AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**A Phase 1/2 open-label, multi-center, safety, preliminary efficacy and pharmacokinetic (PK) study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma**
Protocol number:	**ACT15320**
Amended Protocol:	**02**
Compound number (INN/Trademark):	**SAR650984 isatuximab**
Short title:	**A study of isatuximab-based therapy in participants with lymphoma**
Sponsor name:	
Legal registered address:	
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifying number(s):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	15 December 2020, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 01	All	19 September 2019, version 1 (electronic 4.0)
Original Protocol		14 September 2018, version 1 (electronic 5.0)

Amended protocol 02 (15 December 2020)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment includes clarifications requested by the French Health Authority (ANSM). In addition, this amendment is to make provisions for data collection from patients still on treatment if the sponsor decides to stop the study prematurely. Other modifications or editorial changes are included to correct inconsistencies and improve operational feasibility.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Added IND number	Administrative change.
Section 1.1 Synopsis, Section 1.3 SoA (footnote a), Section 4.1 Overall design and Section 6.1.4. Radiotherapy (for Cohorts A1 and A2) (optional)	Numbering of exclusion criteria corrected to E01, E06, E08, E021, **E30, E32**, instead of E01, E06, E08, E021, E29, E31. Wording has been corrected for exclusion criteria: "does not meet exclusion criteria" instead of "meet exclusion criteria".	Correction.
Section 1.1 Synopsis and Section 1.3 SoA (footnote “f”)	Text has been added to clarify that there will be no survival follow-up period for the cohorts with negative interim analysis results.	Clarification.
Section 1.1 Synopsis, Section 2.3.4. Preventive measures to minimize the risk from the combination, Section 6.1 Study intervention(s) administered, Section 6.1.2 Non-investigational medicinal products and Section 6.1.2.2 Ranitidine 50 mg IV or equivalent	Use of ranitidine or equivalent as premedication is left to medical judgement of the investigator.	To provide option to adapt the premedication depending on individual situation.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 10.1.5 Committees structure	Text in the Study Committee (SC) section has been updated to clarify the composition of the SC during Phase 1 and during Phase 2 for participants who undergo radiotherapy after Cycle 10.	Clarification.
Section 1.3 SoA (footnote “b”), Section 5.2 Exclusion criteria (E33.), Section 6.4 Concomitant therapy, Section 6.5.6 Guidance in case of hepatitis B reactivation occurring under study treatment, and Section 10.2 Appendix 2: Clinical laboratory tests	New text added for prevention of viral reactivation risk.	To complement hepatitis B virus (HBV) investigation.
Section 1.3 SoA	The wording “Continuous” was added for the adverse event (AE)/serious adverse event (SAE) assessment during the treatment period. Follow-up of concomitant medication was modified from 31 days to 90 days when related to AEs/SAEs.	Correction. Clarification.
Section 1.3 SoA, footnote “d” and Section 8.1.1 FDG-PET-CT/CT	Tumor assessment frequency updated to Year 1: Fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT)/ CT scans every 12 weeks, Year 2 and beyond: CT scan every 12 weeks, and FDG PET-CT scan when clinically indicated. Wording of spleen size measurement, standardized uptake value (SUV) max, and 5-point scale (5PS) score were clarified.	To optimize scan frequency in the context of disease setting and response to study treatment.
Section 2.3.4. Preventive measures to minimize the risk from the combination	E08 was corrected as follows: Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), known HBV, or hepatitis C virus (HCV), unless they are **controlled or** negative when tested by polymerase chain reaction (PCR) or equivalent. Active tuberculosis, or severe infection requiring parenteral antibiotic treatment".	Correction. Clarification.
Section 2.3.4 Preventive measures to minimize the risk from the combination, Section 6.1.1 Investigational medicinal product(s), and Section 6.5.5 General guidelines for the management of IRs	Improvement in isatuximab administration.	Switching to faster infusion schedule with a fixed distribution volume will reduce hospital chair time (particularly in some specific challenging situations like pandemic restrictions) and increase convenience for patients and sites.
Section 2.3.4 Preventive measures to minimize the risk from the combination and Section 6.5.5 General guidelines for the management of IRs	Updated management guidelines on Grade 3 IR including permanent discontinuation of study treatment at third IR.	Clinical management of Grade 3 infusion reaction was updated to align with isatuximab IB ed11.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	Inclusion criterion number 6 (I 06.) updated.	Clarification.
Section 5.2 Exclusion criteria	Exclusion criterion number 15 (E15.): Cohort A1 and A2 were added.	Richter syndrome, a high-grade transformation of chronic lymphocytic leukemia (CLL) or low-grade lymphoma, will not be allowed.
Section 6. Study intervention, Section 6.5.2 Dose delay and dose omission, Section 7.1 Discontinuation of study intervention, Section 8 Study assessments and procedures, Section 9.3 Populations for analyses, Section 10.1.3 Informed consent process, Section 10.14 Appendix 14: Contingency Measures for a regional or national emergency that is declared by a governmental agency.	Contingency measures for a regional or national emergency such as Covid-19 are added.	To include instructions for the team to add flexible language in the protocol that may be implemented during regional or national emergencies.
Section 8.3 Adverse events and serious adverse events	Wordings related to reporting of SAEs and adverse events of special interest (AESIs) has been revised.	Clarification.
Section 8.11 Data collection after premature stop of the study	Details are provided for data collection from patients still on treatment if the sponsor decides to prematurely stop the study	Provisions for data collection after the premature stoppage of the study are included.
Section 9.3 Population of analyses	The text has been updated to: "The response evaluable population will include all participants in the all treated population **who fulfilled all inclusion and exclusion criteria without any major or critical deviation with** an evaluable baseline assessment and at least one evaluable post-baseline assessment during the treatment period. This population is the secondary analysis population for efficacy."	The definition of response evaluable population was clarified.
Section 10.1.7 Data quality assurance	Addition of wordings regarding monitoring techniques as per the latest template version.	Correction.
Section 10.6 Appendix 6: Disease assessment and Lugano classification	Replaced the blurry Lugano 2014 tumor assessment table with clear table for better readability.	Clarification
Section 11 References	Addition of missing references 25 to 27.	Correction.
Throughout the document	In addition, editorial corrections for consistency and clarity, and document formatting revisions have been made. Standardization of wordings as per the latest template version.	To improve readability and be compliant with the latest template.

TABLE OF CONTENTS

AMENDED CLINICAL TRIAL PROTOCOL 02 1

PROTOCOL AMENDMENT SUMMARY OF CHANGES 2

TABLE OF CONTENTS 6

LIST OF TABLES 11

LIST OF FIGURES 11

1 PROTOCOL SUMMARY 12

1.1 SYNOPSIS 12

1.2 SCHEMA 20

1.3 SCHEDULE OF ACTIVITIES (SOA) 21

1.4 PHARMACOKINETIC/PHARMACODYNAMICS FLOW CHART 27

1.4.1 Intervention period: Cycle 1 (Rich sampling) 27

1.4.2 Intervention period: from Cycle 2 and beyond (Sparse sampling) 28

2 INTRODUCTION 29

2.1 STUDY RATIONALE 29

2.2 BACKGROUND 31

2.2.1 Isatuximab 31

2.2.2 Cemiplimab 31

2.3 BENEFIT/RISK ASSESSMENT 32

2.3.1 Benefits 32

2.3.2 Potential and identified risks 32

2.3.3 Potential risk related to the combination 33

2.3.4 Preventive measures to minimize the risk from the combination 33

2.3.5 Conclusion 35

3 OBJECTIVES AND ENDPOINTS 36

3.1 APPROPRIATENESS OF MEASUREMENTS 37

4 STUDY DESIGN 38

4.1 OVERALL DESIGN 38

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN 41

4.3 JUSTIFICATION FOR DOSE 41

4.4 END OF STUDY DEFINITION 42

5 STUDY POPULATION 43

5.1 INCLUSION CRITERIA 43

5.2 EXCLUSION CRITERIA 45

5.3 LIFESTYLE CONSIDERATIONS 48

5.4 SCREEN FAILURES 49

6 STUDY INTERVENTION 50

6.1 STUDY INTERVENTION(S) ADMINISTERED 50

6.1.1 Investigational Medicinal Product(s) 51

6.1.2 Non-Investigational Medicinal Products: 53

6.1.3 Dosing sequence 54

6.1.4 Radiotherapy (for Cohorts A1 and A2) (optional) 55

6.1.5 Blinding procedures 56

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY 56

6.2.1 General rules 56

6.2.2 Storage conditions 57

6.2.3 Preparation, reconstitution and administration: 57

6.3 STUDY INTERVENTION COMPLIANCE 58

6.4 CONCOMITANT THERAPY 58

6.5 DOSE MODIFICATION 60

6.5.1 General rules 60

6.5.2 Dose delay and dose omission 61

6.5.3 Dose modifications 62

6.5.4 General guidelines for the management of Immune-Related Adverse Events 63

6.5.5 General guidelines for the management of IRs 64

6.5.6 Guidance in case of hepatitis B reactivation occurring under study treatment 67

6.5.7 Guidelines for the management of potential Tumor Lysis Syndrome 67

6.6 INTERVENTION AFTER THE END OF THE STUDY 67

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 68

7.1 DISCONTINUATION OF STUDY INTERVENTION 68

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY 70

7.3 LOST TO FOLLOW-UP 70

8 STUDY ASSESSMENTS AND PROCEDURES 72

8.1 EFFICACY ASSESSMENTS 72
8.1.1 FDG-PET-CT/CT 72
8.1.2 Bone marrow biopsy & aspirate: 74

8.2 SAFETY ASSESSMENTS 74
8.2.1 Physical examinations 74
8.2.2 Vital signs 75
8.2.3 Electrocardiograms 75
8.2.4 ECHO or MUGA 75
8.2.5 Pulmonary function test: 75
8.2.6 Clinical safety laboratory assessments 75

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 78
8.3.1 Time period and frequency for collecting AE and SAE information 80
8.3.2 Method of detecting AEs and SAEs 81
8.3.3 Follow-up of AEs and SAEs 81
8.3.4 Regulatory reporting requirements for SAEs 81
8.3.5 Pregnancy 82
8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs 82
8.3.7 Guidelines for reporting product complaints 83

8.4 TREATMENT OF OVERDOSE 83

8.5 PHARMACOKINETICS 83
8.5.1 Sampling time 83

8.6 PHARMACODYNAMICS 85

8.7 GENETICS 85

8.8 BIOMARKERS 86
8.8.1 RNA transcriptome research 86

8.9 IMMUNOGENICITY ASSESSMENTS 86

8.10 [HEALTH ECONOMICS] OR [MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS] 87

8.11 DATA COLLECTION AFTER PREMATURE STOP OF THE STUDY 87

9 STATISTICAL CONSIDERATIONS 89

9.1 STATISTICAL HYPOTHESES....89
9.2 SAMPLE SIZE DETERMINATION....89
9.3 POPULATIONS FOR ANALYSES....90
9.4 STATISTICAL ANALYSES....91
9.4.1 Efficacy analyses....91
9.4.2 Safety analyses....92
9.4.3 Other analyses....93
9.5 INTERIM ANALYSES....94
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS....95
10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS....95
10.1.1 Regulatory and ethical considerations....95
10.1.2 Financial disclosure....95
10.1.3 Informed consent process....96
10.1.4 Data protection....96
10.1.5 Committees structure....97
10.1.6 Dissemination of clinical study data....97
10.1.7 Data quality assurance....98
10.1.8 Source documents....98
10.1.9 Study and site closure....99
10.1.10 Publication policy....99
10.2 APPENDIX 2: CLINICAL LABORATORY TESTS....99
10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING....101
10.4 APPENDIX 4: RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC CEMIPLIMAB DRUG RELATED ADVERSE EVENTS....105
10.5 APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION....115
10.6 APPENDIX 6: DISEASE ASSESSMENT AND LUGANO CLASSIFICATION....119
10.7 APPENDIX 7: MITIGATING THE ANTI-CD38 INTERFERENCE WITH SEROLOGIC TESTING....122
10.8 APPENDIX 8: GENETICS....126
10.9 APPENDIX 9: MODIFICATION OF DIET IN RENAL DISEASE (MDRD) EQUATION....126

10.10 APPENDIX 10: DEFINITION OF LINE OF THERAPY 127

10.11 APPENDIX 11: COUNTRY-SPECIFIC REQUIREMENTS 127

10.11.1 Amendment for France 127

10.12 APPENDIX 12: ABBREVIATIONS 128

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY 130

10.13.1 Amended protocol 01 (19 September 2019) 130

10.14 APPENDIX 14: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY 135

11 REFERENCES 136

LIST OF TABLES

Table 1 - Objectives and endpoints 36
Table 2 - Overview of study interventions administered 51
Table 3 - Isatuximab and cemiplimab dose modification guidelines 62
Table 4 - General guidelines for immune-related adverse events 64
Table 5 - IR management 66
Table 6 - Laboratory and clinical abnormalities possibly consistent with TLS 67
Table 7 - Bioanalytical methods for isatuximab and functional cemiplimab pharmacokinetic 84
Table 8 - List of pharmacokinetic parameters and definitions 84
Table 9 - Bioanalytical methods for immune response assessment 87
Table 10 - Determination of sample size in Phase 2 90
Table 11 - Populations for analyses 90
Table 12 - Efficacy analyses 92
Table 13 - Safety analyses 92
Table 14 - Protocol-required safety laboratory assessments 100
Table 15 - Colitis adverse event management 105
Table 16 - Endocrine adverse event management 108
Table 17 - Pneumonitis adverse event management 109
Table 18 - Renal adverse event management 110
Table 19 - Dermatologic adverse event management 111
Table 20 - Hepatitis adverse event management 112
Table 21 - Ophthalmology (uveitis) adverse event management 113
Table 22 - Nausea and vomiting adverse event management 114
Table 23 - Highly effective contraceptive methods 117
Table 24 - Revised Criteria for Response Assessment 119

LIST OF FIGURES

Figure 1 - Graphical study design 20

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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

Short title: A study of isatuximab-based therapy in participants with lymphoma

Rationale:

Monoclonal antibodies (mAb) that block the programmed cell death/programmed cell death-ligand (PD-1, PD-L1) axis alone have demonstrated benefit in lymphoma therapy. Isatuximab, an anti-cluster of differentiation CD38 (CD38) mAb, has shown clinical response in relapsed refractory multiple myeloma (MM) participants as a single agent and in combination with other agents. Although isatuximab has not been tested in lymphoma, this study is designated to explore whether isatuximab may contribute to reshaping the tumor immune-environment and will enhance the activity of checkpoint inhibitor therapy. A recent report has shown that the combination of anti-PD-L1 and CD38 antibodies induces a greater anti-tumor immune response than anti-PD-L1 monotherapy in a mouse lung cancer model and possibly revert resistance to anti-PD-1/PD-L1 therapies, establishing the hypothesis of targeting CD38 to potentiate anti-PD-1/PD-L1 therapies.

Objectives and endpoints

Responses will be determined per Lugano response criteria 2014, as assessed by the Investigators (1). All tumor assessment imaging data must be kept in sites for potential future use, including independent review.

Objectives	Endpoints
Primary	
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 1:** Safety and tolerability will be assessed based on dose limiting toxicities (DLTs, in Cycle 1), adverse events (AEs)/serious adverse events (SAEs), and laboratory abnormalities.

Phase 2: 1 - Cohort A1 (anti-PD-1/PD-L1 naive cHL): To assess the complete remission (CR) rate of isatuximab in combination with cemiplimab. 2 - Cohort A2 (cHL progressing from PD-1/PD-L1), B (DLBCL) and C (PTCL): To assess the objective response rate (ORR) of isatuximab in combination with cemiplimab.	**Phase 2:** 1 - Cohort A1: CR rate as defined by as the proportion of participants who have a CR as a best overall response during the isatuximab + cemiplimab therapy period using the Lugano response criteria 2014 (1) (Appendix 6 Section 10.6). 2 - Cohorts A2, B, and C: ORR defined as the proportion of participants who have a CR or partial response (PR) as a best overall response during isatuximab + cemiplimab therapy period using the Lugano response criteria 2014 (1) (Appendix 6 Section 10.6).
Secondary	
1 - To evaluate the safety of the RP2D of isatuximab in combination with cemiplimab.	1 - AEs/SAEs and laboratory abnormalities for isatuximab+ cemiplimab.
2 - To evaluate the safety of the combination of isatuximab with cemiplimab and radiotherapy in participants with cHL	2 - AEs/SAEs and laboratory abnormalities in isatuximab + cemiplimab + radiotherapy treated participants (Cohort A1 and A2).
3 - To evaluate the immunogenicity of isatuximab and cemiplimab when given in combination.	3 - Immunogenicity: Anti-drug antibody (ADA) against isatuximab and against cemiplimab.
4 - To characterize the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.	4 - PK evaluation using non-compartmental analysis for both compounds using serum concentrations for cemiplimab and plasma concentrations for isatuximab.
5 - To assess overall efficacy of: • isatuximab in combination with cemiplimab, And • isatuximab in combination with cemiplimab and radiotherapy.	5 - Efficacy: • Tumor burden change, duration of response (DoR), disease control rate (DCR), defined as the percentage of participants who achieve CR, partial response (PR) or stable disease (SD) and progression-free survival (PFS). • For Cohort A1, ORR during isatuximab + cemiplimab ± radiotherapy periods. CR rate during isatuximab + cemiplimab + radiotherapy period. • For Cohort A2, ORR during isatuximab + cemiplimab + radiotherapy period. CR rate during isatuximab + cemiplimab ± radiotherapy periods.

