STATISTICAL ANALYSIS PLAN

A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab (SAR650984) in combination with other anti-cancer therapies in participants with lymphoma

SAR650984-ACT15320

STATISTICIAN: [redacted]

Statistical Project Leader: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibodies
ADI:	actual dose intensity
AEs:	adverse events
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic category
AUC:	area under the curve
BOR:	best overall response
BUN:	blood urea nitrogen
CD38:	cluster of differentiation 38
CR:	complete response
DCR:	disease control rate
DLT:	dose limiting toxicity
DoR:	duration of response
ECG:	electrocardiogram
ECOG:	eastern cooperative oncology group
eCRF:	electronic case report form
EOC:	epithelial ovarian cancer
GBM:	glioblastoma multiforme
HCC:	hepatocellular carcinoma
IAR:	infusion associated reaction
INR:	international normalized ratio
IV:	intravenous
LDH:	lactate dehydrogenase
MDRD:	modified diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
NIMP:	non-investigational medicinal product
PCSA:	potentially clinically significant abnormality
PFS:	progression-free survival
PFS-6:	progression free survival rate at 6 months
PK:	pharmacokinetic
PR:	partial response
PT:	preferred term
PTT:	partial thromboplastin time
Q3W:	once every 3 weeks
QW:	once weekly
RBC:	red blood cell
RDI:	relative dose intensity
ROI:	region of interest

RP2D:	recommended phase 2 dose
RR:	response rate
SAEs:	serious adverse events
SCCHN:	squamous cell carcinoma of the head and neck
SD:	stable disease
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TSH:	thyroid stimulating hormone
TTR:	time to response
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 1/2 open-label, non-randomized, multi-center, safety, preliminary efficacy, and PK study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma. The study will be conducted in 2 phases.

1.1.1 Phase 1 (safety run-in)

Participants with relapsed and refractory classic Hodgkin's lymphoma (cHL), diffuse large B cell lymphoma (DLBCL) and peripheral T-cell lymphoma (PTCL) will be enrolled in Phase 1.

1.1.1.1 Starting dose and de-escalation design

Starting dose is isatuximab given 10 mg/kg once weekly (QW) for the first cycle, once every two weeks (Q2W) for Cycle 2 - Cycle 6, followed by once every 3 weeks (Q3W) for Cycle 7 and beyond, with cemiplimab at 250 mg once every 2 weeks (Q2W) for the first six cycles then 350 mg once every 3 weeks (Q3W) for Cycle 7 and beyond. Dose de-escalation will be performed if necessary as defined in Table 1 below:

Table 1 - Dose modification for Phase 1

	Isatuximab		**Cemiplimab**	
Dose level (DL)	**Cycle 1 ~ Cycle 6 1 cycle = 28 days**	**Cycle 7 and beyond 1 cycle = 21 days**	**Cycle 1 ~ Cycle 6 1 cycle = 28 days**	**Cycle 7 and beyond 1 cycle = 21 days**
Starting dose	10 mg/kg QW x 4 (Cycle 1) 10 mg/kg Q2W (Cycle 2 - Cycle 6)	10 mg/kg Q3W	250 mg Q2W	350 mg Q3W
Minus -1 (DL-1)	5 mg/kg QW x 4 (Cycle 1) 5 mg/kg Q2W (Cycle 2 - Cycle 6)	5 mg/kg Q3W	250 mg Q2W	350 mg Q3W

Abbreviations: DL: Dose level; QW: once weekly, Q2W: once every 2 weeks Q3W: once every 3 weeks.

The dose limiting toxicity (DLT) observation period is 1 cycle (28 days).

To account for DLT non-evaluability because of AEs that do not qualify as DLTs, approximately 6 participants may be enrolled without interruption to receive the starting dose. At the starting dose, DLTs will be assessed among the first 3 DLT evaluable participants provided that they will have received at least 90% of the planned cumulative doses of the first cycle (unless they discontinue IMP(s) due to DLT), based on the rules listed below. The totality of the AEs collected from all treated participants will be taken into consideration when deciding recommended Phase 2 dose (RP2D).

- If 0/3 participants experiences a DLT, the starting dose will be the RP2D.
- If 1/3 participants experiences a DLT, 3 additional participants will be enrolled at the starting dose level:
  - If a total of 1/6 participant treated at starting dose experiences a DLT, the starting dose will be the RP2D,
  - If a total of ≥2/6 participants experience a DLT, the dose will be de-escalated to dose level minus 1 (DL-1).
- If ≥2/3 participants experience DLTs, dose will be de-escalated to DL-1.

At DL-1, the same DLT observation rules will be applied for selecting a RP2D, and if ≥2/6 or ≥2/3 participants experience DLTs, an alternative dose/schedule might be considered from a safety viewpoint by the Sponsor after consulting with the Investigators who have recruited participants for Phase 1.

Enrollment of participants within DL and between cohorts is to be staggered by at least 3 days.

Following the identification of the RP2D, the Phase 2 of the study will be initiated.

1.1.1.2 Dose limiting toxicity

Dose limiting toxicity (DLT) is defined in Section 4.1 in the protocol.

1.1.1.3 Recommended Phase 2 dose

The RP2D is defined as the dose selected for the Phase 2 portion.

1.1.2 Phase 2 (efficacy signal search with a 2-stage design in each cohort)

Phase 2 will include 4 cohorts: Cohorts A1, A2, B, and C will be initiated in parallel.

- Cohort A1: cHL anti-PD-1/PD-L1 naïve, isatuximab and cemiplimab combination.
- Cohort A2: cHL anti-PD-1/PD-L1 progressor, isatuximab and cemiplimab combination.
- Cohort B: DLBCL, isatuximab and cemiplimab combination.
- Cohort C: PTCL, isatuximab and cemiplimab combination.

A 2-stage design will be used in each cohort.

The participants treated at the RP2D of isatuximab and cemiplimab in combination during Phase 1 will be included in the efficacy analysis together with participants of the same tumor type in Phase 2 Stage 1. Based on the predefined number of objective responses in participants with cHL anti-PD-1/PD-L1 naïve, cHL anti-PD-1/PD-L1 progressor, DLBCL, or PTCL, as well as any other relevant data observed within a treatment cohort in Phase 2 Stage 1, the study will proceed with Phase 2 Stage 2. After enrollment completion of Phase 2 Stage 1, if efficacy results do not

warrant initiation of Stage 2, enrollment will be paused until sufficient results or analyses warrant initiation of Phase 2 Stage 2. In the case of inadequate efficacy for a cohort at interim analyses, the Sponsor will notify study sites regarding modification or termination of study procedures/scheduled activities for patients in that specific cohort.

1.2 OBJECTIVES

1.2.1 Primary objectives

Phase 1:

- To characterize the safety and tolerability of isatuximab in combination with cemiplimab in participants with relapsed and refractory classic Hodgkin's lymphoma (cHL), diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma (PTCL), and to confirm the recommended Phase 2 dose (RP2D).

Phase 2:

- Cohort A1 (anti-PD-1/PD-L1 naïve cHL): To assess the complete remission (CR) rate of isatuximab in combination with cemiplimab.
- Cohort A2 (anti-PD-1/PD-L1 progressor cHL), B (DLBCL) and C (PTCL): To assess the objective response rate (ORR) of isatuximab in combination with cemiplimab.

