluable tumor assessment	Censored	Alive without documented progression

a Not applicable for DOR.
b Evaluable TA means an evaluation different from non-evaluable.
c Two consecutive tumor assessments are considered as missed/non-evaluable if the duration between two consecutive tumor assessments done (non-missing) and evaluable is strictly longer than 20 weeks.

3.3.2 Supportive secondary endpoint(s)

Not applicable

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

3.4.1 Definition of endpoint(s)

[redacted].

3.4.2 Main analytical approach

[redacted]

3.5 MULTIPLICITY ISSUES

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

3.6 SAFETY ANALYSES

All safety analyses will be performed on the exposed population as defined in Section 2.

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

3.6.1 Extent of exposure

If applicable, summaries will be provided by trial impact (disruption) due to COVID-19.

3.6.1.1 Overall exposure

The dose information will be assessed by the following variables:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study interventions is administered.
- Duration of IMP exposure (in months) is defined as (Last day of exposure – first day of exposure +1)/30.4375.
- The first day of exposure is defined as the first administration date with non-zero dose for at least one of the IMP (SAR444245 or pembrolizumab).

The last day of exposure is the day before the theoretical date of the next administration (after the last administration), defined as the maximum between:

For cohort A

- The last administration date + 20 days for SAR444245
- The last administration date + 20 days for pembrolizumab

For cohort C1

- The last administration date + 13 days for SAR444245

The total number of cycles started, and number of cycles started by participants will be summarized by category.

The duration of overall exposure will be summarized quantitatively.

The following variable will be computed to describe overall dose modification (cycle delay):

- Cycle delay: A cycle is deemed as delayed if the start date of the current cycle – theoretical duration of a cycle – start date of the previous cycle is ≥ 4 days (in cohort A); ≥ 3 days in cohort C1. Cycle delay is not defined for the first cycle.

Cycle delay will be analyzed at the participant (with number of participants used as denominator) and cycle (with number of cycles used as denominator) levels, as follows:

- Number (%) of participants with at least 1 cycle delayed
  - Number (%) of participants with a cycle delayed between 4 and 7 days (using maximum delay across all cycles)
  - Number (%) of participants with a cycle delayed > more than 7 days (using maximum delay across all cycles)
- Number (%) of cycles delayed
  - Number (%) of cycles delayed between 4 and 7 days
  - Number (%) of cycles delayed > more than 7 days

3.6.1.2 SAR444245 exposure

The dose information will be assessed by the following:

- Total number of cycles started per participants
- Duration of SAR444245 exposure (in months) is defined by (date of last administration of SAR444245 + X– date of first administration of SAR444245) /30.4375 (X equals 20 for cohort A, and 13 for cohort C1)
- Actual dose (µg/kg)
- Cumulative dose (µg/kg): the cumulative dose is the sum of all actual doses of SAR444245, given from first to last administration

- Actual dose intensity (ADI in µg/kg/week): defined as the cumulative dose divided by the duration of SAR444245 exposure (in weeks)
- Planned dose intensity (PDI in µg/kg /week): corresponds to the planned C1D1 dose divided by the theoretical cycle duration expressed in weeks (i.e., 3 weeks)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (µg/kg /week)}}{\text{PDI (µg/kg /week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized by category. Duration of SAR444245 exposure, cumulative dose, ADI and RDI will be summarized quantitatively. RDI will also be summarized by category if relevant.

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

- Dose reduction: The first administration will not be counted as a dose reduction. For the second and subsequent SAR444245 administrations, dose reduction will be determined using the dose level intervals provided in Table 6, by comparing the current dose level to the previous dose level. If the current dose level is below the dose level interval of the previous dose administration, then the current dose level is considered reduced.