Overall design:

This is a Phase 1/2 open-label, non-comparative, multi-center, safety, preliminary efficacy and PK study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma. This study will be conducted in 2 phases (see Section 1.2 for study design schema).

Phase 1 (Safety run-in)

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

Dose levels and schedules are described in the table below.

Dose levels and schedules for Phase 1

Dose level (DL)	Isatuximab		Cemiplimab	
	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 every week (QW) × 4 (Cycle 1) 10 mg/kg every 2 weeks (Q2W) (Cycle 2 ~ Cycle 6)	10 mg/kg every 3 weeks (Q3W)	250 mg Q2W	350 mg Q3W
Minus -1 (DL-1)	5 mg/kg QW × 4 (Cycle 1) 5 mg/kg Q2W (Cycle 2 ~ Cycle 6)	5 mg/kg Q3W	250 mg Q2W	350 mg Q3W

The dose limiting toxicity (DLT) observation period is the first 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 investigational medicinal product (IMPs) due to DLT), based on the rules listed below. The totality of the adverse events (AEs) collected from all treated participants will be taken into consideration when deciding recommended Phase 2 dose (RP2D).

- If 0/3 participants experience a DLT, the starting dose will be the RP2D.
- If 1/3 participants experience a DLT, 3 additional participants will be enrolled at the starting dose level:
  - If a total of 1/6 participants treated at the starting dose experience 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, the 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 at least one participant for the Phase 1.

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

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

The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator (Section 8.3). The DLTs will be confirmed by the Sponsor and recruiting Investigators.

Phase 2 (Efficacy signal/Simon 2-stage design):

Phase 2 includes 4 cohorts:

Cohort A1: cHL anti-PD-1/PD-L1 naïve.

Cohort A2: cHL anti-PD-1/PD-L1 progressor.

Cohort B: DLBCL anti-PD-1/PD-L1 naïve.

Cohort C: PTCL anti-PD-1/PD-L1 naïve.

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 indication in Stage 1 of Phase 2.

In both Phases 1 and 2, participants with cHL who achieve best overall response of PR or stable disease (SD) at the disease assessment planned for Week 36, if deemed appropriate (and does not meet exclusion criteria E01, E06, E08, E21, E30, and E32) by the Investigator, may begin radiotherapy between D1 to D14 (preferably between D1 to D7) of the next immediate cycle.

Number of participants:

In Phase 1, approximately 3 to 12 DLT evaluable participants are expected to be enrolled.

In Phase 2, participants will be screened to achieve approximately 118 treated participants with study intervention in Cohorts A1, A2, B, and C (see Section 9.2 for details of the sample size determination).

Intervention groups and duration:

The duration of the study for a participant will include a screening period (up to 28 days), a treatment period (up to 96 weeks), a post safety follow-up period up to 90 days and a survival follow-up period (except for the cohorts where the results of interim analysis are not positive) until death or study cut-off date. 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.

Treatment period: The cycle duration is 28 days during the 6 first cycles then 21 days. Participants will continue treatment until disease progression, unacceptable AE, participant's decision to stop the treatment, 96 weeks (at least 48 weeks from initial signal of CR, whichever is longer) of delivery of IMP(s) without documented progressive disease (PD), or any other reason.

Safety follow-up period: After treatment discontinuation, participants will return to the study site 30 days (±7 days) after the last dose of IMP(s), or when the participant receives another anti-cancer therapy, whichever is earlier, for end of treatment (EOT) assessments. In addition, there will be an extended safety follow-up period for 90 days after the last dose of IMP(s) including 60 days (±7 days) visit after the last IMP for safety assessment and 90 days (±7 days) visit after the last IMP for ADA assessment (only for isatuximab) and for safety assessment.

Participants who discontinue the study treatment without PD will be followed at 90 days (±7 days) for disease assessment.

Survival follow-up period: The further follow-up schedule beyond 90 days after last dose of IMP(s) is according to the disease progression status:

- Participants who discontinue study treatment due to PD: phone call follow-up will be done every 90 days from the date of last IMP(s) administration until death or final study cut-off date.
- Participants who discontinue the study treatment without PD: will be followed every 90 days for disease assessment until confirmation of PD or start treatment with another anti-cancer therapy, or study cut-off date whichever comes first. After PD, participant will be followed by phone call until death or final study cut-off date.
- Participants who are still on study treatment after study cut-off date: will continue to receive study treatment if they benefit, and will undergo planned study procedures (except PK and ADA) until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

After EOT, all the ongoing related non-serious AEs, the ongoing SAEs and the new related AE/SAEs are to be followed until resolution or stabilization. Stabilization is defined as an event ongoing without any change for at least 3 months.

Investigational medicinal product(s): Isatuximab with cemiplimab and radiotherapy (Cohorts A1 and A2) or isatuximab in combination with cemiplimab (Cohort B and C). Isatuximab and cemiplimab could be given up to 96 weeks (at least 48 weeks from initial signal of CR whichever is longer).

Isatuximab:

Formulation:

- Drug product concentrated solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine. 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0.

Route(s) of administration: IV infusion.

Dose regimen: Refer to the dose levels and schedule for Phase 1. Dose for Phase 2 will be determined based on safety data from Phase 1.

Cemiplimab:

Formulation

- Drug product concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.

Or

- Drug product concentrated solution 50 mg/mL in 10 mL vials with 7.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.

Route(s) of administration: IV infusion.

Dose regimen: Refer to the dose levels and schedule for Phase 1.

Non-investigational medicinal products: will be locally sourced and formulations may vary.

Premedication

All participants will receive the following 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). The standard premedication regimen will include see Section 6.1.2:

- Acetaminophen (paracetamol) 650 to 1000 mg oral route (PO) (or equivalent).
- Ranitidine 50 mg IV (or equivalent at Investigator's discretion).
- Diphenhydramine 25 to 50 mg IV (or equivalent).
- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg PO (or equivalent).

Criteria for optional premedication for IRs:

- For a patient who has no IR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IR Grade ≤2 during their first infusion only and then experiences no further IRs during their next 3 infusions: The Investigator should discuss with the Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next infusion without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.

Radiotherapy (for Cohorts A1 and A2) (optional):

- Formulation: Not applicable.
- Route(s) of administration: Stereotactic radiation therapy.
- Dose regimen: see Section 6.1.4.

Statistical considerations:

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 indication Phase 2 Stage 1. Data from cHL (Cohorts A1 and A2), DLBCL, and PTCL cohorts in Phase 2 will be analyzed and reported separately by cohort.

- **Analysis of primary efficacy endpoints:**
  - 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 alpha level defined in the sample size calculation section.
- **Analysis of secondary 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 progression-free survival (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 from both isatuximab + cemiplimab and isatuximab + cemiplimab + radiotherapy periods, and for participants in Cohorts A1 and A2 who receive isatuximab + cemiplimab + radiotherapy.

- **Analysis of safety endpoints:**

  In Phases 1, the DLTs will be listed by participant using the DLT evaluable population.

  In Phases 1 and 2, the AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). AEs and laboratory abnormalities will be graded according to NCI CTCAE version 5.0.

  - The number (%) of participants experiencing treatment-emergent AEs (TEAEs) by primary system organ class (SOC) and preferred term (PT) will be summarized by CTCAE grade (all grades and Grade ≥3) for the all-treated population. Same table will be prepared for treatment-related TEAEs, AEs of special interest (AESIs), TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. The post-treatment AEs will be analyzed separately,
  - The number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the all-treated population.

- **Analysis of pharmacokinetic endpoints:**
  - Individual concentrations and pharmacokinetic (PK) parameters of both isatuximab and cemiplimab will be descriptively summarized.

- **Analysis of immune response and pharmacodynamic endpoints:**
  - Findings from immune markers and pharmacodynamics markers will be descriptively summarized and tabulated.

Data Monitoring Committee: Yes

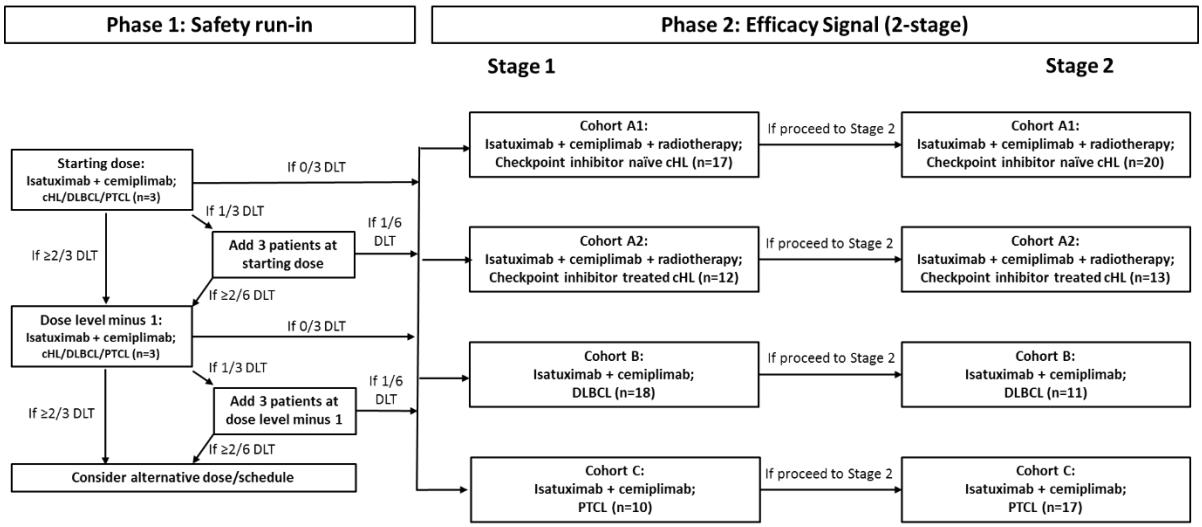
Independent from the Sponsor and Investigators, the Data Monitoring Committee (DMC) role will be to monitor the safety of the participants enrolled in the study (ie, exposed to study treatment and/or to study procedures) and to provide the Sponsor with appropriate recommendations in due time to ensure the safety of the participants. During this exercise, the DMC will also institute any measures that may be required for ensuring the integrity of the study results during the execution of its primary mission.

Study Committee:

During Phase 1, the study committee (SC) will review clinical data approximately every 2 weeks. During Phase 1, composition of the SC will vary based on the matter discussed, but it will generally include Sponsor representatives and at least two Investigators with participants participating to Phase 1. For Phase 2, the SC will consist of Sponsor representatives and at least two Investigators participating in Phase 2 Stage 1 or Stage 2. A radiotherapist will be included in the SC meetings to discuss the radiotherapy option after Cycle 10. The SC meetings will occur on an as needed basis to review data and provide strategic recommendations on study medical decisions.

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: cHL = Classic Hodgkin's lymphoma; DLBCL = Diffuse large B cell lymphoma; DLT = Drug toxicity limit, PTCL = Peripheral T-cell lymphoma

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening	Intervention Period												End of Treat-ment (EOT)	Post-treatment Safety FUP		Survival Phone-call FUP	Notes
		For Cohort A1 and A2: Isatuximab + Cemiplimab Therapy Period							For Cohort A1 and A2: Isatuximab + Cemiplimab + Radiotherapy Therapy Period									
		For Cohorts B and C: Isatuximab + Cemiplimab Therapy Period																
		1 Cycle = 28 Days							1 Cycle = 21 Days									
		C1					C2~C6		C7~C10	C11			C12~C30					
	D-28 to D-1	D1	D2	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±2)	D1 (±3)	D1 (±3)	D3 (±1)	D5 (±1)	D1 (±3)	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin	> 90 (±7) days after last IMP admin	
Informed Consent/ Inclusion/Exclusion Criteria	X									X[a]								Informed consent may be signed prior to D -28. Section 5.1
Demography, Medical/Surgical and Disease History	X																	Section 5.1
Physical Examination	X (<14 days prior to first dose)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.1
Height	X																	Section 8.2.1

Procedure	Screening	Intervention Period												End of Treat-ment (EOT)	Post-treatment Safety FUP		Survival Phone-call FUP	Notes
		For Cohort A1 and A2: Isatuximab + Cemiplimab Therapy Period											For Cohort A1 and A2: Isatuximab + Cemiplimab + Radiotherapy Therapy Period					
		For Cohorts B and C: Isatuximab + Cemiplimab Therapy Period																
		1 Cycle = 28 Days							1 Cycle = 21 Days									
		C1					C2~C6		C7~C10	C11			C12~C30					
	D-28 to D-1	D1	D2	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±2)	D1 (±3)	D1 (±3)	D3 (±1)	D5 (±1)	D1 (±3)	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin	> 90 (±7) days after last IMP admin	
Weight	X	X	X	X	X	X	X	X	X	X			X	X				See I 09 Section 8.2.1
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
Performance Status (ECOG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.1
12-Lead ECG	X																	Section 8.2.3
ECHO or MUGA	X																	Section 5.2 & Section 8.2.4
Pulmonary Function Test	X																	Section 5.2 & Section 8.2.5
Urine or Serum Pregnancy Test (WOCBP only)	X (within 7 days prior to first dose)						X		X	X			X	X	X	X	X	Section 10.2, Section 10.5, & Section 8.2.6.7
Blood Chemistry	X	X	X	X	X	X	X	X	X	X			X	X	X	X		Section 10.2 & Section 10.9 for eGFR
Hematology	X	X	X	X	X	X	X	X	X	X			X	X	X	X		Section 10.2

Procedure	Screening	Intervention Period											End of Treatment (EOT)	Post-treatment Safety FUP		Survival Phone-call FUP	Notes
		For Cohort A1 and A2: Isatuximab + Cemiplimab Therapy Period										For Cohort A1 and A2: Isatuximab + Cemiplimab + Radiotherapy Therapy Period					
		For Cohorts B and C: Isatuximab + Cemiplimab Therapy Period															
		1 Cycle = 28 Days							1 Cycle = 21 Days								
		C1					C2~C6		C7~C10	C11			C12~C30				
	D-28 to D-1	D1	D2	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±2)	D1 (±3)	D1 (±3)	D3 (±1)	D5 (±1)	D1 (±3)	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin	> 90 (±7) days after last IMP admin	
Coagulation (prothrombin time or INR, and aPTT)	X	X	As clinically indicated														Section 10.2
TSH and free T4	X	Every other cycle												X	X	X		Section 10.2
Blood Typing Interference test	X						Cycle 2 only											Section 8.2.6.5, Section 10.2 & Section 10.7
Serology HIV, HBV and HCV (Participants with prior history of these infections)	X		As clinically indicated															Section 8.2.6.6
Hepatitis viral serology[b]	X	As clinically indicated																Section 6.4, Section 6.5.6 & Section 10.26.2.2.2
Urinalysis	X	As clinically indicated												X	X	X		Section 10.2 & Section 8.2.6.3
PK		See Pharmacokinetic/pharmacodynamics Flow Chart																Section 8.5
ADA		See Pharmacokinetic/pharmacodynamics Flow Chart																Section 8.9

Procedure	Screening	Intervention Period												End of Treat-ment (EOT)	Post-treatment Safety FUP		Survival Phone-call FUP	Notes
		For Cohort A1 and A2: Isatuximab + Cemiplimab Therapy Period											For Cohort A1 and A2: Isatuximab + Cemiplimab + Radiotherapy Therapy Period					
		For Cohorts B and C: Isatuximab + Cemiplimab Therapy Period																
		1 Cycle = 28 Days							1 Cycle = 21 Days									
		C1					C2~C6		C7~C10	C11			C12~C30					
	D-28 to D-1	D1	D2	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±2)	D1 (±3)	D1 (±3)	D3 (±1)	D5 (±1)	D1 (±3)	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin	> 90 (±7) days after last IMP admin	
Bone Marrow Biopsy/Aspirate	As per Lugano response criteria 2014																	Section 8.1.2
Freshly Collected Tumor Biopsy for Biomarker Analysis	X[c]						X (within 7 days prior to C2D1)											Section 8.6 & Section 8.8.1
Blood Draw for Biomarker Analysis		X																Section 8.7 & Section 8.8
Neck, Chest, Abdominal, Pelvic FDG-PET-CT, CT[d]	X	Year 1: FDG-PET-CT/CT scans every 12 weeks, Year 2 and beyond: CT scan every 12 weeks, FDG-PET-CT scan as clinically indicated .												X				Section 8.1.1 & Section 10.6
Assessment of Lymphoma B Symptoms	X	In accordance with disease response assessment												X				Section 8.1.1
Isatuximab Administration			X	X	X	X	X	X	X	X			X					Section 6.1.1
Cemiplimab Administration		X			X		X	X	X	X			X					Section 6.1.1
Radiotherapy Administration[e] (optional)										X	X	X						Section 6.1.4

Procedure	Screening	Intervention Period											End of Treatment (EOT)	Post-treatment Safety FUP		Survival Phone-call FUP	Notes
		For Cohort A1 and A2: Isatuximab + Cemiplimab Therapy Period										For Cohort A1 and A2: Isatuximab + Cemiplimab + Radiotherapy Therapy Period					
		For Cohorts B and C: Isatuximab + Cemiplimab Therapy Period															
		1 Cycle = 28 Days							1 Cycle = 21 Days								
		C1					C2~C6		C7~C10	C11			C12~C30				
	D-28 to D-1	D1	D2	D8 (±1)	D15 (±1)	D22 (±1)	D1 (±3)	D15 (±2)	D1 (±3)	D1 (±3)	D3 (±1)	D5 (±1)	D1 (±3)	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin	> 90 (±7) days after last IMP admin	
AE/SAE Assessment	X	continuous												X (ongoing related AEs, ongoing SAEs, new related AE/SAEs)				Section 8.2, Section 8.3 & Section 10.3
Prior/Concomitant Medication	X (within 28 days prior to first dose)	X												X (related to AE/SAEs)				Section 6.4
New Anticancer Therapy													X	X		X		
Survival status																X[f]		

a Re-check exclusion criteria (E01, E06, E08, E21, E30 and E32) for participants in Cohort A1 and A2 for eligibility of radiotherapy.

b Screening with serological tests for hepatitis B and C to be done prior to randomization/enrollment (HBsAg, anti-HBs, anti-HBc [total and IgM], anti-HCV, HCV RNA level) if not performed within 1 year.
For patients with anti-HBc positive (HBsAg positive patients being not eligible), HBV DNA testing by PCR will also be done at baseline.
For patients with positive anti-HBc IgG, negative HBsAg and undetectable (under limit of quantification) HBV DNA at study entry (HBV carriers: past resolved infection, resolving acute infection or receiving antiviral treatment with controlled infection), specialist advice should be requested, close monitoring of viral reactivation (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or HBV DNA in resolved infection) throughout and following the end of study treatment should be proposed (ALT, AST and HBV DNA at least every 3 months, up to 6 months after treatment discontinuation or initiation of further anticancer therapy). See Section 6.5 for patients presenting viral reactivation under treatment.
In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination.
Note: eCRF pages to be designed to collect quantitative values for HBV DNA; for the other parameters only qualitative data will be collected.

c Tumor biopsy is mandatory (unless clinically unfeasible and after discussion with Sanofi Medical Monitor for Phase 1 and Phase 2 Stage 1); mandatory for Phase 2 Stage 2 and possibly at Cycle 2 Day 1. If disease location is in a superficial lymph node, excisional biopsy or resected tissue is required if clinically feasible; otherwise, core needle biopsy is acceptable. Fine needle aspirates are not acceptable. Archival tumor material may be used to replace baseline biopsy, if the sample was obtained after progression from immediate prior therapy.

d Please ensure that spleen measurement and FDG-PET data (SUV max/5PS score) for liver, mediastinal pool, and all assessed lesions are recorded during each response assessment.

e Radiotherapy for "no fly zone", 2Gy × 2 fractions in 2 consecutive days (eg, Monday and Tuesday) will be administered once a week every 3 weeks for 3 times (treatment lasts for a total of 9 weeks), starting in the same week when isatuximab and cemiplimab are administered.

f Survival status follow-up should not be performed for the cohorts where the results of interim analysis are not positive.