1.2.2 Secondary objectives

- To evaluate the safety of the RP2D of isatuximab in combination with cemiplimab.
- To evaluate the safety of the combination of isatuximab with cemiplimab and radiotherapy in participants with cHL.
- To evaluate the immunogenicity of isatuximab and cemiplimab when given in combination.
- To characterize the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.
- To assess overall efficacy of:
  - isatuximab in combination with cemiplimab

  and
  - isatuximab in combination with cemiplimab and radiotherapy.

1.3 DETERMINATION OF SAMPLE SIZE

Phase 1

For RP2D assessment, up to between 3 (assuming 3 participants for the starting dose) and 12 (assuming 6 participants for the starting dose plus 6 participants for DL-1) DLT evaluable

participants are needed. For 3 DLT evaluable participants on starting dose, approximately 6 participants could be enrolled without interruption. The actual sample size will vary depending on DLTs observed and the number of dose levels explored.

Phase 2

Approximately 118 participants are expected to be treated (assuming all cohorts complete 2 stages), including approximately 57 participants in Phase 2 Stage 1 and approximately 61 participants in Phase 2 Stage 2.

The participants who are treated with RP2D in Phase 1 will be counted as Phase 2 participants. The efficacy evaluation is based on Simon's 2-stage design with 85% power at 1-sided alpha level of 5% for each cohort, respectively. The assumption of response rate, the required sample sizes, and the number of responders at each stage for each of the four cohorts are provided in Table 2:

Table 2 - Sample size calculation for Phase 2

Indication	H0	H1	Sample size		Number (%) of responses to reject H0	
			Stage 1	Final	Stage 1	Final
A1 (cHL anti-PD-1/PD-L1 naive)	20%	40%	17	37	≥4 CR	≥12 CR
A2 (cHL anti-PD-1/PD-L1 progressor)	20%	45%	12	25	≥3	≥9
B (DLCBL anti-PD-1/PD-L1 naive)	35%	60%	18	29	≥8	≥15
C (PTCL anti-PD-1/PD-L1 naive)	25%	50%	10	27	≥3	≥11

Abbreviations: H0=null hypothesis; H1=alternative hypothesis; cHL=classic Hodgkin lymphoma; DLBCL=diffuse large B-cell lymphoma; PTCL=peripheral T-cell lymphoma.
Note: Based on the number of complete or objective responses and the totality of data observed within a treatment cohort in Phase 2 Stage 1, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with the Investigators.

1.4 STUDY PLAN

The complete study plan is presented in Section 1.2 of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

Patients treated at the RP2D in Phase 1 will be included in the analysis with patients of the same tumor type in Phase 2. If the RP2D is the starting dose, all data from the patients in Phase 1 will be summarized together with the data from the patients of the same tumor type in Phase 2 except for the DLT analysis.

Data from cHL anti-PD-1/PD-L1 naive, cHL anti-PD-1/PD-L1 progressor, DLBCL, and PTCL cohorts (Cohorts A1, A2, B, and C) in Phase 2 will be analyzed and reported separately by cohort.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last assessment for this parameter before first administration of study treatments unless otherwise noted.

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.6).

Demographic characteristics

Demographic variables include race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), age in years, weight (kg), height (cm), and eastern cooperative oncology group (ECOG) performance status.

Medical or surgical history

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor under study.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock.

Disease characteristics at diagnosis

The following disease characteristics at initial diagnosis will be summarized:

- Time from initial diagnosis to first study treatment administration (in years).
- Histology (diagnosis as collected in electronic case report form [eCRF]).
- Histopathology type (as collected in eCRF).
- Stage of the disease (as collected in eCRF).

Disease characteristics at study entry

The following disease characteristics at study entry will be described:

- Patient with FDG-avid histology.
- Ann Arbor Staging.
- Designation applicable to the stage.
- International Prognostic score.
- FDG bone marrow uptake.

Prior anticancer therapies

Prior anti-cancer treatments are collected by regimen in the eCRF. The following variables will be summarized for each cohort:

- Number of prior regimens (by category).
- Prior radiation therapy: number (%) of patients with any prior radiation therapy by curative or palliative intent.
- Prior surgery related to disease: number (%) of patients with any prior surgery by type of procedure (Preferred Term).
- Time from completion of last regimen of treatment to first study treatment (months)
- Best overall response to last regimen
- Reason for discontinuation of last regimen
- Duration of last regimen (months)
- Prior transplant (Yes/No)

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications (other than anticancer therapies)

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

- Prior medications are those the patient used prior to first study treatment administration. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the study treatment from first administration to the last administration +30 days. A given medication can be classified both as a prior medication and as a concomitant medication.

Infusion reaction (IR) medications

As defined in Section 6.1 of the study protocol, all participants will receive premedications to prevent or reduce incidence or severity of infusion reactions (IRs), 30 to 60 minutes prior to isatuximab infusion (no longer than 60 minutes). For participants who do not experience an IR during the first 4 administrations of isatuximab, subsequent premedication is optional at the Investigator's discretion. Premedications are defined in the protocol as non-investigational medicinal product(s). Premedications are reported on a specific eCRF page.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint for the Phase 2 part of the study is CR rate for cHL anti-PD-1/PD-L1 naïve patients, or ORR for cHL anti-PD-1/PD-L1 progressor, DLBCL, and PTCL patients.

For cHL anti-PD-1/PD-L1 naïve patients, the CR rate is defined as the proportion of patients with complete remission as best overall response (BOR), assessed by investigators per Lugano response criteria 2014(1), relative to the total number of patients in the all treated population. For cHL anti-PD-1/PD-L1 progressor, DLBCL, and PTCL patients, the ORR is defined as the proportion of patients with CR or PR as BOR, assessed by investigators per Lugano response criteria 2014, relative to the total number of patients in the analysis population.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- Tumor burden change: Tumor burden change is defined as the best percent-change from baseline in a sum of product of lesion diameters (longest for non-nodal lesion, short axis for nodal lesions) for all target lesions.
- Area under the curve (AUC) of percent-change from baseline in tumor burden is defined as the area under the percent-change from baseline versus time curve calculated using the trapezoidal method from the date of the first post-baseline assessment to the date of the last assessment.
- The time-adjusted AUC of percent-change from baseline in tumor burden is defined as AUC of percent-change from baseline in tumor burden divided by the duration of the assessment.
- Disease control rate (DCR): DCR is defined as the sum of the complete response (CR), partial response (PR) and stable disease (SD) rates. CR, PR, and SD are assessed by Investigator per Lugano response criteria 2014.

- Duration of response (DoR): DoR is the date of first response (CR for cohort A1, PR or CR whichever is first for cohort A2, B, and C) to the first date that recurrent or radiologically progressive disease progression is objectively documented, or the date of death, whichever occurs first. First disease progression refers to radiographic disease progression. The Lugano response criteria 2014 will be followed for assessment of radiographic disease progression. In the absence of disease progression or death before the analysis cut-off date or the date of initiation of a further anticancer treatment, the DoR will be censored at the date of the last valid response assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date, whichever is earlier. DoR will not be calculated for patients who do not achieve a response.

  Progression-free survival (PFS): PFS is defined as the time from first study treatment administration to the date of first documented radiographic progression per Lugano criteria, or the date of death from any cause, whichever occurs first.