Table 6 – SAR444245 dose reduction criteria

Actual dose level	Dose level interval
8 µg/kg	[redacted]
16 µg/kg	
24 µg/kg	

- Dose omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: a dose will be considered as interrupted if SAR444245 administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant and dose as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose modification
    - Number (%) of participants with at least 1 dose reduction
    - Number (%) of participants with at least 1 dose omission
  - Number (%) of participants with a least 1 dose interrupted
    - Number (%) of participants with at least 1 dose interrupted and restarted
    - Number (%) of participants with at least 1 dose interrupted and not restarted
  - Number (%) of participants with at least 2 dose interruptions
- **Dose** (number of doses started will be used as denominator)

- Number (%) of doses
- Number (%) of doses interruptions
- Number (%) of doses interruptions and restarted
- Number (%) of doses interruptions definitively stopped
- Number (%) of doses interruptions more than once
- Number (%) of doses interrupted at 1st dose, 2nd dose, subsequent doses
- Time from dose start to first interruption in minutes summarized as a continuous variable and by category.

3.6.1.3 Pembrolizumab exposure (cohort A)

The dose information will be assessed by the following:

- Total number of cycles started per participant
- Duration of pembrolizumab exposure (in weeks) is defined by (date of last administration of pembrolizumab + 21 – date of first administration of pembrolizumab) /7
- Actual dose (mg)
- Cumulative dose (mg): the cumulative dose is the sum of all actual doses of pembrolizumab, given from first to last administration
- Actual dose intensity (ADI in mg/week): defined as the cumulative dose divided by the duration of pembrolizumab exposure (in weeks)
- Planned dose intensity (PDI in mg /week): corresponds to the planned dose at C1D1 divided by the theoretical cycle duration expressed in weeks (i.e., 3 weeks per cycle started)
- Relative dose intensity (RDI, in %): $100 \times \frac{\text{ADI (mg/week)}}{\text{PDI (mg/week)}}$

The total number of doses, total number of cycles started, number of cycles started by participant will be summarized by category. Duration of pembrolizumab exposure, cumulative dose, ADI and RDI will be summarized quantitatively. RDI will also be summarized by category if relevant.

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

- Dose omission is defined as a dose not administered at the scheduled visit.
- Dose interruption: a dose will be considered to be interrupted if the pembrolizumab administration is stopped during an infusion regardless of whether it is restarted or not.

Dose modifications and dose interruptions will be analyzed by participant as follows:

- **Participant** (number of participants treated will be used as denominator)
  - Number (%) of participants with at least 1 dose omission

- Number (%) of participants with a least 1 dose interruption
  - Number (%) of participants with at least 1 dose interruption restarted
  - Number (%) of participants with at least 1 dose interrupted and not restarted
- Number (%) of participants with at least 2 dose interruptions

3.6.2 Adverse events

General common rules for adverse events

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

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs occurring during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened (according to the Investigator's opinion) or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that are developed, worsened or became serous during the post-treatment period.

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

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

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

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

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

The AE tables will be sorted as indicated in Table 7.

Table 7 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the AE incidence.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (e.g., treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

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

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

The AE summaries of Table 8 will be generated with number (%) of participants experiencing at least one event. The analyses will be performed for all grades combined and for grades ≥3. The all TEAE summary by Primary SOC and PT (and other safety summaries (e.g., SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to COVID-19.

Table 8 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT Primary SOC and PT
TEAE related to IMP (overall) as per Investigator's judgment	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP (overall) as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent full intervention discontinuation	Primary SOC and PT
TEAE leading to permanent partial intervention discontinuation (for each individual drug)	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
AE leading to death[a]	Primary SOC and PT
- In context of disease progression[b]	
- In context other than disease progression[c]	
Pre-treatment AE	Primary SOC and PT
Post-treatment AE	Primary SOC and PT
TEAE leading to dose interruption	Primary SOC and PT
TEAE leading to dose modification (including dose reduction, dose omission and dose delay)	Primary SOC and PT

a Death as an outcome of the AE as reported by the Investigator in the AE page
b Death within 30 days from last IMP administration and the cause of death is disease progression
c Death within 30 days from last IMP administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last IMP administration and the cause of death is AE

Analysis of deaths

In addition to the analyses of deaths included in Table 8 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by main reason for death
- An overview of Grade 5 AEs will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless of date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment-emergent period,
    - Any Grade TEAE with a fatal outcome during the post-treatment period.

- Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).

Analysis of adverse events of special interest (AESIs)

Number (%) of participants experiencing at least one adverse event of special interest will be provided, by SOC and PT. The selection will be made using the eCRF specific **AESI** tick box. Tables will be sorted as indicated in Table 7.

In addition, the following analyses will be done for infusion reactions categories (i.e., infusion related reactions (IRRs), cytokine release syndrome (CRS) , flu-like symptoms (FLS) and anaphylaxis):

- Description of the infusion reactions by predefined grouping and other reported PT.
- Worst grade
- Action taken for each IMP
- Corrective treatment given (Yes, No)
- Number (%) of patients with only 1 episode, ≥2, ≥3, ≥4 and ≥5 episodes
- Onset of first episodes of infusion reaction (at the first infusion and subsequent infusions)
- Number (%) of patients with infusion reactions (any episodes) at the first and subsequent infusions
- Number (%) of patients with at least one infusion with two episodes of infusion reaction
- Total number of infusion reaction episodes
- Time to onset from infusion (by category: Infusion Day/1 day after infusion/ 2 to 3 days from infusion/ More than 3 days from infusion when applicable)
- Duration of infusion reaction (in days) (by category 1 day/ 2 to 3 days/ More than 3 days/not recovered)
- Number (%) of patients with infusion reactions' symptoms (as reported by investigator) by SOC and PT.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs

The following laboratory variables and vital signs variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, platelet count
  - White blood cells: leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: glucose, albumin, lipase, amylase
  - Electrolytes: sodium, potassium, chloride, calcium corrected, bicarbonate, magnesium

    Calcium Corrected (mmol/L) = Total calcium (mmol/L) + 0.8 * 0.25 * [4 – Serum albumin (g/L) * 0.1]
  - Renal function: creatinine, eGFR, blood urea nitrogen
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin
- Vital signs: heart rate, systolic and diastolic blood pressure, respiratory rate, temperature, ECOG Performance status

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

For hematological parameters and some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading (see list of parameters in Section 5.4). For other biochemistry parameters, grading will be derived using local laboratory normal ranges.

Quantitative analyses

When relevant, for laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using local measurements for laboratory variables.

Analyses according to PCSA and NCI grading

For laboratory variables, analyses according to NCI grading will be made based on NCI-CTCAE version 5.0. In addition, for eGFR, blood urea nitrogen, hematocrit, monocytes, basophils and chloride, PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

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

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

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

For laboratory variables graded by NCI-CTCAE,

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

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

No PK parameters will be assessed, as only sparse sampling for pharmacodynamic concentrations of SAR444245 is implemented in the study.

Table 9 - List of PK concentrations and definitions

PK concentrations	SAR444245	Definition
C_{eoi}	X	concentration sample taken at EOI
C_{D2}	X	concentration sample taken any time at day 2 after previous administration
C_{D3}	X	concentration sample taken any time at day 3 after previous administration

Applicable concentrations will be described on the PK population for each planned visit using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum. These analyses will be performed by specific subgroups (e.g., gender, BMI, age) if appropriate.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics. Geometric mean will not be computed in case at least one concentration is below LLOQ.

3.7.1.2 Immunogenicity analyses

Participant's ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA population.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

ADAs against SAR444245 (negative, positive, inconclusive) and corresponding titers, ADAs directed against PEG moiety of SAR444245 status (negative, positive),) and ADAs cross-reacting with endogenous IL-2 status (negative, positive) will also be described overtime using descriptive statistics.