Abbreviations: 5PS = 5-point scale; ADA = Anti-drug antibody; AE = Adverse event; ALT = Alanine aminotransferase; AP = Plasma antibody; aPTT = Activated partial thromboplastin time; AS = Serum antibody; AST = Aspartate-Amino-Transferase; C = Cycle; CT = Computed tomography; D = Day; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = End of infusion (Actual EOI sample should be taken when the pump beeps (end of infusion) before flush); EOT = End of Treatment (Post-treatment Safety); FDG = Fluorodeoxyglucose; FUP = Follow-up period (Post-treatment safety); HBc =Hepatitis B core antigen; HBV = Hepatitis B virus; HBsAg = Surface antigen of the hepatitis B; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; ID = Identification; Ig = Immunoglobulin; IMP = investigational medicinal product; INR = International normalized ratio; IV = Intravenous, MUGA = Multigated Acquisition; P = Plasma; PET = Positron emission tomography; PD = Progressive disease; PK = Pharmacokinetic; RNA = Ribonucleic acid; RNT = relative nominal time; SAE = Serious adverse event; S = Serum; SOI = Start of infusion; SUV = Standardized uptake value; TSH = Thyroid stimulating hormone; WOCBP = Women of child-bearing potential.

1.4 PHARMACOKINETIC/PHARMACODYNAMICS FLOW CHART

1.4.1 Intervention period: Cycle 1 (Rich sampling)

Procedure		Intervention period											
		C1											
		D1			D2			D5	D8	D15			D22
Cemiplimab	IV infusion	X----------X								X----------X			
	Sample RNT (hours) Ref. Cemiplimab SOI	SOI	EOI	EOI+4h				96h	168h	336h (SOI C1D15)	EOI		
	Sample time window	[-24h,SOI]	[-5 min,EOI]	±30min				±5h	±24h	[-24h,SOI]	[-5 min,EOI]		
	PK sample ID[e]	S00	S01	S02				S03	S04	S05[b]	S06		
	ADA sample ID[c]	AS00											
		C1											
		D1			D2			D5	D8	D15			D22
Isatuximab	IV infusion				X----------X				X---		X----------X		X---
	Sample RNT(hours) Ref. isatuximab SOI				SOI	EOI	EOI+4h	72h	144h (SOI C1D8)	SOI		EOI	SOI
	Sample time window				[-24h,SOI]	±10min	±30min	±5h	[-24h,SOI]	[-24h,SOI]		±10min	[-24h,SOI]
	PK sample ID[e]				P00	P01	P02	P03	P04[b]	P05[a]		P06	P07
	ADA sample ID[d]				AP00								

1.4.2 Intervention period: from Cycle 2 and beyond (Sparse sampling)

	Procedure	C2~C3					C4						C5~C30	EOT	FUP	
		D1			D15		D1				D15		D1	30 (±7) days after last IMP admin	60 (±7) days after last IMP admin	90 (±7) days after last IMP admin
Cemiplimab	IV infusion	X------X			X------X		X------X				X------X		X			
	Sample RNT (hours) Ref. Cemiplimab SOI	SOI	EOI		SOI	EOI	SOI	EOI			SOI	EOI	SOI			
	Sample time window	[-24h,SOI]	[-5 min,EOI]		[-24h, SOI]	[-5 min, EOI]	[-24h, SOI]	[-5 min, EOI]			[-24h, SOI]	[-5 min, EOI]	[- 24 h, SOI]			
	PK sample ID[e]	S00	S01		S02	S03	S00	S01			S02	S03	S00[e]	SF00	SF01	
	ADA Sample ID[c]	AS00 (C2 only)											AS00[c]	ASF00		
	Procedure	C2~C3					C4						C5~C30			
		D1			D15		D1				D15		D1			
Isatuximab	IV infusion		X----X			X---		X------X				X---	X---			
	Sample RNT (hours) Ref. isatuximab SOI	SOI		EOI	SOI		SOI		EOI	EOI+1h	SOI		SOI			
	Sample time window			±10min					±10min	±10min						
	PK sample ID [e]	P00[a]		P01 (C2)	P02[a]		P00[a]		P01	P02	P03[a]		P00[a, e]			
	ADA Sample ID[d]	AP00[a]					AP00[a]						AP00[a, d]			APF00[d]

a Isatuximab predose sample (SOI) may be collected at the same time as the predose sample of cemiplimab (SOI) before cemiplimab infusion start.

b Sample (ie, C1 T336h for cemiplimab and C1 T144h for isatuximab) must be collected even if the infusion planned for cemiplimab at C1D15 and for isatuximab at C1D8 is not done or delayed.

c For cemiplimab, from Cycle 5 ADA samples have to be collected every third Cycle (ie, D1 of Cycle 5, 8, 11, 14, etc) till the last study treatment, and at EOT or at the primary analysis cut-off date, whichever comes first. During the intervention period, if isatuximab is stopped and cemiplimab treatment continues cemiplimab ADA samples should be collected as planned per PK/PD flow chart. In response to AE's of special interest, such as anaphylaxis or hypersensitivity, ADA samples may be collected closer to the event, based on the judgment of the Investigator and/or medical monitor. No ADA samples will be collected after the primary analysis cut-off date.

d For isatuximab, from Cycle 5 ADA samples to be collected every third Cycle (ie, D1 of Cycle 5, 8, 11, 14, etc) till the last study treatment, and at FUP 90 (±7) days after last isatuximab administration or at the primary analysis cut-off date, whichever comes first. However, collection can be reduced or stopped earlier upon notification from the Sponsor based on the updated knowledge of isatuximab immunogenicity. After FUP 90(±7) days after last isatuximab administration no further ADA will be sampled even if the status is positive or inconclusive. No ADA samples will be collected after the primary analysis cut-off date.

e Cemiplimab and isatuximab PK sample to be collected at predose each cycle from C5 to C11 then every third Cycle, ie, C14, 17, C20 till the last study treatment or at the primary analysis cut-of date, whichever comes first. For cemiplimab only, PK sample to be collected at EOT and 60 (±7) days after last study treatment or at the primary analysis cut-of date, whichever comes first. No PK samples will be collected for cemiplimab or isatuximab after the primary analysis cut-off date. *For isatuximab only, collection can be reduced or stopped earlier upon notification from the Sponsor based on the updated knowledge of isatuximab PK.*

Abbreviations: AP = Plasma antibody; ADA = Anti-drug antibody; AS = Serum antibody; C = Cycle; D= Day; EOI = End of infusion; EOT= End of Treatment (Post-treatment Safety; FUP = Follow-up period (Post-treatment safety); ID = Identification; IMP = investigational medicinal product; IV = Intravenous; P = Plasma; PK = Pharmacokinetic; RNT= relative nominal time; S = Serum; SOI = start of infusion.

2 INTRODUCTION

2.1 STUDY RATIONALE

Monoclonal antibodies that block the PD-1/PD-L1 axis have demonstrated clinical benefit in lymphoma therapy. Nivolumab and pembrolizumab were granted accelerated approval by the US Food and Drug Administration (FDA) for relapsed or refractory classic Hodgkin lymphoma (cHL). Despite their success, only approximately 20% of the participants achieved complete remission (CR) (2, 3). Cemiplimab monotherapy in an early phase study has demonstrated similar result (4). Combining nivolumab with brentuximab vedotin increased CR rate to 61% in the interim analysis of a Phase 1/2 study (5). However not all participants can tolerate brentuximab vedotin. For the participants who failed nivolumab or pembrolizumab, cytotoxic chemotherapy remains the only available treatment option (6).

In diffuse large B-cell lymphoma (DLBCL) and peripheral T-cell lymphoma (PTCL), objective responses were observed in 4 out of 11 and 2 out of 5 heavily pre-treated participants, respectively, in a nivolumab monotherapy Ph1b study (7). Similarly, objective responses were observed in 3 (all CRs) out of 18 participants with DLBCL treated with cemiplimab monotherapy (4). Limited treatment options are available to participants with DLBCL who failed at least 3 lines of therapy and participants with PTCL who have failed frontline therapy. Tisagenlecleucel (a chimeric antigen receptor T-cell immunotherapy) is recently approved by US Food and Drug Administration for the treatment of adult participants with relapsed or refractory DLBCL. Nevertheless, tisagenlecleucel may not be accessible to all participants.

Many participants will require checkpoint inhibitor combination therapies to improve outcome, despite checkpoint inhibitor monotherapy is an effective treatment strategy. Numerous clinical studies are currently evaluating anti-PD-1/PD-L1 antibodies in combination with chemotherapy, targeted therapies, other immunotherapies and radiotherapy in participants with lymphoma. A recent report has shown that the combination of anti-PD-L1 and CD38 antibodies induces a greater anti-tumor immune response than anti-PD-L1 monotherapy in a mouse lung cancer model and possibly revert resistance to anti-PD-1/PD-L1 therapies, establishing the hypothesis of targeting CD38 to potentiate anti-PD-1/PD-L1 therapies (8, 9).

CD38 expression is well-documented in hematological cancers, including MM and certain types of lymphomas and leukemia (10). The role of CD38 in tumor environment is not completely understood, but there are several findings indicating that CD38 can contribute to the immune-suppressive tumor microenvironment:

A) CD38 catalyzes the conversion of nicotinamide adenine dinucleotide into immunosuppressive adenosine (10).

B) CD38 expression is highly correlated with the expression of PD-1 and its ligands in solid tumor biopsies.

C) CD38 is found upregulated in tumor models that have acquired resistance to anti-PD-L1 (8, 9).

D) CD38 expressing myeloid derived suppressor cells promote growth of human tumors in mice (11).

E) CD38 expressing mouse tumor cells inhibit the proliferation of autologous T cells (12).

Isatuximab (anti-CD38 antibody) can induce different immune-modulatory mechanisms that can contribute to reshape the tumor microenvironment and enhance the anti-tumor activity of anti-PD-1 antibodies:

A) Isatuximab decreases circulating regulatory T cell counts and increases total T cell counts in MM participants (12).

B) Isatuximab restores T cell function inhibited by regulatory T cells (12).

C) Isatuximab induces activation of natural killer (NK) cells and increases their cytolytic activity (13).

D) Isatuximab increases macrophage phagocytic activity and M1 polarization.

In lymphomas, CD38 is found expressed on the tumor cells of Hodgkin's lymphoma (HL), DLBCL, and PTCL (14, 15).

Hodgkin Lymphoma (HL)

It has been shown that a considerable fraction of infiltrating CD4+ T cells in HL represented by T regulatory cells (Treg) have immunosuppressive activity on infiltrating cytotoxic T-cells (16, 17, 18). Gaetano et al. reported that in 108 HL participant samples, 43% of CD4+ T-cells also expresses CD38, and is significantly higher than that detected in benign reactive lymphoid hyperplasia (14). The majority of activated CD4+CD38+ T-cells are also found to be CD26-, which represents a phenotype that contribute to tumor escape by increasing levels of immunosuppressive adenosine and evasion of the host antitumor response.

Diffuse Large B-Cell Lymphoma (DLBCL)

Depending on the cut-off applied, up to 61% and 69% of DLBCL cases were reported to have PD-L1+ tumor cells and PD-1+ tumor infiltrating lymphocytes, respectively (19). CD38 expression was observed in both germinal center B cell-like (GCB) and activated B cell-like (ABC) DLBCL samples, where prevalence and receptor density was higher in GCB than ABC. Through direct targeting of CD38, isatuximab was also shown to induce apoptosis in vitro and in vivo in SU-DHL-8 DLBCL models (13).

Peripheral T-Cell Lymphoma (PTCL)

CD38, PD-1, and PD-L1 are expressed in certain subtypes of PTCL (eg, 80% and 70% of angioimmunoblastic T-cell lymphoma [AITL] samples are CD38 and PD-1 positive, respectively) (15).

Based on the above rationale, it is hypothesized that isatuximab (anti-CD38) in combination with cemiplimab (anti-PD-1) may be effective in participants with HL, DLBCL, and PTCL.

Furthermore, emergent clinical data suggests that radiotherapy, in combination with anti-PD-1/PD-L1, elicits immune-mediated anti-neoplastic effects locally as well as systemically (abscopal) in solid tumors (20, 21, 22). A recent report of a participant with refractory HL who was enrolled in a Phase 1 pembrolizumab study describes an abscopal effect after local radiation administered concurrently with pembrolizumab (6). In an effort to improve CR rate (CRR) and enhance response duration in HL and cutaneous T-cell lymphoma participants, several studies are ongoing combing anti-PD-1 with radiotherapy (NCT03179917, NCT03480334, NCT03385226). The coupling of radiotherapy with immune checkpoint inhibition provides an opportunity for synergistic abscopal anti-tumor effects. The hypothesis of coupling radiotherapy with isatuximab and cemiplimab will be evaluated in the current study.

2.2 BACKGROUND

2.2.1 Isatuximab

Isatuximab (SAR650984) is a mAb that binds selectively to a unique epitope on the human surface antigen CD38. Isatuximab kills tumor cells via multiple biological mechanisms; antibody-dependent cellular-mediated cytotoxicity, antibody-dependent cellular-mediated phagocytosis, complement-dependent cytotoxicity and direct induction of apoptosis (pro-apoptosis) without crosslinking. Isatuximab treatment of CD38-expressing cells also results in inhibition of CD38 enzymatic activity.

At the cut-off date of 05 January 2018, a total of 675 participants were treated with isatuximab single agent or in combination in 10 studies. All participants had hematological malignancy.

Refer to the isatuximab Investigator's Brochure for the most updated nonclinical and clinical studies of isatuximab.

2.2.2 Cemiplimab

Cemiplimab (REGN2810) is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD-L1-mediated T cell inhibition. Cemiplimab displayed a robust, dose-dependent suppression of MC38.Ova tumors in the syngeneic mouse tumor model. The nonclinical activity of cemiplimab is similar to two in-house generated anti-PD-1 comparator antibodies with identical amino acid sequence to nivolumab and pembrolizumab (based on publicly available sequence data). On 28 Sep 2018, the US FDA approved cemiplimab-rwlc for patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC.

Refer to the cemiplimab Investigator's Brochure for the most updated nonclinical and clinical studies of cemiplimab.

2.3 BENEFIT/RISK ASSESSMENT

Detailed information about the known and expected benefits and risks associated with the treatments to be used in study ACT15320 may be found in the Investigator's Brochure of isatuximab and the Investigator's Brochure of cemiplimab.

2.3.1 Benefits

Refer to Section 2.1.

2.3.2 Potential and identified risks

2.3.2.1 Isatuximab

Isatuximab has been investigated either as monotherapy or in combination in participants with hematological malignancies. The safety profile of isatuximab monotherapy has been best characterized in study TED10893 (Phase 1 and Phase 2, including 186 participants with MM), where the most common TEAEs, excluding the AEs corresponding to laboratory abnormalities, include IRs, fatigue, nausea, upper respiratory infection, cough, back pain and diarrhea. Infusion reactions occurred in 49.4% of the participants from the TED10893 Phase 1 study.

The IRs associated with isatuximab in participants who are administered appropriate primary prophylaxis (see also Section 2.3.4) are most common with the first administration of the drug, are not dose-dependent, are Grade 1 to 2 in severity, are manageable with standardized precautions detailed in each study protocol, are resolved either spontaneously or with standard medication by the next day following the infusion, and the participants do not appear to sustain sequelae. The IRs generally do not cause treatment discontinuation, and do not tend to recur at subsequent administrations of isatuximab.