  For patients who did not experience documented radiographic progression or death before the analysis cut-off date or the date of initiation of new anticancer treatment, PFS will be censored at the date of the last valid disease assessment not showing radiographic progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date, whichever comes first. In addition, patient without PFS event (death or documented radiographic progression) and without any valid post-baseline disease assessments will be censored at the date of first treatment (Day 1).

- For cohort A1: ORR, defined as percent of number of patients achieving BOR of CR or PR, relative to the total number of patients in analysis population, during isatuximab + cemiplimab ± radiotherapy periods; CR rate, defined as percent of number of patients achieving BOR of CR, relative to the total number of patients in analysis population, during isatuximab + cemiplimab + radiotherapy period.

  For cohort A2: ORR, defined as percent of number of patients achieving BOR of CR or PR, relative to the total number of patients in analysis population, during isatuximab + cemiplimab + radiotherapy periods; CR rate, defined as percent of number of patients achieving BOR of CR, relative to the total number of patients in analysis population, during isatuximab + cemiplimab ± radiotherapy periods.

2.1.3.3 Tertiary/Exploratory efficacy endpoint(s)

The following tertiary/exploratory efficacy endpoints will be summarized:

- Overall survival (OS) for all treated participants: OS is defined as the time from first study treatment administration to death from any cause. Patients without death prior to the analysis cut-off date will be censored at the last date the patient was known to be alive or the cut-off date, whichever comes first.
- Time to response (TTR) for all treated participants: TTR is defined as the time from first study treatment administration to the first response (PR or CR whichever is first) per Lugano response criteria 2014. When performing descriptive statistics, the patients who

responded will be used as the analysis population; when doing the KM analysis, the all treated population will be used, for non-responders, the censoring rule is that, for patients who had a PFS event (PD or death), censored at the maximum follow-up time; Otherwise, censored at the date of last adequate tumor assessment.

- Time to CR (TTCR) for all treated participants in Cohort A1 and A2.
- OS, TTR, and TTCR during isatuximab + cemiplimab period and for participants who receive isatuximab + cemiplimab + radiotherapy.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight, electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance status.

Observation period

The observation period starts from the time when the patient gives informed consent and is divided into 3 periods:

- **The pre-treatment period** is defined as the time informed consent is signed until the first dose of study treatments administration.
- **The treatment-emergent adverse event (TEAE) period** is defined as the time from the first dose of study treatments up to 30 days after last dose of study treatments.
- **The post-treatment period** is defined as the time starting from 31 days after the last dose of study treatments to the end of the study (as defined in the protocol).

2.1.4.1 Dose limiting toxicities (DLTs)

For the Phase 1 part dose limiting toxicities will be listed by patient using the DLT evaluable population.

2.1.4.2 Adverse events variables

AEs (including serious adverse events [SAEs] and AEs of special interest [AESIs]) will be collected from the time of signed informed consent until the end of study.

Adverse event observation period

- **Pre-treatment AEs** are defined as any adverse event reported during the pre-treatment period.
- **TEAEs** are adverse events that developed or worsened or became serious during the TEAE period.
- **Post-treatment AEs** are adverse events that developed or worsened or became serious during the post-treatment period.

All AEs (including SAEs and AESIs) will be graded according to NCI-CTCAE v5.0 and coded to a lower-level term, preferred term (PT), high-level term, high-level group term and associated primary system organ class (SOC) using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse events of special interest

Specific analyses will be performed for the following AEs:

- **DLTs.**
- **Grade ≥2 acute infusion reactions.**
- **Grade ≥3 immune-related TEAEs.**
- **Immune-related TEAEs of any grade in a participant previously treated with a PI3K inhibitor.**
- **Pregnancy** of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP/non-investigational medicinal product (NIMP).
- **Symptomatic overdose** (serious or non-serious) with isatuximab/NIMP.

2.1.4.3 Infusion reactions

Infusion reactions (IRs) typically occur within 24 hours from the start of each isatuximab/cemiplimab infusion.

Whenever possible, a diagnosis of the IR will be reported by the investigator in a specific AE page. In addition, symptoms of the IRs will be reported on a separate eCRF form.

IRs will be analyzed based on the investigator reported term collected in the specific AE pages.

2.1.4.4 Deaths

The deaths will be summarized as follows:

- Deaths in TEAE period: includes all deaths occurring from the first IMP up to the end of treatment +30 days.
- Deaths in post-treatment period: includes all deaths occurring after the end of TEAE period up to study closure.

2.1.4.5 Laboratory safety variables

All protocol-required laboratory assessments, as defined in Section 10.2 of the protocol, will be performed and to the Schedule of Activities for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Remaining laboratory tests are reported in eCRF pages for Hematology and Biochemistry.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified.

Clinical laboratory data consists of blood and urine analysis including hematology, biochemistry, and urinalysis. Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

Parameters measured on the day of the first study treatment infusion will be considered as part of the baseline measurements..

For laboratory safety variables, the treatment period is defined as the time from the first dose of study treatment (irrespective of treatment) administration to the last dose of study treatments +30 days.

Blood and urine samples for clinical laboratories parameters will be taken as defined in the study flow charts and as clinically indicated. The laboratory parameters will be classified as follows:

- Hematology
  - **Hemoglobin and coagulation**: hemoglobin, hematocrit, red blood cell (RBC) count, platelet counts, prothrombin time or international normalized ratio (INR) and activated partial thromboplastin time (PTT).
  - **White blood cells (WBCs)**: leukocytes, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Biochemistry
  - **Metabolism**: fasting glucose, total protein,
  - **Electrolytes**: sodium, potassium, chloride, calcium, albumin, magnesium, phosphate, bicarbonate/carbon dioxide,
  - **Renal function**: uric acid, serum creatinine, estimated creatinine clearance by modified diet in renal disease (MDRD) formula, urea or blood urea nitrogen (BUN),
  - **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, lactate dehydrogenase (LDH).
  - **Hormonal**: thyroid stimulating hormone (TSH) and free T4.
- Urinalysis
  - Semi-quantitative urinalysis: RBC, protein, glucose, pH, leukocytes.

2.1.4.6 Vital signs variables

Vital signs include: weight, temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate.

Thus, parameters measured pre-infusion on the day of the first study treatment infusion will be considered as part of the baseline measurements.

For a given parameter, a patient (respectively a cycle) will be considered as evaluable if at least one measure of this parameter is available during the on-treatment period.

2.1.4.7 Electrocardiogram variables

12-lead ECG assessments will be described as normal or abnormal.

2.1.4.8 Immunogenicity variables

Anti-drug antibodies (ADA) against isatuximab and cemiplimab will be collected according to the pharmacokinetics/pharmacodynamics (PK/PD) flowcharts in Section 1.4 of the protocol.

ADA attributes

Pre-existing ADA is defined as ADA reactive with the biotherapeutic present in subjects before treatment (or before initiation of the clinical study).

Treatment boosted ADA is defined as pre-existing ADAs that were boosted to a higher level following administration of biotherapeutic (ie, any time after the initial drug administration) the ADA titer is significantly higher than the baseline titer. A low serial dilution schema (2-fold or 3-fold) should be applied during titration. A difference in titer values of two titer steps between treatment or follow-up sample and its baseline sample is considered significant. For examples, at least a 4-fold increase in titers for 2-fold serial dilution schema (or 9-fold increase in titers for 3-fold serial dilution schema). If no titer could be determined for a positive sample, the titer will be reported as the minimal required dilution of the assay.