ADAs directed against PEG moiety of SAR444245 status and ADAs cross-reacting with endogenous IL-2 status will only be determined if ADAs against SAR444245 status is positive.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status against SAR444245

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.
- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA.
    - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed during the treatment-emergent (TE) period and without pre-existing ADA (including participants without pre-treatment samples).
    - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 2-fold serial dilution schema is used during titration, so at least a 4-fold increase will be considered as significant.
- Participants with **unclassified ADA** correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (i.e., a positive ADA sample during the TE period in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample nor unclassified ADA during the TE period.
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

Kinetics of ADA response

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

- **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.
- **Duration of ADA response** is defined as the time between the first treatment-induced/ boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for participants with persistent ADA response.
  - A positive sample (boosted positive sample for participants with pre-existing ADA) occurring after the TE period will be considered as treatment-induced/boosted ADA if a previous treatment-induced/boosted ADA occurred during the TE period and less than 16 weeks before this sample.
- **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of less than 16 weeks and the last sample of the TE period is not treatment-induced/boosted.
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

ADA response variable:

- **ADA incidence** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point during the TE period.
- **Incidence of ADAs** directed against PEG moiety of SAR444245 is defined as the proportion of participants with ADAs directed against PEG moiety of SAR444245 during the TE period among evaluable participants. Participants from ADA population are evaluable for ADAs directed against PEG moiety except if ADAs directed against PEG moiety status is not determined on an ADA against SAR444245 positive sample
- **Incidence of ADAs cross-reacting with endogenous IL-2** is defined as the proportion of participants with ADAs directed against endogenous IL-2 during the TE period among evaluable participants. Participants from ADA population are evaluable for ADAs directed against endogenous IL-2 except if their status is not determined on an ADA against SAR444245 positive sample.

3.7.1.3 Biomarker analyses

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Sex (M, F)
- Age categories (12 to <18, 18 to <65, 65 to <75, ≥75)
- ECOG performance status at baseline
- Previous autologous HSCT (Y/N)
- Previous brentuximab vedotin use (Y/N)
- No. number of lines of previous therapy (e.g., 0, 1-2 vs ≥3?)

The ORR will be provided, as well as the corresponding 90% CI, for each subgroup, using the same method as applied to the primary analysis.

3.8 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 (SB) to decide about continuation of the dose of SAR444245 24 µg/kg or reduced to [redacted]µg/kg or another lower dose level.

In addition, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the independent Data Monitoring Committee (DMC). The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises. DMC will review safety data periodically. Ad hoc DMC meetings 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 ad hoc DMC. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

In addition, for each cohort, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the core phase part of the study, e.g., after 12 participants have undergone at least 1 post-baseline tumor assessments or have discontinued the study intervention, whichever is earlier.

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.

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

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	28-Apr-2022	Cover page: The study acronym "Pegathor Lymphoma 205" was added.	For consistency across the program.
1	28-Apr-2022	6.1.2.1 Premedication for SAR444245 [redacted]	
1	28-Apr-2022	8.3.1 Time period and frequency for collecting AE and SAE information: The instruction to stop collecting AE and SAE information should the	For consistency with Sanofi standards

Amendment Number	Approval Date	Changes	Rationale
		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.	
1	28-Apr-2022	8 Study Assessments and Procedures, 8.2 Safety assessment: The assessment of troponin level has been added.	To allow assessment of any potential cardiotoxicity.
1	28-Apr-2022	8.3.8 Adverse event of specific interest: SARS-CoV-2 infection/COVID-19 disease has been removed from AESIs	For consistency with Sanofi standards
1	28-Apr-2022	9.3 Populations for Analyses: The efficacy population definition was revised to "All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment".	For clarity.
1	28-Apr-2022	Sub-study 03; 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 (2 cycles)	To align with the Cohort C1 Q2W dosing.
1	28-Apr-2022	Sub-study 03; 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 and Day 15".	[redacted]
1	28-Apr-2022	Sub-study 03; 1.4 Biomarker flowchart: C2D1 and C2D8 visits have been added for Cycle 2, and the previous D1 visit for Cycle 2 and 4 have been changes to Cycle 3 and Cycle 5. The full assessment has been added without referring to the master protocol.	To align with the Cohort C1 Q2W dosing.
1	28-Apr-2022	Sub-study 03; 1.5 Pharmacokinetic flowcharts: ADA sampling on C1D15 has been changed to C1D8.	To align with the Cohort C1 Q2W dosing.