In addition to the occurrence of IRs, cytokine release syndrome, influenza-like illness, and fever have also been observed in participants treated with isatuximab; these reactions may involve immunogenicity mechanisms (human antihuman antigen) and hypersensitivity reactions. These adverse reactions, whether acute or delayed, may be serious and systemic (eg, anaphylactic reaction).

Please refer to the current version of the isatuximab Investigator's Brochure.

2.3.2.2 Cemiplimab

Cemiplimab has been generally well tolerated, and the reported AEs have been similar to what have been observed with other PD-1 inhibitors.

As of 27 March 2018, pooled data from the non-randomized studies (R2810-ONC-1423, R2810-ONC-1540, R2810- ONC-1606, R2810-ONC-1620, R2810-ONC-1622, R2810-ONC-1655, and R1979-ONC-1504) were analyzed. A total of 757 participants have been treated with cemiplimab either as monotherapy or in combination with radiotherapy and/or other cancer

therapy in seven of the ongoing studies. A total of 512 participants (67.6%) experienced at least 1 treatment-related AE, of which 96 participants (12.7%) experienced Grade 3 or higher treatment-related AEs. Sixty-four participants (8.5%) experienced investigator-attributed treatment-related SAEs. Seven participants (0.9%) experienced fatal treatment-related AEs: hepatic failure (1 participant with hepatocellular carcinoma) and acute hepatic failure (1 participant with DLBCL), paraneoplastic encephalomyelitis (1 participant with soft tissue sarcoma), toxic epidermal necrolysis (1 participant with follicular lymphoma [FL]), nosocomial pneumonia secondary to Grade 4 mucositis (1 participant with FL), and pneumonitis (2 participants: 1 with NSCLC and 1 with cervical cancer).

Treatment-related AEs were characterized as potential immune-related AEs (irAEs). A total of 339 participants (44.8%) experienced potential irAEs including 123 participants (16.2%) with identified irAEs. The majority of potential irAEs were mild to moderate in severity. Sixty-three participants (8.3%) experienced potential irAEs of Grade 3 or higher including 53 (7.0%) with identified irAEs. Forty-nine participants (6.5%) experienced serious potential irAEs including 41 participants (5.4%) with serious identified irAEs. Six participants (0.8%) experienced fatal irAE including hepatic failure, toxic epidermal necrolysis, pneumonitis, and paraneoplastic encephalomyelitis.

As of 27 March 2018, 71 (9.4%) participants experienced IRs including 2 (0.3%) with Grade 3 IR. The remaining participants experienced Grade 1 or Grade 2 IRs. The most common symptoms reported were pyrexia (14 [1.8%] participants), chills (11 [1.5%] participants), nausea (9 [1.2%] participants), and abdominal pain, vomiting, and rash (4 [0.5%] participants each).

Please refer to the current version of the cemiplimab Investigator's Brochure.

2.3.3 Potential risk related to the combination

Based on the available pre-clinical and clinical data from each individual drug, no serious adverse drug reactions potentially overlapping are anticipated with the isatuximab and cemiplimab combination.

There are 2 ongoing Phase 1/2 clinical studies (Study ACT15319 and Study TCD14906) of isatuximab in combination with cemiplimab in participants with MM (TCD14906), prostate cancer or lung cancer (ACT15319). Both studies have completed their respective Phase 1 components. Recommended Phase 2 doses were confirmed without DLT observed. Recruitment in the Phase 2 components is in progress.

2.3.4 Preventive measures to minimize the risk from the combination

To minimize the risk of IRs, all participants treated with isatuximab should routinely receive primary prophylactic treatment with diphenhydramine 25 to 50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), ranitidine 50 mg IV (or equivalent at investigator's discretion), acetaminophen (paracetamol) 650 to 1000 mg orally (or equivalent), and montelukast 10 mg orally (or equivalent), 30 to 60 minutes (and never longer than 60 minutes) prior to the isatuximab infusion to minimize the incidence and severity of IR commonly

observed with certain mAb. In an attempt to further mitigate the incidence and severity of IRs, it is recommended that the initial infusion rate should not exceed 200 mL of isatuximab per hour. In the absence of IRs after 1 hour of infusion, the first infusion rate can be increased by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour. In the event of a moderate hypersensitivity reaction, the isatuximab infusion should be interrupted and may subsequently resume after recovery, at a slower infusion rate (one half of the initial infusion rate, ie, 12.5 mL/hour), under close monitoring and with supportive care as needed. Prior to restarting the infusion, participants may receive additional medication per the judgment of the Investigator; recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In the event of a severe hypersensitivity reaction, treatment with isatuximab is to be immediately discontinued until resolution or until improvement of the AE to Grade 1. If a severe infusion-related AE (Grade 3) occurs for a 3rd time or in case of life-threatening consequences (Grade 4), treatment with isatuximab will be definitively and permanently discontinued. Detailed guidelines for the management of the IRs are provided in Section 6.5.5.

Criteria for optional premedication for IRs:

- For a patient who has no IR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IR Grade ≤2 during their first infusion only and then experiences no further IRs during their next 3 infusions: The Investigator should discuss with the Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next infusion without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.

To minimize the risk of potential immune-related treatment-emergent adverse events related to cemiplimab, the exclusion criteria in the Study ACT15320 include:

- E 05. Comorbidity requiring systemic corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of study intervention initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent.
- E 07. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). Vitiligo, hypothyroidism, or Sjogren's syndrome are eligible.
- E 08. Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), known hepatitis B virus (HBV), or known hepatitis C virus (HCV), unless they are controlled or negative when tested by polymerase chain reaction (PCR) or equivalent. Active tuberculosis or severe infection requiring parenteral antibiotic treatment.

- E 11. History of or current interstitial lung disease or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted).
- E 18. Prior treatment with idelalisib.
- E 24. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including anti PD-1/PD-L1 agents for Cohort A2) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved or improved to baseline at least 3 months prior to initiation of study intervention. For other agents, treatment related immune mediated (or immune related) AEs that were Grade 2 or above.

Additionally, careful monitoring of AEs and laboratory abnormalities, continuous direct communication between the Investigators and the monitoring team, and the adherence to the dose modification rules specified in the study protocol, are the measures that will continue to be implemented to minimize the risks in study participants.

General guidelines for the management of irAEs, including some specific irAEs such as colitis, endocrine AEs, pneumonitis, renal AEs, dermatologic AEs, hepatitis, ophthalmologic AEs (eg, uveitis) are also provided in the study protocol Section 10.4.

2.3.5 Conclusion

Overall, the anticipated benefit/risk ratio of isatuximab in combination with cemiplimab supports the conduct of study ACT15320 in participants with lymphoma.

More detailed information about the known and expected benefits and risks associated with the treatments to be used in study ACT15320 may be found in the Investigator's Brochure of isatuximab and the Investigator's Brochure of cemiplimab.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
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 1:** Safety and tolerability will be assessed based on dose limiting toxicities (DLTs, in Cycle 1), adverse events (AEs)/serious adverse events (SAEs), and laboratory abnormalities.
Phase 2: 1 - Cohort A1 (anti-PD-1/PD-L1 naive cHL): To assess the complete remission (CR) rate of isatuximab in combination with cemiplimab. 2 - Cohort A2 (cHL progressing from PD-1/PD-L1), B (DLBCL) and C (PTCL): To assess the objective response rate (ORR) of isatuximab in combination with cemiplimab.	**Phase 2:** 1 - Cohort A1: CR rate as defined by as the proportion of participants who have a CR as a best overall response during the isatuximab + cemiplimab therapy period using the Lugano response criteria 2014 (1) (Appendix 6 Section 10.6). 2 - Cohorts A2, B, and C: ORR defined as the proportion of participants who have a CR or partial response (PR) as a best overall response during isatuximab + cemiplimab therapy period using the Lugano response criteria 2014 (1) (Appendix 6 Section 10.6).
Secondary	
1 - To evaluate the safety of the RP2D of isatuximab in combination with cemiplimab.	1 - AEs/SAEs and laboratory abnormalities for isatuximab+ cemiplimab.
2 - To evaluate the safety of the combination of isatuximab with cemiplimab and radiotherapy in participants with cHL	2 - AEs/SAEs and laboratory abnormalities in isatuximab + cemiplimab + radiotherapy treated participants (Cohort A1 and A2).
3 - To evaluate the immunogenicity of isatuximab and cemiplimab when given in combination.	3 - Immunogenicity: Anti-drug antibody (ADA) against isatuximab and against cemiplimab.
4 - To characterize the pharmacokinetic (PK) profile of isatuximab and cemiplimab when given in combination.	4 - PK evaluation using non-compartmental analysis for both compounds using serum concentrations for cemiplimab and plasma concentrations for isatuximab.
5 - To assess overall efficacy of: • Isatuximab in combination with cemiplimab, And • Isatuximab in combination with cemiplimab and radiotherapy.	• - Efficacy: • Tumor burden change, duration of response (DoR), disease control rate (DCR), defined as the percentage of participants who achieve CR, partial response (PR) or stable disease (SD) and progression-free survival (PFS). • For Cohort A1, ORR during isatuximab + cemiplimab ± radiotherapy periods. CR rate during isatuximab + cemiplimab + radiotherapy period. • For Cohort A2, ORR during isatuximab + cemiplimab + radiotherapy period. CR rate during isatuximab + cemiplimab ± radiotherapy periods.

Tertiary/exploratory	
1 - To explore the preliminary overall efficacy.	1 - Overall survival (OS) and time to response (TTR) for all treated participants; • For Cohorts A1 and A2, time to CR (TTCR) for all treated participants • For Cohorts A1 and A2, OS, TTR, TTCR during isatuximab + cemiplimab period and for participants who receive isatuximab + cemiplimab + radiotherapy
2 - To evaluate the relationships between clinical response and biomarkers in tumor tissue.	2 - The relationship between clinical response and analyses in tumor tissue of: • CD38, PD-L1, MHC-II expression, • Possibly beta-2-microglubulin, and MHC-I expression, • Genomic and genetic analysis, • Immune contexture.
3 - To explore immune genetic markers in blood.	3 - Immune genetic determinants (including polymorphisms in FcγR receptors) in blood at baseline.
4 - To perform PK/pharmacodynamics analysis if possible with any relevant pharmacodynamics markers mentioned above, and correlation with safety/efficacy endpoints.	4 - PK/pharmacodynamics analysis: • Pharmacodynamic biomarkers in response to investigational medicinal product (IMPs): immune contexture and possibly transcriptomic analyses in tumor tissue at baseline and upon treatment. • Determination of exposure-response relationships with efficacy, safety, and biomarkers, if possible.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy and safety assessments chosen for use in this study is considered well established and relevant in a hematology setting. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1/2 open-label, non-comparative, multi-center, safety, preliminary efficacy and PK study of isatuximab in combination with other anti-cancer therapies in participants with lymphoma. This study will be conducted in 2 parts (see Section 1.2 for study design schema).

Phase 1 (safety run-in):

Participants with cHL, DLBCL, or PTCL will be enrolled in the Phase 1.

Dose levels and schedules are described in the table below.

Dose levels and schedules 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 every week (QW) × 4 (Cycle 1) 10 mg/kg every 2 weeks (Q2W) (Cycle 2 ~ Cycle 6)	10 mg/kg every 3 weeks (Q3W)	250 mg Q2W	350 mg Q3W
Minus - 1 (DL-1)	5 mg/kg QW × 4 (Cycle 1) 5 mg/kg Q2W (Cycle 2 ~ Cycle 6)	5 mg/kg Q3W	250 mg Q2W	350 mg Q3W

The 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 RP2D.

- If 0/3 participants experience a DLT, the starting dose will be the RP2D.
- If 1/3 participants experience a DLT, 3 additional participants will be enrolled at the starting dose level:
  - If a total of 1/6 participants treated at the starting dose experience 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, the 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 is to be staggered by at least 3 days.

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

The NCI CTCAE version 5.0 will be used to assess the severity of AEs. Causal relationships are to be determined by the Investigator. The DLTs will be confirmed by the Sponsor and recruiting Investigators.

Dose limiting toxicity is defined as:

All AEs specified below occurring during the first cycle of treatment, unless due to disease progression or to a cause obviously unrelated to IMP. The duration of the DLT observation period will be longer for participants who delay initiation of Cycle 2 due to treatment-related AE whose duration must be assessed in order to determine if that AE meets the definition of a DLT.

Hematological abnormalities are defined as any of the following:

- Grade 4 neutropenia for 7 or more consecutive days.
- Grade 3 to 4 neutropenia complicated by fever (temperature ≥38.5°C on more than 1 occasion) or microbiologically or radiographically documented infection.
- Grade 3 to 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention.

Non-hematological abnormalities

- Grade 4 non-hematologic AE.
- Grade ≥2 uveitis.
- Grade 3 non-hematological AE lasting >3 days despite optimal supportive care, except:
  - Grade 3 fatigue,
  - Allergic reaction/hypersensitivity attributed to isatuximab or cemiplimab,
  - Grade 3 or 4 laboratory abnormalities that are not clinically significant per recruiting Investigators and Sponsor.
- Treatment-related laboratory abnormalities/AEs that lead to delay in initiation of Cycle 2 >14 days.
- In addition, any other AE that the recruiting Investigators and Sponsor deem to be dose limiting, regardless of its grade, may also be considered as DLT.

Phase 2: (Efficacy signal/Simon 2-stage design):

Phase 2 includes 4 cohorts:

Cohort A1: cHL anti-PD-1/PD-L1 naïve.

Cohort A2: cHL anti-PD-1/PD-L1 progressor.

Cohort B: DLBCL anti-PD-1/PD-L1 naïve.

Cohort C: PTCL anti-PD-1/PD-L1 naïve.

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 indication in Stage 1 of Phase 2.

Interim analysis will be performed based on the number of CR (for Cohort A1) or objective responses (for Cohorts A2, B, and C) and the totality of data observed (up to 24 weeks after the last ongoing participant receives first dose of IMP) within a treatment cohort in Phase 2 Stage 1; based on the available data, the Sponsor may decide to advance such a treatment cohort to Phase 2 Stage 2 after consulting with Investigators.

The Sponsor may decide to proceed to Phase 2 Stage 2 without enrollment hold based on the available data.

Based on the positive efficacy signal and the totality of data observed at the end of Phase 2 Stage 2, the Sponsor may decide to open additional cohorts to study isatuximab in combination with radiotherapy, or cemiplimab in combination with radiotherapy in participants with cHL in this study. The Sponsor may also decide to test alternative IMP doses and schedules in case of inadequate efficacy and PK results.

In both Phases 1 and 2, participants with cHL who achieve best overall response of PR or SD at the disease assessment planned for Week 36, if deemed appropriate (and does not meet exclusion criteria E01, E06, E08, E21, E30, and E32) by the Investigator, may begin radiotherapy between D1 to D14 (preferably between D1 to D7) of the next immediate cycle.

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 is up to 48 and 96 weeks, respectively, from the date the last participant treated in individual cohort.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Treatment beyond the first in those 3 indications remains challenging with a significant unmet need for participants with advanced lymphomas. Combination strategies with immunotherapy agents have a potential to increasing their individual effectiveness in these participants.

Phase 1 is designed to assess the safety and tolerability of isatuximab in combination with cemiplimab in participants with 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 is designed to assess the CR rate of isatuximab in combination with cemiplimab in participants with cHLPD-1 naïve (Cohort A1) and objective response rate (ORR) of isatuximab in combination with cemiplimab in participants with cHL progressing from PD-1/PD-L1 (Cohort A2), DLBCL (Cohort B), and PTCL (Cohort C).

4.3 JUSTIFICATION FOR DOSE

The proposed isatuximab dose is selected based on the clinical data from the participants with MM. In participants with MM, isatuximab exhibits non-linear PK due to the presence of target-mediated drug disposition. In addition, tumor burden impacts the PK of isatuximab.

Based on safety, efficacy, PK, and PK/pharmacodynamic analyses, the dosing schedule selected for isatuximab when used in combination with other therapies for the treatment of MM is 10 mg/kg QW × 4 followed by Q2W. The half-life of isatuximab associated to the linear elimination is 18 days. Since it is hypothesized that the immuno-modulatory mechanisms of isatuximab would also be involved in the pharmacological activity of isatuximab and because 10 mg/kg Q2W ×2, Q4W have shown some activity in MM (Study TED10893). The current 10 mg/kg QW ×4 followed by Q2W schedule was adapted for this study ACT15320 for the first 6 cycles: 10 mg/kg QW ×4 followed by Q2W, and then maintained by 10 mg/kg Q3W from Cycle 7. Of note, based on updated pharmacokinetic characterization of isatuximab in 2019, the plasma half-life has been re-estimated to 28 days.

To support the development program of isatuximab in pediatrics, simulations of isatuximab exposure were conducted in children for different body weight categories with showing comparable exposure to those observed in adults (Study ACT14596) up to 12.2 kg corresponding to 2-year-old children (OMS classification).

The proposed cemiplimab dosing schedule of 250 mg Q2W for the first 6 cycles and maintained by 350 mg Q3W from Cycle 7 is selected in this study for participants with lymphoma to better align with the dosing schedule of planned concurrent treatment with isatuximab. The cemiplimab dose of 350 mg Q3W is also selected for ongoing pivotal Phase 3 studies in participants with NSCLC. Cemiplimab dosing regimen of 3 mg/kg Q2W was well tolerated by participants with lymphoma in ongoing Study R1979-ONC-1504.