Treatment-induced ADA is defined as ADAs developed de novo (seroconversion) following administration of the biotherapeutic (ie, formation of ADAs any time after the initial drug administration in a subject without pre-existing ADAs). If the baseline ADA sample is missing or non-reportable and at least one reportable ADA sample is available during the treatment (including follow-up period) the baseline sample will be considered as "negative" for data analysis. This is considered being a conservative approach for ADA assessment.

Subject status

Among evaluable population for immunogenicity (described in Section 2.3.5), following patient status will be defined:

- ADA-positive subject: A subject with at least one treatment induced or treatment boosted ADA-positive sample at any time during the treatment or follow-up observation period.

- **ADA-negative** subject: Subject without any treatment induced or treatment boosted ADA-positive sample during the treatment or follow-up observation period.
- **ADA-inconclusive** subject: A subject who cannot irrefutably be classified as ADA negative (eg, all post baseline samples inconclusive).

Overview of the ADA response

Two main categories can be reported for the epidemiology of an ADA immune response: ADA prevalence and ADA incidence:

- **ADA prevalence** defines the proportion of all subjects tested positive for ADAs (including preexisting antibodies, treatment boosted ADAs and treatment induced ADAs) at any point in time.
- In contrast the term **ADA incidence** only defines the proportion of subjects found to either have seroconverted (treatment induced ADAs) or boosted their pre-existing ADA response during the study. Only evaluable subjects (described in Section 2.3.5) are considered for computing ADA incidence.

Kinetics of the immune response

- **Onset of ADA:** refers to the time period between the initial drug administration and the first instance of treatment induced ADAs. The use of real-elapsed days should be used for the calculations. The "median time to ADA development" and the quartiles Q1 and Q3 should be reported.
- **Duration of ADA:** ADA duration will be calculated as the date of last treatment induced ADA sample minus date of first treatment induced or treatment boosted ADA sample +1; ADA duration will be calculated only for patients with at least two ADA positive samples. Median duration of an induced ADA response and the quartiles Q1 and Q3 should be reported.
- **Transient ADA response** is defined by:
  - Treatment induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point), OR
  - Treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is ADA negative.
- **Persistent ADA response** is defined by:
  - Treatment induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples are separated by at least 16 weeks (irrespective of any negative samples in between).
- **Indeterminate ADA** is defined by:
  - Treatment induced ADA detected only at the last sampling time point, OR

- The last two samples being ADA-positive and separated by a period of less than 16 weeks.

Treatment-boosted ADAs are excluded from the analysis of ADA kinetics.

2.1.5 Pharmacokinetic variables

PK analysis will be done separately for isatuximab and cemiplimab.

The PK sampling times for isatuximab and cemiplimab were provided in the PK/PD flowchart in Section 1.4 of the protocol.

The following PK parameters (listed in Table 3) will be calculated with pharmacokinetic data management system (PKDMS) software (Pharsight) V3.0, using non-compartmental analysis (NCA) from isatuximab and cemiplimab concentrations after the first administration on Cycle 1. The parameters will include, but may not be limited to the following:

Table 3 - List of pharmacokinetic parameters and definitions

Parameters	Analyte		Definition
	cemiplimab	Isatuximab	
C_{eoi}	X	X	Concentration observed at the end of intravenous (IV) infusion
C_{max}	X	X	Maximum concentration observed
t_{max}	X	X	Time to reach C_{max}
C_{last}	X	X	Last concentration observed above the lower limit of quantification
t_{last}	X	X	Time of C_{last}
AUC_{0-14d}	X		Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (14 days)
AUC_{0-6d}		X	Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval (6 days)

For isatuximab and cemiplimab: C_{trough} defined as sample collected just before treatment administration during repeated dosing and C_{eoi} will be measured over the study period.

In addition, population PK approaches may be used for both compounds. If done, the data generated will be reported in a standalone report(s).

2.1.6 Biomarker endpoints

2.1.6.1 Microsatellite instability

Microsatellite instability will be analyzed on tumor samples collected at screening or baseline:

- Results will be of the form of MSI-H (ie, high microsatellite instability) or no-MSI-H (ie, low microsatellite instability or microsatellite stable).

2.1.6.2 PD-L1 expression singleplex IHC

PD-L1 expression on tumor and immune cells will be assessed using tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1.

2.1.6.3 Cluster of differentiation 38 (CD38) expression singleplex IHC

CD38 expression on tumor and immune cells will be assessed using tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1.

2.1.6.4 Immune cell subpopulation tumor infiltration and markers co-expression multiplex immunofluorescence

Immune cell subpopulation tumor infiltration and markers co-expression on different cell sub-populations will be assessed on tumor tissue (freshly collected tumor biopsy or archival tissue) biopsy at Screening/Baseline and (unless clinically unfeasible) at C2D1. Cell sub-populations will be determined by multiplex Immunofluorescence based on the expression of 12 different cell markers. The results will be provided per region of interest (ROI) and the number of cell sub-populations will be provided for 3 regions (total, within tumor, outside tumor).

Per cell sub-population, an average of the results provided per ROI will be calculated for the totality of tumor tissue.

2.1.7 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of study treatment will be collected on a specific eCRF page. The following information will be collected: drug/medication (brand or generic name), start date and end date (if available)/ongoing (otherwise).

2.2 DISPOSITION OF PATIENTS

Patient disposition will be summarized by cohort based on the analysis population defined in Section 2.3.

Screened patients are defined as any patients who signed the study informed consent.

Enrolled patients are screened patients who are planned to receive the study treatment, ie, for whom the investigator ticked “Yes” to the question “Will the patient continue into the study?” at the end of the screening period.

For patient study status, the total number of patients for each of the following categories will be presented in the clinical study report using a flow-chart diagram or a summary table:

- Screened patients.
- Enrolled patients.
- Enrolled and not treated patients.
- Enrolled and treated patients.
- Patients still on treatment.
- Patients completed treatment.
- Patients who discontinued the study treatments period and reasons for permanent discontinuation.

The number and percentage of patients in analysis population (defined in Section 2.3) will be provided in a summary table.

A summary of the reasons for definitive and premature treatment discontinuation for either treatment will be provided. Definitive treatment discontinuation is defined as the discontinuation of all the study treatments. Premature treatment discontinuation is defined as the discontinuation of one of the study treatments but the other one continued. Listing of the reasons for treatment discontinuation will be provided.

The number (%) of patients treated by country and center will be summarized using the all-treated population (defined in Section 2.3).

All critical or major deviations potentially impacting efficacy and safety analyses will be summarized by cohort separately. Critical or major protocol deviations will be listed.

2.2.1 Randomization and drug dispensing irregularities

This is an open-label, non-randomized study; therefore, randomization and dispensing irregularities are not applicable.

2.3 ANALYSIS POPULATIONS

2.3.1 All-treated population

For both Phase 1 and Phase 2 parts of the study, the all-treated population will include all patients who signed the study informed consent and received at least 1 dose (even incomplete) of the study treatment, either isatuximab or cemiplimab.

This population is the primary population for the analyses of efficacy and safety parameters except for DLT evaluation. All analyses using this population will be based on the dose level actually received in the first cycle.

2.3.2 DLT-evaluable population

The DLT evaluable population is defined as patients in the Phase 1 part receiving the planned doses of isatuximab and cemiplimab during Cycle 1, and who completed the DLT observation period after the first IMP administration as per Section 4.1 from protocol, unless they discontinue the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population.