Amendment Number	Approval Date	Changes	Rationale
1	28-Apr-2022	Sub-study 03; 6.5.2 Cycle delay: 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 was renamed as “Dose delay and dose omission” accordingly.	To align with the Cohort C1 Q2W dosing.
1	28-Apr-2022	Sub-study 03; 8.1 Efficacy assessment: Table 7 for imaging or disease assessment collection plan has been newly added, and details on efficacy assessments based on CAR-T trial experience have been added.	For clarity
1	28-Apr-2022	Sub-study 03; 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.

4 SAMPLE SIZE DETERMINATION

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.

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. The plan is to treat a total of approximatively 75 participants: 25 participants in Cohort A and C1.

Table 10 - Estimated complete response rate (CRR) and objective response rate (ORR) with 90% confidence interval according to number of repsonders

Cohort A and C1	
Number of Responders (N=25)	**CRR or ORR in % (90%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%)

* Clopper-Pearson confidence interval

Cohort A and C1: With a sample size of 25 participants, 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.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADA:	anti-drug antibodies
ADI:	actual dose intensity
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
BOR:	best objective rate
CAR-T:	chimeric antigen receptor T
CBR:	clinical benefit rate
cHL:	classic Hodgkin lymphoma
CI:	Confidence Interval
COVID-19:	Coronavirus Disease 2019
CR:	complete response
CRR:	complete response rate
CRS:	Cytokine Release Syndrom
DLBCL:	Diffuse Large B Cell Lymphoma
DLT:	dose limited toxicity
DMC:	Data Monitoring Committee
DoR:	duration of response
ECG:	Electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EOI:	End Of Infusion
FLS:	Flu-Like Symptom
HLGT:	High Level Group Term
HLT:	High Level Term
IE:	Intercurrent event
IHC:	immunohistochemistry
IMP:	investigational medicinal product
IRR:	Infusion Related Reaction, Infusion Related Reaction
LLOQ:	Lower Limit Of Quantification
NAT:	New Anti-cancer Therapy
NCI-CTCAE:	National cancer institute common terminology for adverse events
OR:	objective response
ORR:	Objective response rate
PDI:	planned dose intensity
PFS:	Progression Free Survival
PK:	pharmacokinetic
PR:	partial response
PT:	Preferred Term
RDI:	relative dose intensity
SAE:	serious adverse event
SAP:	statistical analysis plan

SB:	Study Board
SD:	Stable Disease
SD:	standard deviation
SOC:	System Organ Class
TE:	Treatment Emergent
TEAE:	treatment-emergent adverse event
TME:	Tumor Time Microenvironment
TTR:	Time To Response
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized. Reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be summarized.

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

Regarding intervention discontinuation, the following definitions will be used:

- Permanent **partial** intervention discontinuation is defined as the discontinuation of one of the study drugs (SAR444245 or pembrolizumab) but at least one is continued
- Permanent **full** intervention discontinuation is defined as the discontinuation of all the study drugs

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

- Enrolled participants
- Enrolled but not exposed participants
- Exposed participants
- Participants still on study intervention
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation (for **Cohort C1**)
- Participants who did not complete the study treatment period as per protocol and main reason for permanent full intervention discontinuation (for **Cohort A**)
- Participants who did not complete the study treatment period as per protocol for SAR444245 and main reason for permanent partial intervention discontinuation (discontinuation of SAR444245) (for **Cohort A**)
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19, if applicable.

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

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the enrolled population as well as displayed separately as related versus not related to COVID-19 if applicable.