A flat cemiplimab dose of 350 mg Q3W is selected based on population PK modeling and simulation, as it is expected to provide exposure that closely replicates that observed in participants (mean weight: 80 kg) for the 3 mg/kg Q2W regimen in the ongoing first-in-human study R2810-ONC-1423 (NCT02383212). Simulations of cemiplimab exposure in 1000 participants using population PK analyses indicated that:

- A 350 mg Q3W dose in participants resulted in similar (≤20% difference) C_{trough}, area under the curve (AUC)12 weeks, and C_{max} as compared to the 3 mg/kg Q2W dose in the first-in-human participant population (80 kg), and exceeded those observed at the 1 mg/kg Q2W dose.
- The variability in cemiplimab exposure (coefficient of variation) was similar for body-weight adjusted doses as compared to flat doses. Given the similar predicted exposure for 350 mg Q3W when compared to the 3 mg/kg Q2W regimen, a similar efficacy/safety profile is also expected. Therefore, the 350 mg Q3W IV dose of cemiplimab is being proposed across the cemiplimab program.

To support the development program of cemiplimab in pediatrics, simulations of cemiplimab exposure were conducted in children for different body weight categories with mean values of 8 kg to 80 kg and a distribution around these mean values similar to that observed in the adult population in first-in-human study (R2810-ONC-1423).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all periods of the study including the last follow-up visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of study will occur at the final study cut-off planned at 96 weeks after the last participant enters the study whichever the cohort or when all participants have had the opportunity to complete the EOT visit 30 days after the last study treatment administration, whichever is the latest.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

I 01. Age: Participant must be ≥12 years of age inclusive (or the age deemed appropriate per local health authority or IRB approval), at the time of signing the informed consent. Specific to France: refer to Appendix 11 (Section 10.11.1).

I 02. Disease location amenable to mandatory tumor biopsy at baseline (unless clinically unfeasible and after discussion with Sanofi Medical Monitor for Phase 1 and Phase 2 Stage 1; mandatory for Phase 2 Stage 2), and possibly at Cycle 2 Day 1. If disease location is in a superficial lymph node, excisional biopsy or resected tissue is required if clinically feasible; otherwise, core needle biopsy is acceptable. Fine needle aspirates are not acceptable. Archival tumor biopsy sample may be used to replace mandatory baseline biopsy, if the sample was obtained after progression from immediate prior therapy.

I 03. Measurable disease defined as at least one measurable node that must have an LDi (longest diameter) >1.5 cm and/or measurable extranodal lesion that must have an LDi >1 cm according to Lugano criteria 2014 (1). Tumor sites that are considered measurable must not have received prior radiotherapy, unless among them at least one is FDG-avid.

For Phase 1 and Cohort A1 (cHL anti-PD-1/PD-L1 naïve):

I 04. Histologically confirmed advanced cHL that has relapsed or progressed after:

- At least 3 lines of systemic therapies that may include auto-hematopoietic stem cell transplantation (HSCT)(See Appendix 10 Section 10.10 for definition of one line of therapeutic regimen) **OR**
- Auto-HSCT and Brentuximab vedotin.

For Phase 1 and Cohort A2 (cHL anti-PD-1/PD-L1 inhibitor progressor):

I 05. Histologically confirmed advanced cHL which has relapsed or progressed after one previous anti-PD-1/PD-L1 containing regimen as the most recent prior therapy.

I 06. In Cohort A2 Phase 1: Documentation of benefit (defined as CR, PR or SD ≥6 months at ≥1 radiographic imaging scans) but subsequent progression during or after the prior anti-PD1/PD-L1 containing regimen. Progression has to occur within 6 months from last dose of the prior anti-PD1/PD-L1 containing regimen. IMP must be started within 4 months from progression. The site's study team must confirm that radiographic progression has occurred per IWG response criteria for malignant lymphoma following initiation of the anti PD-1/PD-L1 containing regimen.

In Cohort A2 Phase 2: Participants who achieved CR are excluded unless they relapsed on an anti-PD1/PD-L1 containing regimen. Documentation of benefit (defined as PR or SD ≥6 months at ≥1 radiographic imaging scans) but subsequent progression during or after the prior anti-PD1/PD-L1 containing regimen. Progression has to occur within 6 months from last dose of the prior anti-PD1/PD-L1 containing regimen. IMP must be started within 4 months from progression. The site's study team must confirm that radiographic progression has occurred per IWG response criteria for malignant lymphoma following initiation of the anti PD1/PD-L1 containing regimen.

For Phase 1 and Cohort B (DLBCL):

I 07. Histologically confirmed advanced DLBCL that has relapsed or progressed after:

- 2 lines of systemic therapy including auto-HSCT, **OR**
- 2 lines of systemic therapy for participants who are not eligible for auto-HSCT.

For Phase 1 and Cohort C (PTCL):

I 08. Histologically confirmed advanced PTCL that has relapsed or progressed after:

- Chemotherapy and auto-HSCT as consolidation of first remission, **OR**
- First-line chemotherapy if participants are ineligible for auto-HSCT.

Weight

I 09. Body weight of >45 kg for patients with age <18 years.

Sex

I 10. Male or Female

Male participants: A male participant must agree to use contraception as detailed in Appendix 5 (Section 10.5) 2 weeks before study intervention first administration, during the intervention period and for at least 6 months, after the last dose of study intervention and refrain from donating sperm during this period.

Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 5 Section 10.5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 5 (Section 10.5)

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 (Section 10.5) 2 weeks before study intervention first administration, during the intervention period and for at least 6 months after the last dose of study intervention.

Informed Consent

I 11. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where the legal age of majority is above 18 years and for participants less than 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Eastern Cooperative Oncology Group (ECOG) performance status of ≥2.

E 02. Predicted life expectancy <3 months.

E 03. Central nervous system lymphoma, active brain metastases or leptomeningeal metastases. Participants with asymptomatic central nervous system metastases which have been stable (defined as without evidence of progression by magnetic resonance imaging [MRI] or other imaging modality for at least 28 days prior to initiation of study intervention and any neurologic symptoms have returned to baseline) following treatment with surgery or radiation therapy are allowed.

E 04. Symptomatic or impending cord compression at study entry.

E 05. Comorbidity requiring systemic corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of study intervention initiation. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent.

E 06. Significant cardiac dysfunction (defined as left ventricular ejection fraction [LVEF] of <50%), New York Heart Association classification for chronic heart failure III-IV, symptomatic coronary artery disease, major clinically significant electrocardiogram (ECG) abnormality, significant ventricular arrhythmias; myocardial infarction within 6 months; unstable or poorly controlled angina pectoris.

E 07. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs), except for replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). Vitiligo, hypothyroidism, or Sjogren's syndrome are eligible.

E 08. Known seropositive and requiring anti-viral therapy for HIV, known HBV, or HCV, unless they are controlled or negative when tested by polymerase chain reaction (PCR) or equivalent. Active tuberculosis, or severe infection requiring parenteral antibiotic treatment (Section 10.2).

E 09. Diffusing capacity of the lungs for carbon monoxide (DLCO) <60% for participants previously treated with bleomycin.

E 10. Known second malignancy either progressing or requiring active treatment within the last 3 years (except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, DICT or in situ cervical cancer that has undergone potentially curative therapy).

E 11. History of or current interstitial lung disease or pneumonitis that requires oral or IV glucocorticoids to assist with management (radiation pneumonitis in the radiation field is permitted).

E 12. Participant has undergone major surgery ≤3 weeks prior to starting study treatment or has not recovered from the side effects of major surgery.

E 13. Primary mediastinal large B-cell lymphoma.

Phase 1 and Cohorts A1 and A2

E 14. Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL) subtype is not allowed.

Phase 1 Cohorts A1, A2, and B

E 15. Transformed follicular lymphoma (tFL) and chronic lymphocytic leukemia (CLL) Richter transformation subtypes are not allowed.

Phase 1 and Cohort C

E 16. Cutaneous T-cell lymphoma subtype is not allowed.

Prior/concomitant therapy

E 17. Prior treatment with an agent (approved or investigational) that blocks CD38 (participants who joined a study with an anti-CD38 but have written confirmation they were on control arm are allowed providing that therapy is allowed).

E 18. Prior treatment with idelalisib.

E 19. Prior allogeneic HSCT.

E 20. Auto-HSCT less than 90 days prior to initiation of study intervention. Carmustine (BCNU) ≥600 mg/m² received as part of the pre-transplant conditioning regimen.

E 21. Receipt of a live-virus vaccination within 28 days of planned treatment start. Seasonal flu vaccines that do not contain a live virus are permitted.

E 22. Wash out period of less than 2 weeks from previous antitumor chemotherapy, tyrosine kinase inhibitor immunotherapy, or any palliative radiotherapy; less than 4 weeks from previous antitumor biological therapy (eg, rituximab and brentuximab vedotin).

E 23. Participant has received wide field radiotherapy ≤4 weeks prior to starting study treatment, or limited field radiation for palliation ≤2 weeks prior to starting study treatment, or has not recovered from the side effects of such therapy.

E 24. Treatment-related immune-mediated (or immune-related) AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 agents, anti-CTLA-4 monoclonal antibodies, and PI3K δ inhibitors) that caused permanent discontinuation of the agent, or that were Grade 3 or 4 in severity, or that have not resolved or improved to baseline at least 3 months prior to initiation of IMP. For other agents, treatment-related immune-mediated (or immune-related) AEs that were Grade 2 or above.

Cohorts A1, B, and C:

E 25. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti CTLA-4 antibody or LAG-3 (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).

Phase 1 and Cohort A2

E 26. Participants with anti-cancer therapy including radiotherapy or auto-HSCT between failure of anti-PD-1/PD-L1 therapy and initiation of IMP.

Prior/concurrent clinical study experience

E 27. Last dose of prior investigational agent within 28 days from initiation of study intervention.

Diagnostic assessments

E 28. Not applicable. Removed by Protocol Amendment 01.

E 29. Ongoing AEs (excluding alopecia and fatigue) caused by any prior anti-cancer therapy ≥ Grade 2 (NCI CTCAE version 5.0).

E 30. Inadequate organ and bone marrow function prior to IMP administration:

a) Absolute neutrophil count (ANC)<1000/mm^3 ($1.0 \times 10^3/mm^3$; after at least 2 weeks without WBC growth factors).

b) Platelets <50 000/mm^3 ($50 \times 10^3/ mm^3$; after at least a week without platelet transfusion).

c) Hemoglobin <9 g/dL (<5.6 mmol/L; after at least a week without transfusion).

d) Total bilirubin >2 upper limit of normal (ULN), except for participants with Gilbert's syndrome.

e) Aspartate aminotransferase and/or alanine aminotransferase >3 × ULN (or >5 × ULN for participants with liver metastases).

f) Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 using Modified Diet in Renal Disease Formula (MDRD).

E 31. Known intolerance or hypersensitivity to any component of isatuximab and/or cemiplimab.

E 32. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator.

E 33.

a) Uncontrolled or active HBV infection: Patients with positive surface antigen of the hepatitis B (HBsAg) and/or HBV deoxyribonucleic acid (DNA). Of note:

- Patient can be eligible if anti-hepatitis B core antigen (HBc) immunoglobulin (Ig) G positive (with or without positive anti-HBs) but HBsAg and HBV DNA are negative.
- If anti-HBV therapy in relation with prior infection was started before initiation of IMP, the anti-HBV therapy and monitoring should continue throughout the study treatment period (see Section 1.3).
- Patients with negative HBsAg and positive HBV DNA observed during screening period will be evaluated by a specialist for start of anti-viral treatment: study treatment could be proposed if HBV DNA becomes negative and all the other study criteria are still met.

b) Active HCV infection: positive HCV ribonucleic acid (RNA) and negative anti-HCV.

- Patients with antiviral therapy for HCV started before initiation of IMP and positive HCV antibodies are eligible. The antiviral therapy for HCV should continue throughout the treatment period until seroconversion.

- Patients with positive anti-HCV and undetectable HCV RNA without antiviral therapy for HCV are eligible.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. A different participant identification will be issued, while the other identification for this participant should be recorded as Screen Failure. There is no requirement for a waiting period between a screen failure date and the rescreening date. Participants that are rescreened must sign a new consent form and all screening procedures must be repeated.

6 STUDY INTERVENTION

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 14 (see Section 10.14).

6.1 STUDY INTERVENTION(S) ADMINISTERED

Investigational medicinal product(s): Isatuximab with cemiplimab and radiotherapy (Cohorts A1 and A2) or isatuximab in combination with cemiplimab (Cohort B and C). Isatuximab and cemiplimab could be given up to 96 weeks (at least 48 weeks from initial signal of CR whichever is longer).

Isatuximab:

Formulation:

- Drug product concentrated solution for infusion in vials containing 20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine. 10% (w/v) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0.

Route(s) of administration: IV infusion.

Dose regimen: Refer to the dose levels and schedule for Phase 1. Dose for Phase 2 will be determined based on safety data from Phase 1.

Cemiplimab:

Formulation

- Drug product concentrated solution 50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.

Or

- Drug product concentrated solution 50 mg/mL in 10 mL vials with 7.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.

Route(s) of administration: IV infusion.

Dose regimen: Refer to the dose levels and schedule for Phase 1.

Non-investigational medicinal products: will be locally sourced and formulations may vary.

Premedication

All participants will receive the following 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). The standard premedication regimen will include see Section 6.1.2:

- Acetaminophen (paracetamol) 650 to 1000 mg oral route (PO) (or equivalent).
- Ranitidine 50 mg IV (or equivalent at Investigator's discretion).
- Diphenhydramine 25 to 50 mg IV (or equivalent).
- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg PO (or equivalent).

Criteria for optional premedication for IRs:

- For a patient who has no IR for the first 4 infusions: Premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during the subsequent infusions without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.
- If a patient develops an IR Grade ≤2 during their first infusion only and then experiences no further IRs during their next 3 infusions: The Investigator should discuss with the Sponsor Medical Monitor when considering omitting premedication for the next infusion. If no IR is observed for the next infusion without premedication, premedication is optional for the subsequent infusions at the Investigator's discretion. However, if during the next infusion without premedication the patient experiences an IR (any grade), premedication must be restarted for all subsequent infusions.

Radiotherapy (for Cohorts A1 and A2) (optional):

- Formulation: Not applicable.
- Route(s) of administration: Stereotactic radiation therapy.
- Dose regimen: see Section 6.1.4.

6.1.1 Investigational Medicinal Product(s)

Table 2 - Overview of study interventions administered

Study intervention name	Isatuximab	Cemiplimab
Dosage formulation	Concentrate for solution for intravenous infusion	Concentrate for solution for intravenous infusion
Unit dose strength(s)/Dosage level(s)	20 mg/mL (500 mg/25 mL) isatuximab in 20 mM histidine, 10% (w/V) sucrose, 0.02% (w/v) polysorbate 80, pH 6.0	50 mg/mL in 10 mL vials with 5.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80 pH, pH 6.0

		OR 50 mg/mL in 10 mL vials with 7.0 mL withdrawable, containing 10 mM histidine, 5% (w/v) sucrose, 1.5% (w/v) L-proline, and 0.2% (w/v) polysorbate 80, pH 6.0.
Route of administration and duration	Intravenous infusion over 30 minutes per administration	Intravenous infusion over 30 minutes per administration
Dosing instructions	**Phase 1** **Starting dose:** Isatuximab: 10 mg/kg every week (QW) × 4 on Cycle 1, then every 2 weeks (Q2W) from Cycle 2 to Cycle 6, then every 3 weeks (Q3W) from Cycle 7 to Cycle 30 Cemiplimab (administrated before isatuximab): 250 mg every 2 weeks (Q2W) from Cycle 1 to Cycle 6, then 350 mg every 3 weeks (Q3W) from Cycle 7 to Cycle 30 **Dose Level** -1 may be implemented if ≥2/3 with DLT or if ≥2/6 participants with DLT at starting dose: Isatuximab: 5 mg/kg every week (QW) × 4 on Cycle 1, then every 2 weeks (Q2W) from Cycle 2 to Cycle 6, then every 3 weeks (Q3W) from Cycle 7 to Cycle 30 Cemiplimab (administrated before isatuximab): 250 mg every 2 weeks (Q2W) from Cycle 1 to Cycle 6, then 350 mg every 3 weeks (Q3W) from Cycle 7 to Cycle 30 **Phase 2:** For the combination Cohorts A1, A2, B, and C, cemiplimab will be administered first followed by isatuximab. Isatuximab will be administered at the RP2D determined based on safety data from Phase 1.	
Packaging and labeling	In single dose vials 30 mL (C1P2F2) glass vials fitted with elastomeric closure. The label contents will be in accordance with the local regulatory specifications and requirements. **ISATUXIMAB** It will be supplied for parenteral administration as a sterile, nonpyrogenic, injectable, 20 mg/mL concentrate for solution for infusion, essentially free of visible particulates. Each vial will contain a nominal content of 500 mg isatuximab C1P2F2. The fill volume will be established to ensure removal of 25 mL. For participant administration, the appropriate volume of isatuximab will be diluted in an infusion bag of 0.9% sodium chloride solution. The final infusion volume corresponding to the dose of isatuximab will be administered for a period of time that will depend on the dose administered and will be based on protein amount given per hour. Preferred diluents are: **0.9% Sodium chloride** for injection 100 mL, 250 mL or 500 mL bags in polyolefins (so covers also polyethylene (PE) or polypropylene (PP)) or polyvinyl chloride (PVC) (with DEHP) Or **Dextrose**	Cemiplimab is packaged in USP Type 1 clear glass, 10 mL vial with 20 mm gray chlorobutyl rubber stopper with FluroTec® coating and 20 mm red flip-off seal. The content of the labeling at vial and box level is in accordance with the local regulatory specifications and requirements. Cemiplimab concentrated solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution to achieve the appropriate drug concentration for infusion

Rate and duration of infusion:

The duration of infusion for cemiplimab is 250 mg or 350 mg (based on cycle number) over 30 minutes per administration.