2.3.3 Pharmacokinetic population

The PK population will be defined independently for isatuximab and cemiplimab, and include patients from the all treated population who received at least one dose of the drug even if incomplete with at least one reportable concentration after the study drug administration.

2.3.4 Biomarker Population

The biomarker population will include all treated patients who submitted at least one baseline biomarker sample.

2.3.5 Immunogenicity population

The immunogenicity population will be defined independently for isatuximab and cemiplimab, and include subjects from the all treated population who received at least one dose of the drug even if incomplete with at least one sample, taken post-baseline after drug administration during the treatment or follow-up observation period, with a reportable result (positive, negative or inconclusive).

2.3.6 Response evaluable population

The response evaluable population will include all patients in the all-treated population who fulfilled all inclusion and exclusion criteria without any major or critical deviations with an evaluable baseline assessment and at least one evaluable post-baseline disease assessment during the treatment period.

2.4 STATISTICAL METHODS

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

Data listings will be provided separately by cohort and sorted by patient number, unless otherwise specified.

2.4.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized on the all-treated population. Parameters described in Section 2.1.1 will be summarized using descriptive statistics.

The medical and surgical history will be summarized according to the SOC and PT (SOC will be sorted according to the internationally agreed order and PT by overall decreasing frequency).

Disease characteristics at diagnosis and at study entry will be described.

2.4.2 Prior or concomitant medications (other than anticancer therapies)

The prior, concomitant and post-treatment medications will be presented for the all-treated population. The anti-cancer therapy will be presented separately.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic therapeutic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and the patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, the patients may be counted several times for the same medication.

The tables for medications (prior, concomitant and post-treatment) will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs, alphabetical order will be used.

IR medications

Number (%) of patients with IR medications as defined in Section 2.1.2 will be provided.

2.4.3 Anticancer therapies

Prior anti-cancer treatments will be summarized for the all-treated population. Number (%) of patients with the anti-cancer treatments described in Section 2.1.1 will be summarized.

2.4.4 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure will be assessed and summarized on the all-treated population.

2.4.4.1 Extent of investigational medicinal product exposure

The overall extent of exposure will be assessed as:

- Overall number of cycles started, defined as maximum number of cycles started on isatuximab or cemiplimab.

- Duration of overall exposure (weeks): defined as (last day of last cycle - first day of first cycle)/7. The first day of first cycle is defined as the date of the first dose of study treatments. The last day of last cycle is defined as the later date among the following:
  - Date of last dose of isatuximab +7 days if last cycle is QW cycle, or date of last dose of isatuximab +14 days if last cycle is Q2W cycle, or date of last dose of isatuximab +21 days if last cycle is Q3W cycle,
  - Date of last dose of cemiplimab +14 days if last cycle is Q2W cycle, or date of last dose of cemiplimab +21 days if last cycle is Q3W cycle.

Total number of cycles started, number of cycles started by patient as a continuous variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of overall exposure will be summarized using descriptive statistics.

To describe overall dose modification, the cycle delay will be summarized. Within a cycle, the treatment windows are:

- for the weekly administrations during Cycle 1: ±1 day. A dose is deemed to have been delayed if the treatment is ≥2 days beyond the theoretical day of treatment for weekly dose.
- For the Q2W administrations (D15): ±2 days from Cycle 2 to Cycle 6. A dose is deemed to have been delayed if the treatment is ≥3 days beyond the theoretical day of treatment.
- For the 4-week cycle D1 (from Cycle 2 to Cycle 6) and the 3-week cycle D1 (from Cycle 7 to Cycle 30): ±3 days. A dose is deemed to have been delayed if the treatment is ≥4 days beyond the theoretical day of treatment.

The cycle start date is defined by the earlier date of isatuximab or cemiplimab administration within a cycle. Cycle delay is not defined for the first cycle.

Cycle delay will be summarized at both the patient and cycle levels as follows:

- Patient level:
  - Number of patients treated,
  - Number (%) of treated patients with at least 1 cycle delayed,
    - Number (%) of treated patients with a cycle delayed between 4 and 7 days,
    - Number (%) of treated patients with a cycle delayed between 8 and 14 days,
    - Number (%) of treated patients with a cycle delayed more than 14 days.
- Cycle level:
  - Number of cycles started,
  - Number (%) of cycles delayed,
    - Number (%) of cycles delayed between 4 and 7 days,
    - Number (%) of cycles delayed between 8 and 14 days,
    - Number (%) of cycles delayed more than 14 days.

2.4.4.2 Isatuximab exposure

The isatuximab exposure will be summarized as follows:

- Total number of cycles started.
- Number of cycles started by patient as a continuous variable and by category.
- Number of infusions.
- Duration of isatuximab exposure (weeks) is defined as:
  - [date of last dose of isatuximab + 7 days - first dose of isatuximab] / 7 if last cycle is QW cycle or [date of last dose of isatuximab + 14 days - first dose of isatuximab] / 7 if last cycle is Q2W cycle, or [date of last dose of isatuximab + 21 days - first dose of isatuximab] / 7 if last cycle is Q3W cycle,
- Actual dose (mg/kg): is defined as the actual dose (mg) administered divided by the body weight at the time.
- Cumulative dose (mg/kg): the cumulative dose is the sum of all actual doses (mg/kg) of isatuximab given from the first to the last administration.
- Actual dose intensity (ADI, mg/kg/week): is defined as the cumulative dose (mg/kg) divided by the duration of isatuximab exposure (weeks).
- Relative dose intensity (RDI, %): $100 \times \frac{\text{ADI (mg/kg/week)}}{\text{Planned Dose Intensity (mg/kg/week)}}$.

  Planned dose intensity (mg/kg/week) corresponds to the planned dose (mg/kg) multiplied by the theoretical total number of doses during the started cycles (3 for QW cycle and 1 for Q3W cycle) and divided by the theoretical cycle duration (weeks), ie, 3 weeks per cycle started.

The total number of cycles started, number of cycles started by patients as a continuous variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of isatuximab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delay and modification:

- Dose delay within Cycle as described in Section 2.4.4.1.
- Infusion interruption: an infusion is considered to be interrupted (as collected on eCRF) if the isatuximab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are dose(s) administered afterwards.

Dose delay and modification will be summarized at the patient and infusion levels as follows:

- Patient level:
  - Number (%) of patients with at least 1 dose delay within cycle,

- Number (%) of patients with at least 1 dose omission,
- Number (%) of patients with at least 1 infusion interrupted,
  - Number (%) of patients with at least 1 infusion interrupted and re-started,
  - Number (%) of patients with at least 1 infusion interrupted and not re-started.

- Infusion level:
  - Number of isatuximab infusions,
  - Number (%) of infusions interrupted,
    - Number (%) of infusions interrupted and re-started,
    - Number (%) of infusions interrupted and not re-started,
  - Number (%) of infusions interrupted more than once,
  - Number (%) of infusions interrupted at 1st infusion, 2nd infusion, subsequent infusions,
  - Time from infusion start to first interruption in minutes summarized as a continuous variable and by category (<5 minutes, 5-10 minutes, etc).