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

Demographics, baseline characteristics, medical surgical history

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

Demographic and baseline characteristics

- age in years as quantitative variable
- age in categories (12 to <18, 18 to <65, 65 to <75, ≥75)
- gender (Male, Female)
- race (White, Black, or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Not reported, Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Body Mass Index (kg/m^2)
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

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

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

Specific disease characteristics at diagnosis includes:

- Time from initial diagnosis of cancer to first administration of IMP (months)
- Diagnosis (classic Hodgkin's lymphoma, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma)
- Ann Arbor staging (I, II, II Bulky, III, IV)
- Designated applicable of stage (A: Absence of B symptoms, B: Presence of B symptoms, S: disease has spread to the spleen, E: disease is extranodal or spread from lymph nodes to adjacent tissue,)

Disease characteristics at study entry include:

- Patient with FDG-avid histology (Yes/No)
- FDG bone marrow update (Yes/No)
- Ann Arbor staging (I, II, II Bulky, III, IV)
- Designated applicable of stage (A, B, S, E)

Prior or concomitant medications

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

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to any IMP(s) from the first administration of IMP to the last IMP intake + 30 days.
- Post-treatment medications are those the participant took in the period after the end of the concomitant medications period up.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

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

Anticancer therapies

Prior anticancer therapies will be described, including several characteristics such as:

- Intent of prior regimens
- Number of prior regimens
- Time from last relapse/progression to first IMP administration (months)
- Number of prior regimens in advanced settings
- Type of prior regimens (chemotherapy, hormonotherapy, immunotherapy, target therapy, radiation therapy, other)
- Intent of last prior regimens
- Prior radiation
- Prior transplant

- Prior surgery related to lymphoma by preferred term
- Reason for discontinuation of the last regimen
- Best response to the last regimens
- Time to progression of last prior regimen
- Duration of last prior regimen (months)

Subsequent therapies after discontinuation of intervention will be summarized based on WHO-DD coding.

Pre-medications

Number (%) of patients receiving the following pre-medications will be provided at each cycle from cycle 1 to cycle:

- Acetaminophen (paracetamol)
- Diphenhydramine (or equivalent e.g., cetirizine, promethazine, exchlorpheniramine)
- Odansetron (or equivalent e.g., granisetron, dolasetron, tropisetron, palonosetron)
- Others

5.4 APPENDIX 4 SANOFI SPONSOR RANGES

Test	Gender	Unit	Lower/upper limit of normal
Basophils		10^9/L	0 – 0.15
Eosinophils		10^9/L	0 – 0.4
Erythrocytes	Male	10^12/L	4.5 – 5.9
Erythrocytes	Female	10^12/L	4 – 5.2
Hemoglobin	Male	g/L	135 – 175
Hemoglobin	Female	g/L	120 – 160
Hematocrit	Male	v/v	0.41 – 0.53
Hematocrit	Female	v/v	0.36 – 0.46
Leukocytes		10^9/L	4.5 – 11
Lymphocytes		10^9/L	1 – 2
Monocytes		10^9/L	0.18 – 0.5
Neutrophils		10^9/L	1.8 – 3.15
Platelets		10^9/L	150 – 350
Albumin		g/L	35 – 55
Urea Nitrogen		mmol/L	3.6 – 7.1

Test	Gender	Unit	Lower/upper limit of normal
Chloride		mmol/L	80 – 115
Glucose		mmol/L	3.900001 – 6.999999
Bicarbonate (HCO3)		mmol/L	22 – 29
Potassium		mmol/L	3.5 – 5
Magnesium		mmol/L	0.8 – 1.2
Sodium		mmol/L	136 – 145
Phosphate		mmol/L	1 – 1.4
Protein		g/L	55 – 80
Urea		mmol/L	3.6 – 7.1
INR		Ratio	0.8 – 1.2
Calcium corrected		mmol/L	2.2 – 2.6

5.5 APPENDIX 5 DATA HANDLING CONVENTIONS

Unscheduled visits

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

6 REFERENCES

1. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Signature Page for VV-CLIN-0640261 v1.0
act16941-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]