Following Investigator's Brochure (IB) ed11 isatuximab release in which the registered flat infusion administration has been added, patients still receiving isatuximab will switch to the registered infusion rate as described below after amended protocol 02 has been approved.

- **First isatuximab infusions post amended protocol 02**: Initiate infusion at 25 mL/hour. In the absence of IRs after 1 hour of infusion, increase infusion rate by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour. In case of grade 2 IR during first infusion, infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, until the total volume is infused.
- **Second infusion post amended protocol 02**: Initiate infusion at 50 mL/hour. In the absence of Grade 2 IR after 30 minutes of infusion, increase rate to 100 mL/hour for 30 minutes, then, to 200 mL/hour until the total volume is infused.
- In case of Grade 2 IR during second infusion, infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused.
- **Third and subsequent infusions post amended protocol 02**: Initiate infusion at a fixed infusion rate of 200 mL/hour, until the total volume is infused. In case of Grade 2 IR during third infusion, infusion could be restarted at one-half (100 mL/hour) of the infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused.

Guidelines for patients who develop IRs are provided in Section 6.5.5.

6.1.2 Non-Investigational Medicinal Products:

They will be locally sourced and formulations may vary.

Premedication

All participants will receive the following premedication to prevent or reduce incidence or severity of IRs, 30 to 60 minutes prior to isatuximab infusion (no longer than 60 minutes). The standard premedication regimen will include:

- Acetaminophen (paracetamol) 650 to 1000 mg PO (or equivalent).
- Ranitidine 50 mg IV (or equivalent at Investigator's discretion).
- Diphenhydramine 25 to 50 mg IV (or equivalent).

- Methylprednisolone 100 mg IV (or equivalent).
- Montelukast 10 mg PO (or equivalent).

6.1.2.1 Acetaminophen (paracetamol) 650 or 1000 mg PO or equivalent

Commercial supplies of acetaminophen (paracetamol) or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage, and handling purposes.

6.1.2.2 Ranitidine 50 mg IV or equivalent

The use of ranitidine or equivalent to be part or not of IR premedication is left to the medical judgement of the Investigator.

Ranitidine is presented as a solution for IV infusion. Commercial supplies of ranitidine or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage, and handling purposes. Equivalents are other approved H2 antagonists (eg, cimetidine) and oral proton pump inhibitors (eg, omeprazole, esomeprazole).

6.1.2.3 Diphenhydramine 25 to 50 mg IV or equivalent

Diphenhydramine is presented as a solution for IV infusion. Commercial supplies of diphenhydramine or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage, and handling purposes. Equivalents are, eg, cetirizine, promethazine, and dexchlorpheniramine according to local approval and availability. Intravenous route is preferred for at least the first 4 infusions.

6.1.2.4 Methylprednisolone 100 mg IV or equivalent

Methylprednisolone is presented as a solution for IV infusion. Commercial supplies of methylprednisolone or equivalent will be used for this study. Please refer to the package insert for further details as regards to formulation, storage, and handling purposes.

6.1.2.5 Montelukast 10 mg PO or equivalent

Commercial supplies of montelukast will be used for the study. Please refer to the package insert for further details as regards to formulation, storage and handling purposes.

6.1.3 Dosing sequence

All participants will receive isatuximab in combination with cemiplimab.

Emergency equipment and medication for the treatment of IRs (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen [paracetamol], and/or epinephrine) must be available for immediate use.

Premedication will be administered 30 to 60 minutes prior to isatuximab infusion (no more than 60 minutes prior).

Only at Cycle 1, cemiplimab will be administered on D1 and isatuximab on D2.

When isatuximab and cemiplimab are to be administered on the same day, the administration sequence is: premedication, followed by cemiplimab, followed by isatuximab.

When only isatuximab is to be administered on a day, the administration sequence is: premedication, followed by isatuximab.

When only cemiplimab is administered on a day, no premedication is recommended.

Participants will continue treatment until disease progression, unacceptable AE, consent withdrawal, treatment period of 96 weeks (at least 48 weeks from initial signal of CR, whichever is longer) without documented PD, or any other reason.

6.1.4 Radiotherapy (for Cohorts A1 and A2) (optional)

The participants with cHL who achieve best response of PR or SD at the disease assessment planned for Week 36, if deemed appropriate (and does not meet exclusion criteria E01, E06, E08, E21, E30, and E32) by the Investigator, may begin radiotherapy between D1 to D14 (preferably between D1 to D7) of the next immediate cycle.

- Formulation: Not applicable.
- Route(s) of administration: Stereotactic radiation therapy.
- Dose regimen: Plan for radiotherapy is summarized as below:
    1. Irradiation will start with up to 2 lesions. The other lesions (up to the maximum of 5 lesions) will be irradiated only if no response is observed after the initial radiotherapy.
    2. For lesions that have not been previously irradiated and are in the “safe zone”, a total of 12 Gy will be administered as 3 doses of 4 Gy over 1 week (ie, 4 Gy × 3 fractions, eg, Monday, Wednesday, and Friday) in the same week when isatuximab and cemiplimab are administered.
    3. For lesions that have been previously irradiated or any lesions that are in the “no fly zone” (23), 2 Gy × 2 fractions in 2 consecutive days (eg, Monday and Tuesday) will be administered once a week every 3 weeks for 3 times (treatment lasts for a total of 9 weeks), starting in the same week when isatuximab and cemiplimab are administered.
    4. When multiple lesions are treated with radiotherapy in parallel, treatment for radiotherapy -naïve lesions will follow the schedule as per point #2, while treatment for previously irradiated lesions will follow schedule as per point #3.

5. Decision to perform radiotherapy or not will be made by the treating Investigator based on his/her evaluation of the specific participant's situation. Overall safety monitoring will be performed throughout the conduct of the study.

6.1.5 Blinding procedures

This is an open-label study; therefore, blinding procedures are not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 General rules

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Partially-used and used study treatments will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed study treatment will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless Sanofi provides written authorization

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

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

Under no circumstances will the Investigator supply IMPs to a third party (except for a duties and taxes paid shipment, for which a courier company has been approved by the Sponsor), allow the IMPs to be used other than as directed by this clinical trial protocol, or dispose of IMPs in any other manner.

6.2.2 Storage conditions

6.2.2.1 Isatuximab

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

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

Isatuximab is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen and protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

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

6.2.2.2 Cemiplimab

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

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

Cemiplimab is to be stored at +2°C to +8°C (36°F to 46°F), is not to be frozen, and protected from light. All vials must be kept in their box until use. No protection from light is required for storage in the infusion bags.

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

6.2.3 Preparation, reconstitution and administration:

6.2.3.1 Isatuximab

For patient administration, the appropriate volume of isatuximab will be diluted in a 250-mL infusion bag of 0.9% sodium chloride solution or 5% dextrose solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. In case of participants with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator. The final infusion volume corresponding to the dose of isatuximab will be administered by IV infusion for the period of time that depends on total dose administered.

Prior to dosing, each participant's dose will be individually prepared by the study pharmacist and labeled with the protocol number, participant number, and treatment description. The participant's weight should be measured prior to each treatment to allow calculation of the isatuximab dose.

For infusion, an IV tubing administration set with a 0.20 µm in-line filter will be used; if an in-line filter is unavailable, a 0.20 µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

6.2.3.2 Cemiplimab

Cemiplimab concentrate for solution for infusion will be diluted in an infusion bag with 0.9% sodium chloride solution to achieve the appropriate drug concentration for infusion.

Infusion via a central line is preferred if available. In case of participants with local intolerance after peripheral IV infusion, the decision to use a central line is left to the Investigator. The final infusion volume corresponding to the dose of cemiplimab will be administered by IV infusion for the period of time that will depend on total dose administered.

Prior to dosing, each participant's dose will be individually prepared by the study pharmacist and labeled with protocol number, participant number, and treatment description.

For infusion, an IV tubing administration set with a 0.20 µm in-line filter will be used; if an in-line filter is unavailable, a 0.20 µm filter unit may be attached to the administration set before administration. Further details are provided in the Pharmacy Manual.

6.3 STUDY INTERVENTION COMPLIANCE

Administration of the IMP will be supervised by the Investigator or Sub-investigator. The person responsible for drug dispensing is required to maintain adequate records of the IMPs. These records (eg, drug movement form) include the date the IMPs are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the vial must be recorded on the drug accountability form. The person responsible for drug administration to the participant will record precisely the date and the time of the drug administration to the participant.

6.4 CONCOMITANT THERAPY

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

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

- All treatments being taken by the participant 21 days prior to the first study treatment, at any time during the study in addition to the IMP are regarded as concomitant treatments and the type, dose and route of administration must be documented on the appropriate pages of the eCRF.
- Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and recorded in the eCRF.
- Supportive treatment as medically indicated for the participant’s well-being may be prescribed at the Investigator’s discretion. Every medication or treatment taken by the participant during the trial and the reason for its administration must be recorded on the eCRF.

Hepatitis B vaccination could be considered, following Investigator’s discretion, for patients with negative HBsAg, total anti-HBc, anti-HBs and HBV-DNA. At least 3 doses of vaccine will be administered at monthly intervals, the first one 1 to 2 weeks before start of study treatment. Anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination. Anti-HBs above 100 mU/mL will indicate a good seroconversion, between 10 and 100 mU/mL moderate seroconversion that can be limited in time, less than 10 mU/mL will indicate no response to vaccination.

If antiviral therapy for HBV or HCV was started before initiation of IMP and patient was eligible for the trial, the antiviral therapy for HBV or HCV should continue throughout the treatment period as recommended by specialist. In case of trial testing combo, to check that there is no drug-drug interaction (DDI) with the drug associated with isatuximab.

In case of viral reactivation during study treatment (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection*), study treatment will be held and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Re-start of study treatment should be agreed between Sponsor, Investigator and specialist (hepatologist) if controlled infection. Close monitoring of alanine aminotransferase (ALT), aspartate-aminotransferase (AST) every month, up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

*previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal ALT levels.

Prohibited concomitant treatments:

- Concurrent treatment with any other anti-lymphoma therapy not specified in the protocol, including immunotherapy, hormonal therapy, targeted therapy or biological therapies, or other investigational drug, or curative radiotherapy.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Concomitant systemic corticosteroids are prohibited, except for:
  - Use in premedication defined in the study protocol,
  - Treatment of an irAE,
  - Treatment of any life-threatening emergency,
  - Physiologic replacement as long as they are not being administered for immunosuppressive intent, and
  - A brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions caused by contact allergen).
- Live vaccines should be avoided. However, giving the increased risk of infection, routine vaccinations are recommended for the participants and their contacts. Prophylactic vaccination is recommended for influenza A and B virus, pneumococci and hemophilus influenza.
- Prophylactic use of hematopoietic growth factors (eg, G-CSF, GM-CSF, and erythropoietin) during the DLT observation period. Curative treatment is allowed.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications are permitted according to the guidelines described in this section.

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

Dose adjustment and/or cycle delay are permitted in case of adverse reaction. Dose adjustments will be made according the worst grade of adverse reaction observed within a cycle. If a participant experiences several adverse reactions and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed.

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

If one of the 2 drugs (cemiplimab or isatuximab) is prematurely permanently discontinued, the other drug can be continued until disease progression, unacceptable adverse reaction, participant's refusal of further treatment, or in the absence of a clear benefit from therapy. The EOT assessment in this case will be 30 days after the date of the last IMP administration.

All changes to study treatment administration must be recorded in the eCRF.

6.5.2 Dose delay and dose omission

Within a cycle, the treatment windows are:

- For the weekly administrations during the 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 reason for dose delay will be captured. The participant will receive the next infusion after recovery of the AE as described in Section 6.5.3.
- If infusion has been delayed within a cycle, next study treatment should be administered at the planned time interval between 2 administrations (eg, if infusion has been delayed by 2 days, Day 15 Cycle 1 administration is actually administered on Day 17, the planned Day 22 should be administered on Day 24).

Participants may have dose omission if an AE occurs and does not recover according to following rules:

- In Cycle 1 if AE occurs and does not recover on the day of planned infusion or within the following 3 days, infusion of isatuximab and/or cemiplimab (D8 or D15) may be omitted.
- From Cycle 2 to Cycle 6, if an AE occurs and does not recover on the day of planned infusion or within the following 7 days, infusion of isatuximab and/or cemiplimab may be omitted for participants on Q2W (D15) dose schedule.

In case of consecutive dose omissions/delay for the recovery of AE, following rules should be followed for restart or discontinue the treatment:

- Dose delay (cycle delay) up to 14 days, it is per Investigator's decision to restart the treatment of cemiplimab and isatuximab.
- After dose delay of >14 days and ≤84 days, it is per Investigator's decision to restart the treatment of cemiplimab and isatuximab, if a clear benefit from therapy is observed and after consultation with the Sponsor.
- Treatment with isatuximab and cemiplimab must be definitely discontinued if the delay is longer than 84 days.

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Appendix 14 (see Section 10.14) should be considered for screening, enrollment, and administration of study intervention.

6.5.3 Dose modifications

Guidelines for isatuximab and cemiplimab dose modifications and treatment discontinuation due to hematological and non-hematological adverse reactions in general are outlined in the table below.

See Table 3 and Appendix 4 (Section 10.4) for guidance for irAEs correlated with cemiplimab, and Section 6.5.5 for IRs correlated with isatuximab and cemiplimab.

The final decision will be per Investigator's judgment for the best interest of the participant.

Table 3 - Isatuximab and cemiplimab dose modification guidelines

Adverse Events NCI CTCAE V5.0	Isatuximab dose management	Cemiplimab Dose management	Action and Guidelines
Hematological adverse events			
Grade 1, 2, and 3	No change in dose		Participant should be given supportive care and monitored closely.
Grade 3 thrombocytopenia lasting >7 days or associated with bleeding	Delay the dose until bleeding is controlled and platelet >50 000/mm^3. Restart treatment with same dose and schedule.		Participant should be given supportive care and monitored closely.
Grade 4	Delay the cycle until absolute neutrophil count >1000/mm^3, and platelet >50 000/mm^3. Restart with same dose and schedule. Grade 4 lymphopenia: no change in dose.		Permanent discontinuation should be considered if the abnormality does not resolve within 84 days of last infusion.
Febrile neutropenia and/or neutropenic infection	Delay the dose until fever and infection recover and ANC>1000/mm^3. Restart with same dose and schedule.		
Non-hematological adverse events (other than irAE and IR)			
Grade 1	No Change in Dose		N/A

Adverse Events NCI CTCAE V5.0	Isatuximab dose management	Cemiplimab Dose management	Action and Guidelines
Grade 2 (except alopecia)	Delay the dose until improves to Grade ≤1 or baseline.	Restart treatment at same dose and schedule.	It is up to the Investigator's judgment whether to restart the treatment of isatuximab and cemiplimab if the delay is within 14 days. If the treatment delay is longer than 14 days, before restarting the treatment, the Investigator must discuss with the Sponsor; if it is determined that it is to the best interest of the participant, the treatment may be restarted.
Grade 3	Delay the dose until improves to Grade ≤1 or baseline.	Restart treatment at same dose and schedule.	
Grade 4	Permanent discontinue treatment for treatment-related AEs		If the delay is longer than 84 days, the treatment must be definitely discontinued.

Immune-related AE (irAE): see Table 4 and Appendix 4 (Section 10.4) for dose modification and participant management guideline).

6.5.4 General guidelines for the management of Immune-Related Adverse Events

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle.

- Detailed guidance for the management of specific irAEs (Colitis, Endocrine AE, Pneumonitis, Renal AE, Dermatologic AE, Hepatitis, Ophthalmologic AE [Uveitis]), plus Nausea and Vomiting is provided in Appendix 4 (Section 10.4).
- General guidance is provided in Table 4.
- If a participant experiences several irAEs which involve different recommendations, the most conservative recommendation should be followed.

The recommendations provided in Table 4 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual participant.

Any participant currently receiving cemiplimab who was previously treated with a PI 3-K inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these participants, the Sponsor should be informed as soon as possible to discuss further management of the participant. An irAE of any grade in a participant previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

Table 4 - General guidelines for immune-related adverse events

Severity	Withhold/Restart /Discontinue isatuximab Treatment	Withhold/Restart/Discontinue cemiplimab Treatment	Supportive Care
Grade 1	No action	No action	Provide symptomatic treatment.
Grade 2	No action	May delay the dose until Grade ≤1	Consider systemic corticosteroids (Prednisone 0.5 to 1 mg/kg/day or equivalent) in addition to appropriate symptomatic treatment.
Grade 3 and Grade 4	Delay the cycle until when toxicity improves to Grade ≤1 or baseline. Discontinue prematurely cemiplimab if unable to reduce corticosteroid dose to <10 mg/day prednisone equivalent within 84 days of toxicity.		For any Grade 3-4 immune-related adverse event, if symptoms worsen or do not improve on adequate corticosteroids (Prednisone 1 to 2 mg/kg/day or equivalent) within 48 to 72 hours), consider additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, and mycophenolate mofetil). Referral of the participant to a specialized unit for assessment and treatment should be considered.

6.5.5 General guidelines for the management of IRs

Participants should routinely receive premedication prior to isatuximab infusion as detailed in Section 8.2 to reduce the risk and severity of IRs commonly observed with mAbs.

Infusion reactions typically occur within 24 hours from the start of the infusion. If an IR is observed, the participants must be informed of the potential risk of recurrent IRs at subsequent infusions.

Summary of IR management is provided in Table 5.