2.4.4.3 Cemiplimab exposure

The cemiplimab exposure will be summarized as follows:

- Total number of cycles started.
- Number of cycles started by patient as a continuous variable and by category.
- Duration of cemiplimab exposure (weeks) is defined as [Date of last dose of cemiplimab + 14 days - first dose of cemiplimab] / 7 if last cycle is Q2W cycle, or [date of last dose of cemiplimab + 21 days - first dose of isatuximab] / 7 if last cycle is Q3W cycle.
- Actual dose (mg): is defined as actual dose administered.
- Cumulative dose (mg): the cumulative dose is the sum of all actual cemiplimab doses.
- ADI (mg/week): is defined the cumulative dose (mg) divided by the duration of cemiplimab exposure (weeks).
- RDI (%): $100 \times \frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$, where the planned dose intensity is 250 mg for Q2W schedule, and 350mg for Q3W schedule.

The total number of cycles started, number of cycles started by patients as a continuous variable and by category (ie, number [%] of patients receiving at least 1 cycle, at least 2 cycles, etc), duration of cemiplimab exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following variables will be derived to describe dose delay and modification:

- Infusion interruption: An infusion will be considered to be interrupted (as collected on eCRF) if the cemiplimab administration is stopped during an infusion before it is completed regardless of whether it is further restarted or not.
- Dose omission: a dose is considered omitted if the dose is not administered for the scheduled visit and there are positive dose(s) afterwards.

Dose delay and modification will be summarized at the patient and infusion levels as follows:

- Patient level:
  - Number (%) of patients with at least 1 dose omission,
  - Number (%) of patients with at least 1 infusion interrupted,
    - Number (%) of patients with at least 1 infusion interrupted and re-started,
    - Number (%) of patients with at least 1 infusion interrupted and not re-started.
- Infusion level:
  - Number of cemiplimab infusions,
  - Number (%) of infusions interrupted,
    - Number (%) of infusions interrupted and re-started,
    - Number (%) of infusions interrupted and not re-started,
  - Number (%) of infusions interrupted more than once,
  - Number (%) of infusions interrupted at 1st infusion, 2nd infusion, subsequent infusions,
  - Time from infusion start to first interruption in minutes summarized as a continuous variable and by category (<5 minutes, 5-10 minutes, etc).

2.4.5 Analyses of efficacy endpoints

All efficacy analysis will be performed using the all-treated population. In addition, efficacy analysis will be performed using the response evaluable population.

The data cut-off for the primary end-of-cohort analysis is up to 24 weeks from the date the last participant treated in individual cohort. The data cut-off for the intermediate and final end-of-cohort analysis are up to 48 and 96 weeks respectively, from the date the last participant treated in individual cohort.

2.4.5.1 Analysis of primary efficacy endpoint(s)

For cHL cohort A1: CR rate during isatuximab + cemiplimab period will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using Clopper-Pearson method. The statistical inference will be based on the hypothesis and alpha level defined in the sample size calculation section.

For cHL cohort A2, DLBCL and PTCL: ORR during isatuximab + cemiplimab period will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using Clopper-Pearson method. The statistical inference will be based on the hypothesis and apha level defined in the sample size calculation section.

2.4.5.2 Analyses of secondary efficacy endpoints

For each cohort, separate analyses of the following endpoints will be performed for all participants during isatuximab + cemiplimab period for all 4 cohorts, for participants in Cohorts A1 and A2 including the data from both isatuximab + cemiplimab and isatuximab + cemiplimab + radiotherapy periods, and for participants in Cohorts A1 and A2 who receive isatuximab + cemiplimab + radiotherapy.

- Tumor burden change: the best percent-change from baseline in tumor burden for all target lesions will be summarized and presented graphically.
- DoR and PFS will be summarized using Kaplan-Meier method.
- DCR will be summarized with descriptive statistics.

In addition, ORR during isatuximab + cemiplimab period will be summarized in a similar fashion as described in the primary efficacy analysis for participants in Cohort A1. Similar analyses will be provided for CR rate and ORR for all participants in Cohorts A1 and A2 including the data form both isatuximab + cemiplimab and isatuximab + cemiplimab + radiotherapy periods, and for participants in Cohorts A1 and A2 who receive isatuximab + cemiplimab + radiotherapy.

2.4.5.3 Analyses of exploratory efficacy endpoints

OS and TTR for all treated patients will be summarized by descriptive statistics by cohort.

For cohorts A1 and A2, CR (TTCR) for all treated patients will be summarized by descriptive statistics by cohort.

For cohorts A1 and A2, OS, TTR, TTCR during isatuximab + cemiplimab period and for participants who receive isatuximab + cemiplimab + radiotherapy will be summarized by descriptive statistics by cohort.

2.4.5.4 Multiplicity issues

Not applicable.

2.4.6 Analyses of safety data

The all-treated population will be used for all safety analyses except for the DLT analysis in Phase 1, which will be performed based on the DLT-evaluable population.

2.4.6.1 Analyses of DLTs (Phase 1 only)

The DLTs will be listed by patient using the DLT-evaluable population in Phase 1.

2.4.6.2 Analyses of adverse events

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an AE date of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined when 1 of the IMPs is permanently discontinued, subjects will continue receiving the other IMP until study treatment permanent discontinuation.
- **Definitive** treatment discontinuation is defined as the discontinuation of all the study drugs.

The severity grade will be taken into account in the summary. For patients with multiple occurrences of the same AE, the maximum (worst) severity grade by period of observation will be used. Summaries will be provided for all grades and for Grade ≥3 (including Grade 5). Missing grades handling is provided in Section 2.5.3.

Sorting within tables should ensure the same presentation for the set of all AEs for each observation period (pre-treatment, treatment-emergent and post-treatment). For that purpose, tables of all TEAEs by SOC and PT will be sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs. This order will define the presentation order for all other tables unless otherwise specified.

Overall summary of TEAEs

An overall summary of TEAEs will be provided. The number (%) of patients who experience any of the following will be provided:

- TEAE.
- TEAE of Grade ≥3.
- TEAE of Grade 5.
- Serious TEAE.
- Treatment-related TEAEs (any grade).

- Treatment-related TEAEs of Grade ≥3.
- Serious treatment-related TEAEs.
- TEAE leading to definitive study treatment discontinuation.
- TEAE leading to premature discontinuation of isatuximab.
- TEAE leading to premature discontinuation of cemiplimab.
- AESI.
- AESI of Grade ≥3.

Analysis of all TEAEs

The number (%) of patients experiencing TEAEs by primary SOC and PT will be summarized by grade (all grades and Grade ≥3). Similar tables will be presented for treatment-related TEAEs, serious TEAEs, and TEAEs leading to definitive/premature discontinuation.

TEAEs with an incidence ≥5% will be summarized by PT for all grades and Grade ≥3.

Listings of serious TEAEs, TEAEs leading to definitive or premature treatment discontinuation will be provided.

Infusion reactions (IRs)

IR analysis will include all adverse events regardless of relationship to isatuximab, cemiplimab or NIMP. The IRs will be summarized as follow:

- Number (%) of patients experiencing IRs according to investigator reported AEs presented by primary SOC and PT will be summarized by grade.
- Description of the IR diagnoses (using the diagnosis reported and excluding symptoms).
  - Number (%) of patients action taken,
  - Number (%) of patients with only 1, ≥1, ≥2, ≥3, ≥4 and ≥5 episodes,
  - Number (%) of patients with first occurrence of IR at the first infusion and subsequent infusions,
  - Number (%) of patients with IR at the first and subsequent infusions,
  - Number (%) of patients with at least two episodes of IRs at the same infusion,
  - Day of onset from infusion,
  - Duration (in days).
- Number of patients with symptoms of IRs (as reported by investigator) by SOC and PT.

Analysis of adverse events of special interest

A listing of patients with at least one AESI described in Section 2.1.4.2 will be provided.

Analysis of pre-treatment and post-treatment adverse events

The following analysis will be provided by grade (all grades and Grade ≥3).

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.
- All post-treatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

2.4.6.3 Deaths

The following summaries of deaths will be generated:

- Number (%) of patients who died by study period (on-treatment, post-treatment) and reasons for death (disease progression, AE, other).
- TEAEs with fatal outcome (on the AE eCRF page as reported by the Investigator), TEAEs that started as non-fatal during treatment period but became fatal during post-treatment period, and TEAEs with fatal outcome during the post-treatment period summarized by SOC and PT.

2.4.6.4 Analyses of laboratory variables

Each laboratory test result will be graded by CTCAE criteria (Version 5.0), when applicable. For hematological parameters and for some biochemistry parameters, Sanofi sponsor generic normal ranges will be used for the grading of laboratory abnormalities (see list of parameters in Table 6 and Table 7). For other biochemistry parameters (eg, for hepatic parameters), grading will be derived using the local laboratory normal ranges.

The number (%) of patients with abnormal laboratory tests at baseline and during the on-treatment period will be presented by all grades and each grade. For patients with multiple occurrences of the same laboratory variable during the on-treatment period, the maximum grade (worst) per patient will be used.

The denominator used for percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

When appropriate, the summary table will present the frequency of patients with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

2.4.6.5 Analyses of vital sign variables

The incidence of vital signs potentially clinically significant abnormality (PCSA) (Table 4) any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

Table 4 - Potentially clinically significant abnormalities criteria for vital signs

Parameter	PCSA
HR	≤50 bpm and decrease from baseline ≥20 bpm
	≥120 bpm and increase from baseline ≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg
	≥160 mmHg and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg
	≥110 mmHg and increase from baseline ≥10 mmHg
Weight	≥5% increase from baseline
	≥5% decrease from baseline

Temperature and respiratory rate will be summarized at baseline and end of treatment. A listing of patients with at least one PCSA will be provided.

2.4.6.6 Analyses of electrocardiogram variables

A listing of patients with ECG results will be provided.

2.4.6.7 Analysis of Immunogenicity

Immunogenicity analysis will be done separately for isatuximab and cemiplimab.

Number of evaluable patients, number (%) of pre-existing ADA and negative patients at baseline, number (%) of boosted and induced patients (either transient, persistent or indeterminate) will be reported, along with descriptive statistics of titer, by cohort and possibly overall. Prevalence and incidence will also be presented.

In addition, for positive ADA patients, time to onset, duration of ADA response, and the characterization of the immune response (transient, persistent, indeterminate) will be provided.

An individual data listing with ADA samples status (positive, negative or inconclusive), the titer if applicable, date of first/last dose, duration of exposure, study period, cycle/day, time point and date/time of sampling along with Ctrough value of the drug will be provided for all patients.

The impact on safety and efficacy endpoints may be further explored by graphical methods or descriptively, depending on the ADA prevalence.

2.4.7 Analyses of pharmacokinetic variables

PK analysis will be done separately for isatuximab and cemiplimab.

2.4.7.1 Cycle 1 non-compartmental analysis: following the 1st administration

Following the first administration, individual concentrations and PK parameters of drug will be listed and summarized by descriptive statistics (such as the number of observations, arithmetic and geometric mean, median, standard deviation (SD), standard error (SE), coefficient of variation (CV)%, minimum, and maximum) by cohort and possibly overall.

Individual and mean concentration profiles over time will be plotted by cohort and possibly overall under the responsibility of Sanofi, Pharmacokinetic, Dynamic and Metabolism (PKDM), Translational Medicine and Early Development (TMED) department.

2.4.7.2 Over treatment concentrations: C_{trough} and C_{eoi}

C_{trough} defined as a sample collected before dosing, in a time window of 6 to 8 days after the previous infusion for the QW administration (5 to 7 days after the first isatuximab infusion) , in a time window of 12 to 16 days after the previous infusion for the Q2W administration, and in a time window of 18 to 24 days after the previous infusion for the Q3W administration will be included in the descriptive analysis irrespectively of interruption of infusion. However C_{trough} drawn outside time collection window described in the protocol PK/PD flowchart or collected after a dose deviation higher than ±50% from intended dose will be excluded from the analyses.

C_{eoi} collected after significant infusion interruption, drawn outside collection of time window described in the PKPD flowchart of the protocol or collected after a dose deviation higher than ±50% from intended dose will be excluded from the analyses.

Individual C_{trough} and C_{eoi} will be listed and summarized with same descriptive statistics as above by cohort and possibly overall.

Mean (±SE) of C_{trough} will be plotted over treatment phase by cohort and possibly overall for isatuximab and for cemiplimab.

Individual C_{trough} ratio and C_{eoi} ratio (described in Table 5) will be listed and summarized by descriptive statistics by cohort and possibly overall as described above.

Table 5 - C_{trough} and C_{eoi} ratio

Analyte	C_{trough}	C_{eoi}
Isatuximab	C2D1 vs C1D8	C2D1 vs C1D2
	C4D1 vs C1D8	C4D1 vs C1D2
Cemiplimab	C4D1 vs C1D15	C4D1 vs C1D1

NA = Not applicable.

2.4.7.3 Immunogenicity impact on PK

Immunogenicity impact on PK analysis may be explored, depending on the ADA prevalence.

A descriptive statistics of C_{trough} as described above will be provided at each cycle in the subset of negative patients by cohort and possibly overall where positive or inconclusive patients will be observed.

A graphical representation of individual C_{trough} profile will be provided throughout the course of treatment by cohort and possibly overall where positive or inconclusive patients will be observed. Positive patients profile will be highlighted (eg, color or bold) and the concentration of the administered drug at the same time as ADA positive result will be notified.

2.4.8 Analyses of biomarker variables

The biomarker variables may be summarized by clinical group (eg, SD >6 months vs. others) and overall depending on availability of assessable tumor biopsy samples. Graphics will be provided as appropriate. The biomarker variables include, but not limited to, the following variables:

- CD38 expression.
- PDL1 expression.

Additional biomarker analysis may be conducted in an exploratory manner. Additional analysis, not specified in the protocol but related to the drug action and/or effect of isatuximab/Cemiplimab, may be conducted on remaining samples pending evolving literature.

2.4.9 Analyses of quality of life/health economics variables

Not applicable.

2.4.10 Further therapy after discontinuation of investigational medicinal product administration during the study

A listing of further therapy after discontinuation of investigational medicinal product administration during the study may be provided.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Estimated glomerular filtration rate (eGFR) using the equation of MDRD formula:

$$GFR = 175 \text{ x } (Scr)^{-1.154} \text{ x } (Age)^{-0.203} \text{ x } (0.742 \text{ if Female}) \text{ x } (1.212 \text{ if African American})$$

with serum creatinine (sCr) in mg/dL and age in year.