Participants who experience Grade 2 IRs may resume cemiplimab/isatuximab infusion after temporary interruption, under close monitoring and with therapy as needed. Participants may receive additional medication per the judgment of the Investigator. Additional recommended medications are: diphenhydramine 25 mg IV (or equivalent) and methylprednisolone 100 mg IV (or equivalent).

Once a Grade 2 IR or first/second Grade 3 IR has improved or resolved to Grade ≤1, the infusion may be restarted:

- For cemiplimab, the infusion should be restarted at one half the original infusion rate.
- For isatuximab, the infusion should be restarted at one half the original infusion rate, see Section 6.1.1 for infusion rate.
  - First infusion: Infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, until the total volume is infused or reaching 150 mL/hour, whichever is earlier.
  - Second infusion: Infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused or reaching 200 mL/hour, whichever is earlier.
  - Third and subsequent infusions: Infusion could be restarted at one-half (100 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused or reaching 200 mL/hour, whichever is earlier.

Participants with Grade 3 IR (third Grade 3, or do not fulfil criteria to restart infusion as per Table 5) or Grade 4 IR must have cemiplimab and/or isatuximab permanently discontinued and appropriate therapy should be administered.

If a Grade 3 or high IR occurred during cemiplimab infusion, cemiplimab should be permanently discontinued. The participant can continue treatment with isatuximab.

Grade 2 or higher IRs must be reported as AESIs (see Section 8.3). Study personnel should consult the Medical Monitor for further guidance regarding retreatment of participants with IRs and regarding issues of premedication management (eg, alternative medications for participants allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

Table 5 - IR management

Infusion Related Reaction grading (NCI CTCAE v5.0 criteria)	Recommendation
Mild Grade 1 Transient reaction; infusion interruption or intervention not indicated	Continuation of cemiplimab/ isatuximab infusion is per the judgment of the Investigator following close direct monitoring of the participant's clinical status. Cemiplimab/isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IR will be classified as Grade 2 as per NCI CTCAE definition.
Moderate Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours).	Stop cemiplimab/isatuximab infusion. Give additional medication(s) with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Cemiplimab*/isatuximab** may be resumed only after participant recovery, with close monitoring.
Severe or Life-threatening. Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Stop cemiplimab/isatuximab infusion. Give additional medication(s) with diphenhydramine 25 mg IV (or equivalent) and/or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed until the resolution of the AE or until the AE improves to Grade 1. Only then, the infusion may be restarted at the Investigator's discretion; if so, the infusion rate should be half of the initial infusion rate before the interruption, and it may be increased subsequently, at the Investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for that participant. If symptoms do not resolve rapidly, do not improve after interruption of the isatuximab infusion, they recur after initial improvement with appropriate medications, or they require hospitalization, treatment with isatuximab should be definitively discontinued.
Grade 4: Life-threatening consequences; urgent intervention indicated.	If IR occurred during cemiplimab infusion, permanently discontinue cemiplimab. Continue treatment with isatuximab. If IR occurred after the start of isatuximab infusion, permanently discontinue both cemiplimab and isatuximab.

*Cemiplimab: The prepared infusion bag should be kept no more than 8 hours at room temperature between +15°C to +25°C (59°F to 77°F), or no more than 24 hours at 5°C (with an acceptable operating range of 2°C to 8°C refrigerator).
**Isatuximab: the resulting solution for infusion should be used within 16 hours at room temperature between +15°C to +25°C (59°F to 77°F) from the bag preparation to the end of IV infusion of the participant or a new infusion should be prepared with the remaining dose to be administered the same day.

6.5.6 Guidance in case of hepatitis B reactivation occurring under study treatment

In case of viral reactivation during study treatment (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection*) study treatment will be held and specialist consulted for initiation of anti-viral treatment and monitoring of the patient. Re-start of study treatment should be agreed between Sponsor, Investigator and specialist (hepatologist) if infection is controlled. Close monitoring of ALT, AST every month, up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

* previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal ALT levels.

6.5.7 Guidelines for the management of potential Tumor Lysis Syndrome

In case of tumor lysis syndrome (TLS), study treatment should be held until all serum chemistries have resolved. To ensure normal hydration, correct laboratory abnormalities, fluid overload, electrolyte, or acid-base deviation. Management must be done according to the local site guideline. Use of xanthine oxidase or urate oxidase is allowed.

TLS complications including renal function should be monitored, and study treatment can be reinstituted at full doses after resolution.

The laboratory abnormalities normally associated with TLS, and the possible clinical manifestations which can be associated with TLS are presented in Table 6.

Table 6 - Laboratory and clinical abnormalities possibly consistent with TLS

Laboratory	Clinical
Uric acid >8 mg/dL (>475.8µmol/L) Potassium >6.0 mmol/L Phosphorus >4.5 mg/dL (>1.5mmol/L) Corrected calcium[a] <7.0 mg/dL(<1.75mmol/L) or ionized calcium <1.12 mg/dL (<0.3mmol/L)	Acute kidney injury: increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hour for 6 hours. Seizures, cardiac dysrhythmia, neuromuscular irritability (tetany, paresthesia, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia. Dysrhythmias probably or definitely caused by hyperkalemia.

a The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 x 4-albumin in grams per deciliter

6.6 INTERVENTION AFTER THE END OF THE STUDY

The IMPs will not be provided after the end of the treatment period.

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The duration of the study for a participant will include a period for screening of up to 28 days. The cycle duration is 28 days from Cycle 1 to Cycle 6 then 21 days from Cycle 7 to Cycle 30. Participants will continue treatment until disease progression, unacceptable adverse events, consent withdrawal, treatment period of 96 weeks (at least 48 weeks from initial signal of CR, whichever is longer) without documented PD, or any other reason.

After study treatment discontinuation, participants will return to the study site 30 days (+7 days) after the last dose of study treatments, for EOT.

The post-treatment follow-up period includes an extended safety follow-up period of 90 days after the last dose of IMP, including 60 day (±7 days) and 90 day (±7 days) visits after the last IMP for safety and anti-drug antibody (ADA) isatuximab (90 day [±7 days] only) assessments and further follow-up period beyond 90 days after the last dose of study treatments until death or study cut-off date, whichever occurs first. The further follow-up schedule beyond 90 days after last treatment is adjusted according to the disease progression:

- Participants who discontinue study treatment due to PD: phone call follow-up visit will be done every 90 days from the date of last study treatment administration until death or study cut-off date.
- Participants who discontinue the study treatment without PD: will be followed every 90 days for disease assessment until confirmation of PD or start of treatment with another anti-cancer therapy whichever comes first. PD participants will be followed every 3 months as described just above until death or study cut-off date.
- Participants who are still on study treatment after study cut-off date will continue to receive study treatment if they benefit, and will undergo planned study procedures (except PK and ADA) until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first.

7.1 DISCONTINUATION OF STUDY INTERVENTION

The IMPs should be continued whenever possible.

In case the IMPs are stopped, it should be determined whether the stop can be made temporarily; definitive IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible until the documentation of PD.

Temporary intervention discontinuation may be considered by the treating Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.14). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate eCRF pages.

Pregnancy will lead to definitive treatment discontinuation in all cases.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

All efforts should be made to document the reason for discontinuation of treatment with the study treatment:

- At the participant's request, at any time and irrespective of the reason (consents withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical records check.
  Participants requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. The Investigator should make every effort to re-contact the participant, to identify the reason why he/she decided to withdraw, and to determine his/her health status, including at least his/her vital status.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Disease progression,
  - Unacceptable AE,
  - Poor compliance to the study protocol,
  - Any other reason such as inter-current illness that prevents further administration of study treatment (will be specified),
  - Participant is lost to follow-up,
  - Completion of the 96-week treatment period.

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

Handling of participants after definitive intervention discontinuation

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

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or any other reason.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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

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

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

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

Isatuximab or cemiplimab can be discontinued prematurely. Participants will remain on study treatment until the last IMP (isatuximab or cemiplimab) is discontinued see Section 6.5.1. The reason for premature discontinuation will be captured in the appropriate eCRF page.

7.3 LOST TO FOLLOW-UP

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

  Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 14 (see Section 10.14).

- In exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic disease, terrorist attack), onsite visits may be replaced with telephone/remote visits. For example, patient interview for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by patient and permissible per local regulations. In such circumstances, visit window may be expanded, if needed (eg, ±14 days for visits).

8.1 EFFICACY ASSESSMENTS

Please refer to study SoA flow chart **(**Section 1.3**)**.

8.1.1 FDG-PET-CT/CT

ORR is defined as the proportion of participants with complete response, and PR based on responses as assessed using the Lugano response criteria 2014. Uniform Response Criteria (see Appendix 6: Section 10.6). All enrolled participants must have at least one measurable lesion for inclusion (Section 5, I 03).

Tumor assessment will include FDG-PET-CT scan in case of avid lymphomas and CT in case of non-avid lymphomas and they will be performed at fixed intervals as described in SoA, and the assessment window is not impacted by dose delay or dose omission.

For fluorodeoxyglucose (FDG) avid lesions, standardized uptake value (SUV) max is mandatory and should be reported for all lesions at each time point assessment. For purposes of the 5-point scale (5PS), SUV of a lesion is compared to the SUV of the liver and mediastinum. The 5PS is noted below:

- 1. No uptake above background
- 2. Uptake ≤ mediastinum
- 3. Uptake > mediastinum but ≤ liver
- 4. Uptake moderately higher than liver
- 5. Uptake markedly higher than liver (> 2 × maximum SUV of the liver) and/or new lesions
- X. New areas of uptake unlikely to be related to lymphoma (1).

If CT and PET scans at Screening are negative for disease involvement in the neck, subsequent CT scans may not include neck. If PET or CT scan at Screening is positive for disease involvement of the neck, subsequent CT scans must include neck.

Following screening, for the first year FDG-PET-CT and CT scans should be performed every 12 weeks (3 months). For the second year and beyond, CT scans should be performed every 12 weeks and FDG-PET-CT should be done when clinically indicated.

Response assessments should occur at Screening (within 28 days prior to first IMP), and every 12 weeks (±7 days), starting from C1D1. Imaging timing should follow calendar days and should not be adjusted for delays in cycle. For participants who discontinue for reasons other than PD, assessments should continue until the participant has documented PD or start a new anti-cancer therapy. The first assessment may be performed earlier than 12 weeks after C1D1 if in the opinion of the Investigator the participant is clinically progressing.

Measurement of spleen size is mandatory and is to be assessed whenever response assessment is done.

If participants have partial response (PR), or complete response, a repeat CT scan is not required for confirmation, they should continue on every 12-week assessment schedule. In the setting where a participant is clinically stable, but imaging shows PD at the Week 12 disease response assessment, study drug may be continued, at the discretion of the PI, until the next disease response assessment. However, imaging should occur at any time where there is clinical suspicion of progression.

Assessment of lymphoma B symptoms should occur with each disease response assessment.

In participants with PD at Week 12, who continued study therapy beyond Week 12 a radiological assessment should be performed at the time of treatment discontinuation. If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory.

8.1.2 Bone marrow biopsy & aspirate:

All participants will have bone marrow biopsy/aspirate performed as clinically indicated as per Lugano 2014 criteria (Section 10.6). FDG-PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of bone marrow. Bone marrow biopsy confirmation can be considered if necessary at baseline (if the FDG-PET-CT is negative in the bone marrow site then biopsy/aspirate is performed to identify involvement as per the Investigator's judgment and based on other factors consistent with advanced stage or poor prognosis). Subsequent bone marrow assessments will only be performed in participants who have bone marrow involvement at baseline.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA. **Please refer to study SoA flow chart** (Section 1.3).

The NCI CTCAE version 5.0 will be used in this study to grade the severity of clinical and laboratory AEs.

The safety profile will be mainly based on incidence, severity, and cumulative nature of TEAEs. TEAEs are defined as AEs that develop or worsen in grade or become serious during the on-treatment period.

Adverse events will be coded to a "Low Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Group Level Term (HGLT)" and associated primary SOC" using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be summarized with respect to the type, frequency, severity, seriousness, and relatedness.

All the AEs, including AEs of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of study treatment. After the 30-day interval EOT, all the ongoing related non-serious AEs, the ongoing SAEs and the new related AE/SAEs are to be followed until resolution or stabilization. Stabilization is defined as an AE ongoing without any change for at least 3 months.

The primary objective is to evaluate the safety of isatuximab and cemiplimab when administered as an IV infusion to participants with lymphoma. The safety profile will be assessed from the findings of physical examination (preferably by the same physician), laboratory tests, etc, and will be based on incidence, severity, and cumulative nature of AEs.

8.2.1 Physical examinations

- A complete physical examination will include, at minimum, assessments of the major body systems. Height (only at baseline) and weight will also be measured and recorded.
- To be performed at baseline (within 14 days from C1D1), then within 3 days prior to premedication and IMP administration, at the EOT visit, during follow-up, and as clinically indicated.

- Performance status as measured by the ECOG.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at baseline, to be taken just before starting infusion of IMP, 1 hour after the start of the infusion, at the end of infusion, and as clinically indicated during the infusion or during any interruption due to an infusion reaction. The measurements will also be performed at the EOT visit and post-treatment follow-up visits at 60 and 90 days after last treatment.
- Blood pressure and pulse rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television and cell phones).

8.2.3 Electrocardiograms

- 12-lead ECG at baseline and as clinically indicated during the study treatment period.
- 12-lead ECG will be obtained as outlined in the SoA (Section 1.3), using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Clinically significant abnormalities should be reported as AE, except for at the screening assessment if the detected finding is linked to a preexisting condition. In that case, the diagnosis should be recorded in the participant's medical history.

8.2.4 ECHO or MUGA

Left ventricular ejection fraction (LVEF) will be performed at baseline (within 90 days of Day 1) for participants previously treated with anthracyclines (Section 5.2).

8.2.5 Pulmonary function test:

Diffusing capacity of the lungs for carbon monoxide (DLCO) will be performed at baseline for participants previously treated with bleomycin (Section 5.2).

8.2.6 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA 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. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition and that either leads to IMP(s) discontinuation or dose modification or fulfills a serious or AESI definition.
- All laboratory tests with values considered clinically and significantly abnormal during participation in the study or within 30 days 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 and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the system provided by the Sponsor.

8.2.6.1 Blood Chemistry:

To be done at baseline (within 14 days from C1D1), then within 3 days prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Biochemistry should be performed every 7 days in case of Grade 3/4 abnormalities. Blood chemistry includes: aspartate aminotransferase, alanine aminotransferase, bilirubin (total and direct), Alkaline phosphatase, Lactate dehydrogenase, sodium, potassium, chloride, bicarbonate/carbon dioxide (to be performed as clinically indicated), calcium, magnesium, phosphate, uric acid, urea or blood urea nitrogen, serum creatinine, eGFR (MDRD formula; Appendix 9 [Section 10.9]), glucose (fasting), albumin and total protein.

8.2.6.2 Hematology:

To be done at Screening (within 14 days from C1D1), then within 3 days prior to premedication and IMP administration, at the EOT visit, during follow-up and as clinically indicated. Hematology includes: hemoglobin, hematocrit, red blood cells, white blood cells with differential, and platelet counts. If Grade 4 neutropenia, assess ANC every 2 to 3 days until ANC $\geq 0.5 \times 10^9$/L and at least weekly thereafter until ANC $\geq 1.0 \times 10^9$/L. Blood group card to be obtained before study entry.

8.2.6.3 Urinalysis

Semi-quantitative (according to site practice and if such method can provide absolute numeric value of the parameters) (includes RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, and specific gravity) to be done at baseline (within 14 days from C1D1), then within 3 days prior to Cycle 1 Day 1, EOT, during follow-up, and during the treatment period if hematuria is observed or clinically indicated. Dipstick will be performed on Day 1 of each new cycle if clinically indicated. In case of positive dipstick results, quantitative or semi-quantitative analysis would be required.

Blood chemistry, hematology, and urinalysis are not required to be repeated prior to Cycle 1 Day 1 if the baseline laboratory assessments were performed within 3 days prior to first IMP administration.

8.2.6.4 TSH

It will be assessed at baseline, within 3 days prior to every second ie, other cycle, EOT, during follow-up visits (60 and 90 days after last treatment); free T4 will be assessed if thyroid stimulating hormone (TSH) is outside of the normal range.

8.2.6.5 Blood typing interference test

At baseline: blood type (if not already done) and phenotype (according to the site protocol). Recommended phenotype includes Rh system (C/c and E/e), Kell system (K/k); Duffy system (Fya/Fyb); Kidd system (Jka/Jkb); MNS system (M/N, S/s), and indirect antiglobulin test (indirect Coombs test) if considered standard of care in the site. On Cycle 2 Day 1 and before each transfusion: IAT (indirect Coombs test or antibody screen). Blood type card will be kept by the participant with the study card. Blood transfusions are to be recorded in the eCRF. The blood bank needs to be informed that the participant is receiving a treatment with an anti-CD38 and a potential interference with the Coombs test is possible. During the treatment period the transfusion service should follow the recommendations issued in the AABB bulletin in case a red blood cell transfusion is needed. The web link to the AABB bulletin will be indicated on the study patient card.

- The AABB Clinical Transfusion Medicine Committee has developed a bulletin (Appendix 7 Section 10.7) to provide background information and guidance to members regarding anti-CD38 interference with serologic testing.

8.2.6.6 Serology HIV, HBV, and HCV

Only for participants with prior history of these infections, including for viral genomes (PCR).

8.2.6.7 Pregnancy test

Urine or Serum Pregnancy Test for WOCBP only at baseline within 7 days prior to first dose, on Day 1 of each cycle prior to study treatment from Cycle 2, at EOT, and monthly up to 6 months following study treatment discontinuation.