Corrected calcium formula using SI unit:

$$\text{Corrected Calcium} = \text{Calcium} + 0.25 * 0.8\ (4 - \text{Albumin} / 10)$$

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of patients with non-missing observation in the considered population. When relevant, the number of patients with missing data is presented.

When incomplete or missing dates are found in the eCRF, attempts will be made to retrieve the complete date, especially for dates within the month prior to first dose. However, if some dates remain incomplete, the following rules will be applied:

Handling of disease characteristics missing/partial dates

- If the day is missing, it will be estimated by 1.
- If the month is missing, it will be estimated by 1 (only for medical history variables).
- If the year is missing, no estimation will be performed.

Handling of medication missing/partial dates

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For prior anti-cancer therapies, following rules will be applied:

Missing/partial start date will be imputed as follows:

- If year and month exist, day is missing, impute as the first day of the month.
- If only year exists, month and day are missing, impute as the first day of the year.
- If year, month, and day are all missing, no imputation will be applied.

Missing/partial end date will be imputed in a two-step approach as follows:

- Step 1: Use the following rule to impute end date:
  - If year and month exist, day is missing, impute as the first day of the month,
  - If only year exists, month and day are missing, impute as the first day of the year,
  - If year, month, and day are all missing, no imputation will be applied.
- Step 2: If imputed end date is earlier than start date, set the imputed end date the same as start date.

Imputation of incomplete date for post anti-cancer treatment start date

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date +1.
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start day will be set equal to the treatment end day +1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date +1.

No imputation will be done for the missing/partial end date.

Handling of adverse events with missing or partial date of onset

Missing or partial adverse event onset dates (occurrence or becoming serious) will be imputed so that if the partial adverse event onset date information or visit number does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. In case of an AEs worsening during the study, the emergence will also be based on the cycle of worsening. No imputation of adverse event end dates will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date of adverse event resolution.

Handling of death with missing or partial date of death

The imputation for missing or partial death date will proceed as follows:

- If the death day is missing and the death month and year are the same as the last month and year the patient was last known to be alive, the death day will be set equal to the last day the patient was known to be alive +1.
- If the death day is missing and the death month is after the month the patient was last known to be alive and the death year is the same as the year the patient was last known to be alive, the death day will be set to 01.

- If the death day and month are missing and the death year is the same as the year the patient was last known to be alive, the death date will be set equal to the date the patient was last known to be alive +1.
- If the death day and month are missing and the death year is after the year the patient was last known to be alive, the death day and month will both be set to 01.

If the date the patient was last known to be alive is partial or missing, no imputation for missing or partial death date will be performed. The last date the patient was known to be alive is the last of: date of last dose, date of last visit performed (when the patient is known to be alive according to subject vital status), date of last laboratory assessment, and date of last vital signs.

Handling of AEs with missing grade

No imputation of AE grade will be done.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level. No imputation will be done for relationship to NIMP.

Handling of parameters expressed as inequality or approximation

For some parameters (such as laboratory parameters), the following imputation rule will be implemented.

Rule of imputation	Example of imputation	
	Character Result/Finding in Std Format (LBSTRESC)	Analysis Value (AVAL)
Character results including ">" are imputed to the numeric value after ">"	>3	3
Character results including "<" are imputed to the numeric value after "<" divided by 2	<3	1.5

Handling of missing date/time in duration of infusion calculation

When both cemiplimab and isatuximab are given to a patient on the same visit:

- Missing cemiplimab end date/time will be imputed by isatuximab start date/time (if available).
- Missing isatuximab start date/time will be imputed by cemiplimab end date/time (if available).

Other types of missing date/time will not be imputed, and data will be excluded from the analysis of duration of infusion.

Handling of other missing dates

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month.
- If day and month of the cancer diagnosis are missing, no imputation will be done.

Incomplete date of progression for the last prior regimen:

- If the day of the progression for the last prior regimen is missing, the date will be imputed to the end day of the month.
- If day and month of the progression for the last prior regimen are missing, no imputation will be done.

Incomplete date of prior surgery:

- If the day of the last prior surgery is missing, the date will be imputed to the end day of the month.
- If day and month of the last prior surgery are missing, no imputation will be done.

Incomplete date of prior radiotherapy:

- If the day of the last prior radiotherapy is missing, the date will be imputed to the end day of the month.
- If day and month of the last prior radiotherapy are missing, no imputation will be done.

2.5.4 Windows for time points

Laboratory data

A protocol planned laboratory test is considered to have occurred during a cycle if the date of sampling is after (>) the first day of the cycle, but prior to or equal (≤) to the first day of the next cycle. For unscheduled tests, a lab test is not required per protocol, a test is considered to have occurred during a cycle if the date of sampling is equal to or after (≥) the first day of the cycle, but prior (<) to the first day of the next cycle.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs and ECG will be used for computation of worst values and/or grades on treatment. Unscheduled visits prior to first administration will be also be used for computation of baseline except if they are not collected on the day of first administration.

2.5.6 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

An interim analysis will be performed for cHL PD-1/PD-L1 naïve cohort A1, cHL PD-1/PD-L1 progressors cohort A2, DLBCL, and PTCL cohorts when approximately the first 17, 12, 18 and 10 participants, respectively, in Phase 2 have been treated and followed-up for 24 weeks. The analysis will include the following parameters/analyses (defined in Section 2.1): CR for patients with cHL PD-1/PD-L1 naïve, or ORR for patients with cHL PD-1/PD-L1 progressor, DLBCL, and PTCL. Demographics and baseline characteristics, prior or concomitant medication, AEs (TEAE, death, SAE, TEAE leading to discontinuation, IR, AESI), and laboratory variables (abnormality of hematological and chemistry test). If needed, more data will be analyzed to inform the futility decision including additional efficacy, PK, and biomarker.

4 DATABASE LOCK

The database will be locked when clinical review of the database has been completed and all critical queries have been resolved.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS® Version 9.4 or higher.

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.

2. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Case records of the Massachusetts General Hospital. Laboratory reference values. N Engl J Med. 2004;351:1548-63.

7 LIST OF APPENDICES

Appendix A Generic ranges for hematological and biochemistry parameters

Table 6 - Generic ranges for hematological parameters

Test	Gender	Unit	Lower/Upper limit of normal
Hemoglobin	F	g/L	120 - 160
Hemoglobin	M	g/L	135 - 175
Lymphocytes		109/L	1 - 2
Neutrophils		109/L	1.8 - 3.15
Platelets		109/L	150 - 350
Leukocytes		109/L	4.5 - 11
Eosinophils		109/L	0 - 0.4
Basophils		109/L	0 - 0.15
Monocytes		109/L	0.18 - 0.5
Hematocrit	M	Ratio	0.41 -0.53
Hematocrit	F	Ratio	0.36 - 0.46
Erythrocytes	F	1012/L	4 - 5.2
Erythrocytes	M	1012/L	4.5 -5.9
INR		ratio	0.8 -1.2

Based on Kratz et al (2).

Table 7 - Generic ranges for biochemistry parameters

Test	Unit	Lower - Upper limit of normal
Albumin	g/L	35 - 55
BUN	mmol/L	3.6 - 7.1
Calcium	mmol/L	2.2 - 2.6
Chloride	mmol/L	80 - 115
Corrected calcium	mmol/L	2.2 - 2.6
Glucose	mmol/L	3.9 - 7
Bicarbonate (HCO3)	mmol/L	22 - 29
Carbon dioxide	mmol/L	21 - 30
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

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