8.2.6.8 Blood draw for biomarker analysis

A sample of peripheral blood will be drawn at Cycle 1 Day1, prior to IMP administration.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

Adverse events

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

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

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

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

Adverse event of special interest

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

The following AEs are considered AESIs:

- **Grade ≥2 acute infusion reactions** (IRs; Section 6.5.5 for manifestation/symptoms typical of an IR). An IR occurs typically within 24 hours from the start of the infusion.
- **Grade ≥3 immune-related TEAEs**.
- **Immune-related AEs of any grade** in a participant previously treated with a PI 3-K inhibitor.

- **Dose limiting toxicities** (as defined in Section 4.1) are considered as AESIs, and as such, the Investigators will be required to report them to the Sponsor within 24 hours of the Investigator becoming aware of the event. The Investigator will attach the DLT-specific CRF page to the DLT/AESI form.
- **Pregnancy** of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP.
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 Section 10.3),
  - In the event of pregnancy in a female participant, treatment with the IMP should be discontinued,
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 5 Section 10.5).
- **Symptomatic overdose** (serious or non-serious) with IMP/NIMP. An overdose (accidental or intentional) with the isatuximab is defined as increase of at least 30% of the intended administered dose at each infusion expressed in unit per body weight) to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration,
  - An overdose (accidental or intentional) with the NIMP is defined as increase of at least 30% of the intended administered dose at each administration expressed in unit per body weight),
  - Cemiplimab symptomatic overdose: accidental or unintentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.
  - In case of accidental or intentional overdose with the IMP/NIMP, even not fulfilling a seriousness criterion, is to be reported to the Sponsor immediately (within 24 hours) using the AE form together with the SAE complementary form to be entered in the eCRF.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Information about AEs will be obtained from the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

Serious Adverse Events , Adverse Events of Special Interest (including pregnancy and overdose)

- In the case of a SAE or an AESI, the Investigator must report the SAE or AESI to the Sponsor within 24 hours of the initial receipt of the information about SAE or AESI.
- The information about the SAE/AESI need to be entered in the appropriate sections of the eCRF; the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the eCRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.
- When cohorts of more than one participant begin accruing, the monitoring team will notify the study Investigators of the occurrence of DLTs and SAEs within 24 hours.
- All further data updates should be recorded in the eCRF (or a system provided by the Sponsor) as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medication, and participant status) should be sent (by fax or e-mail) to the Monitoring Team within 1 working day of knowledge. In addition, any effort should be made to further document each Serious Adverse Event that is fatal or life-threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the eCRF system does not work

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs will be collected from the signing of the ICF until the follow-up visit.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

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

Follow-up information for any adverse events entered in the pharmacovigilance database will be entered in the pharmacovigilance database at any time irrespective of the clinical database lock. GPV may also request follow-up on Individual Case Safety Reports received for entry in the pharmacovigilance database.

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and non-serious AEs of special interest (as defined in Section 8.2), will be followed until resolution, stabilization, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 3, Section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected are specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants, will be collected after the start of study intervention and the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5 (Section 10.5).

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.
- Of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP.
- Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria.
- In the event of pregnancy in a female participant, treatment with the IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

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

The following disease-related events (DREs) are common in participants with cancer and can be serious:

- Progression of underlying disease, as it is the study endpoint.
- Death due to progression of underlying disease, if it occurs after 30 days of the last IMP administration. The causes for all other deaths that occur within 30 days of last IMP administration, however, should be reported as SAEs.

Because these DREs are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

There is no information on specific recommendations regarding overdose with isatuximab or cemiplimab. In case of overdose, participants should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

8.5 PHARMACOKINETICS

8.5.1 Sampling time

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

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

The cemiplimab and isatuximab PK sampling times for blood collection can be found in the PK/PD Flow Chart (Section 1.4). For isatuximab, samples for PK assessment are to be collected during the course of the study; however, collection can be stopped earlier upon notification from the Sponsor based on the updated knowledge of PK.

For both cemiplimab and isatuximab, PK samples will be collected over C1 to C4 and from C5, both compounds will be collected at predose each cycle until C11 then every third cycle, ie, C14, C17, and C20 till the last study treatment or at the primary analysis cutoff date whichever comes first. For cemiplimab only, further samples to be collected at the end of treatment and at the follow-up treatment visit at 60 (±7) days or at the primary analysis cut-off date, whichever comes first. No PK collection will occur after the primary analysis cut-off date.

8.5.1.1 Pharmacokinetic sample handling procedure

Special procedures for collection, storage, and shipment will be provided in a separate laboratory manual.

8.5.1.2 Bioanalytical Methods

Bioanalytical methods are summarized in Table 7.

Table 7 - Bioanalytical methods for isatuximab and functional cemiplimab pharmacokinetic

Analyte	Isatuximab	Cemiplimab
Matrix	Plasma	Serum
Analytical technique	Immunoassay	Immunoassay
Lower limit of quantification	5.00 µg/mL	78.0 ng/mL
Site of bioanalysis	Covance Harrogate, UK	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

8.5.1.3 Pharmacokinetic parameters

Not applicable.

8.5.1.4 Non-compartmental analysis

The following PK parameters will be calculated with PKDMS software (Pharsight), using non-compartmental methods, from plasma concentrations of isatuximab and serum concentrations of cemiplimab. The parameters will include, but may not be limited to, the following in Table 8:

Table 8 - List of pharmacokinetic parameters and definitions

Parameters	Definition
Ceoi	Concentration observed at the end of intravenous (IV) infusion
Cmax	Maximum concentration observed after the first infusion
tmax	Time to reach Cmax
Clast	Last concentration observed above the lower limit of quantification after the first infusion

Parameters	Definition
tlast	Time of Clast
Ctrough	Concentration observed just before treatment administration during repeated dosing
AUC0-T	Area under the concentration versus time curve calculated using the trapezoidal method over the dosing interval; ie, 6 days for isatuximab or 21 days for cemiplimab)

8.5.1.5 Population approach

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

8.6 PHARMACODYNAMICS

Tumor biopsies will be collected at baseline (cf I02) and during treatment*, for the following pharmacodynamic biomarker analyses:

- CD38 positive cells, PD-L1 positive cells, immune-contexture (such as T cells, B cells, and activating or inhibitory receptors) and possibly MHC-I positive cells, MHC-II positive cells and beta-2-microglobulin positive cells by immunohistochemistry (IHC) or Fluorescent Multiplex IHC in formalin-fixed paraffin-embedded (FFPE) tumors.

* During treatment, on-treatment biopsy at Cycle 2 Day 1 may be obtained within 7 days prior to IMP administration on Cycle 2 Day 1 (after IMP administration on C1D22 wherever applicable), unless clinically unfeasible and after discussion with Sanofi Study Medical Manager.

8.7 GENETICS

Genetic and genomic analyses may be conducted on tumor material (such as FFPE preserved tumor samples). For the DNA exome sequencing, a sample of peripheral blood may be taken as a control at C1D1 and will not be used to determine the likelihood of the participant or his/her family members developing a disease. Other techniques might also be used to detect gene amplification, deletion, or gene rearrangement. Genetic analyses will particularly enable discrimination between subtypes of DLBCL.

Peripheral blood samples will be collected for DNA isolation at C1D1 for Immune genetic determinants (including FcγRIII polymorphisms) analysis. Blood DNA for Immune genetic determinants will not be used to determine the likelihood of the participant or his/her family members developing a disease.

See Appendix 8 (Section 10.8) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in laboratory manual.

8.8 BIOMARKERS

This section refers to additional analyses and future use of samples:

- During the study additional analyses, not specified in the protocol but related to the drug action and/or effect of isatuximab/cemiplimab, may be conducted on samples pending evolving literature.
- After study completion, for participants who have consented to it, remaining samples will be kept for other possible exploratory analyses. Results of these analyses will not be included in the clinical study report but in a stand-alone report, if applicable.
- These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.
- These samples will remain labeled with the same identifiers used during the study (ie, participant ID).
- They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting participant confidentiality and personal data (Section 10.1.4). These samples maybe stored for a period of up to 5 years after completion of the final study report. After that period, any samples remaining will be destroyed.

8.8.1 RNA transcriptome research

Transcriptome studies will be conducted using NGS (RNAseq) or by Nanostring and/or alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of ribonucleic acid (RNA) species resulting in a transcriptome profile for each and tumor biopsy sample. This analysis will be performed on available tumor sample (such as FFPE or RNA later preserved tumor samples). This analysis will particularly enable discrimination between different subtypes of DLBCL. This might also enable the evaluation of changes in transcriptome profiles (such as immune related genes) that may correlate with biological response relating to disease or the action of study intervention.

The same samples may also be used to confirm findings by application of alternative technologies.

8.9 IMMUNOGENICITY ASSESSMENTS

It is of utmost importance to collect all blood samples at the specified times and according to the specifications for collection, storage, and shipment as defined in a separate laboratory manual.

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

The cemiplimab and isatuximab ADA sampling times for blood collection can be found in the PK/PD Flow Chart (Section 1.4).

- No isatuximab and cemiplimab ADA collection will be done after primary analysis cut-off date.
- For isatuximab during intervention period, samples for immunogenicity assessment will be collected at each cycle from C1 to C5 then every third Cycle (ie, on D1 of C5, C8, C11, C14, etc) until the last study treatment, and at FUP 90 (±7) days after last isatuximab administration or at the primary analysis cut-off date, whichever comes first. However, collection can be stopped earlier upon notification of the Sponsor based on the updated knowledge of isatuximab immunogenicity. After FUP 90 (±7) days after last isatuximab administration no further ADA will be sampled even if the status is positive or inconclusive.
- For cemiplimab during intervention period, samples for immunogenicity assessment will be collected at C1, C2, then every third cycle from C5 Cycle (ie, D1 of Cycle 5, 8, 11, 14, etc.) till the last study treatment, and at EOT or at the primary analysis cut-of date, whichever comes first. During the intervention period, if isatuximab is stopped and cemiplimab treatment continues cemiplimab ADA samples should be collected as planned per PK/PD flow chart. In response to AE's of special interest, such as anaphylaxis or hypersensitivity, ADA samples may be collected closer to the event, based on the judgment of the Investigator and/or medical monitor.

Bioanalytical methods used for immunogenicity assessment are summarized in Table 9.

Table 9 - Bioanalytical methods for immune response assessment

Analyte	ANTI ISATUXIMAB ANTIBODY	ANTI CEMIPLIMAB ANTIBODY
Matrix	Plasma	Serum
Analytical technique	PandA method	Non-quantitative bridging immunoassay
Lower Limit of Quantification	Not applicable	Not applicable
Site of bioanalysis	Covance Harrogate (UK))	Regeneron Pharmaceuticals, Inc. (Tarrytown, NY)

8.10 [HEALTH ECONOMICS] OR [MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS]

Not applicable.

8.11 DATA COLLECTION AFTER PREMATURE STOP OF THE STUDY

If the sponsor decides to stop prematurely the study, eg, not to open Phase 2 Stage 2 if the interim analysis met protocol criteria. All participants still on treatment after premature stop of the study may continue to receive treatment if they accept as far as they continue to benefit from it as per investigator assessment until disease progression, unacceptable AE, participant's decision to stop the treatment, 96 weeks of delivery of IMP(s) without documented progressive disease (PD), or 48 weeks of treatment after achieving a complete response to study treatment (whichever is longer), or any other reason.

Procedure and data collection for these patients will be as follows:

- Study treatment administration (SAR650984, Cemiplimab, premedications)
- ECOG PS
- Pregnancy test (urine sample or approximately 1 teaspoon [ie, 5 mL] of blood sample will be collected) on D1 of each cycle from cycle 2, at EOT and monthly up to 6 months following study treatment discontinuation for women who can become pregnant.
- All SAEs regardless of relationship, ongoing and new related AEs and AESIs are to be collected until stabilization or resolution and all associated concomitant medication. Stabilization is defined as an AE ongoing without any change for at least 3 months
- All laboratory values leading to treatment modification should be reported
- No more PK, ADA and BM to be collected
- No efficacy data including FDG PET CT and CT Scan will be collected
- EOT visit should be done approximately 30 days after last study drugs
- After EOT visit, no follow up visit will be performed

Patients with ongoing related AEs/AESIs and ongoing SAEs after treatment discontinuation will be followed until resolution or stabilization of the AEs/AESIs/SAEs.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Phase 1

There is no formal statistical hypothesis in Phase 1 safety run-in.

Phase 2

For Cohort A1 (cHL anti-PD-1/PD-L1 naïve), the null hypothesis is that the true CR during isatuximab + cemiplimab period is ≤20%, and the alternative hypothesis is that the true CR is ≥40%.

For Cohort A2 (cHL anti-PD-1/PD-L1 inhibitor progressor), the null hypothesis is that the true ORR during isatuximab + cemiplimab period is ≤20%, and the alternative hypothesis is that the true ORR is ≥45%.

For Cohort B (DLBCL), the null hypothesis is that the true ORR is ≤35%, and the alternative hypothesis is that the true ORR is ≥60%.

For Cohort C (PTCL), the null hypothesis is that the true ORR is ≤25%, and the alternative hypothesis is that the true ORR is ≥50%.

9.2 SAMPLE SIZE DETERMINATION

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 enrolled (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 are provided in Table 10:

Table 10 - Determination of sample size in Phase 2

Indication	H0	H1	Sample size		Number of required response	
			Stage 1	Final	Stage 1	Final
Cohort A1 (cHL anti-PD-1/PD-L1 naïve)	20% (2, 3)	40%	17	37	≥4 CR	≥12 CR
Cohort A2 (cHL anti-PD-1/PD-L1 progressor)	20% (6)	45%	12	25	≥3	≥9
Cohort B (DLBCL anti-PD-1/PD-L1 naïve)	35% (20, 21)	60%	18	29	≥8	≥15
Cohort C (PTCL anti-PD-1/PD-L1 naïve)	25% (22, 24, 11)	50%	10	27	≥3	≥11

Abbreviations: H0 = Null hypothesis; H1 = Alternative hypothesis; cHL = Classic Hodgkin's lymphoma; DLBCL = Diffuse large B-cell lymphoma; PTCL = Peripheral T-cell lymphoma.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined:

Table 11 - Populations for analyses

Population	Description
All treated	For both Phase 1 and Phase 2 of the study, the all-treated population will include all participants who have given their informed consent and received at least 1 dose (even incomplete) of either isatuximab or cemiplimab
Dose limiting toxicity (DLT) evaluable (Phase 1)	The DLT evaluable population is defined as participants in Phase 1 who received at least 90% of the planned doses of isatuximab and cemiplimab during Cycle 1, and completed the DLT observation period after the first IMP administration, unless they discontinued the study treatment(s) due to DLT. The dose recommended for Phase 2 will be determined on the DLT evaluable population.
Response evaluable population	The response evaluable population will include all participants in the all treated population who fulfilled all inclusion and exclusion criteria without any major or critical deviation with an evaluable baseline assessment and at least one evaluable post-baseline assessment during the treatment period. This population is the secondary analysis population for efficacy.
Pharmacokinetics (PK)	The PK population will include all participants from the all treated population with at least 1 drug concentration after drug administration.
Anti-drug antibody (ADA) evaluable	The ADA evaluable population includes all participants from the all treated population with at least 1 non-missing ADA result after the drug administration.
Pharmacodynamics (PDy)	The pharmacodynamics population will include all participants from the all treated population with at least 1 pharmacodynamic marker result after the first dose of study treatment.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 14 (see Section 10.14).

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

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 indication in Stage 1 of Phase 2. Data from cHL (Cohorts A1 and A2), DLBCL, and PTCL cohorts in Phase 2 will be analyzed and reported separately by cohort.

Planned date for analysis cut-off:

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.

9.4.1 Efficacy analyses

All treated population will be the primary analysis population for efficacy endpoints. In addition, similar analysis will be performed using the response evaluable population as a secondary analysis.

Analysis of primary efficacy endpoints

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 alpha level defined in the sample size calculation section.

Analysis 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 from both isatuximab + cemiplimab and isatuximab + cemiplimab + radiotherapy periods, and for participants in Cohorts A1 and A2 who receive isatuximab + cemiplimab + radiotherapy.

Table 12 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	
cHL Cohort A1: CR rate during isatuximab+cemiplimab period	Descriptive statistics and Clopper-Pearson method
cHL Cohort A2, DLBCL and PTCL: ORR during isatuximab+cemiplimab period	Descriptive statistics and Clopper-Pearson method
Secondary	
Tumor burden change	Descriptive statistics
DoR and PFS	Kaplan-Meier method
DCR	Descriptive statistics
cHL Cohort A1: ORR during isatuximab+cemiplimab period	Descriptive statistics and Clopper-Pearson method
cHL Cohort A1 & Cohort A2: CR rate and ORR 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.	Descriptive statistics and Clopper-Pearson method
Exploratory	Will be described in the statistical analysis plan finalized before database lock

Abbreviations: cHL = Classic Hodgkin's lymphoma; CR = Complete remission; DCR = Disease control rate; DLBCL = Diffuse large B cell lymphoma; DoR = Duration of response, ORR = Objective response rate; PFS = Progression free survival; PTCL = Peripheral T-cell lymphoma

9.4.2 Safety analyses

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

Table 13 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	
DLTs, AEs/SAEs, and laboratory abnormalities in Phase 1	Descriptive statistics
Secondary	
AEs/SAEs and laboratory abnormalities in Phase 2	Descriptive statistics
AEs/SAEs and laboratory abnormalities in isatuximab + cemiplimab + radiotherapy treated participants for Cohort A1 and A2	Descriptive statistics
ADA against isatuximab and against cemiplimab	Descriptive statistics
Exploratory	Will be described in the statistical analysis plan finalized before database lock

ADA = Anti-drug antibody; AE = Adverse event; DLT = Dose limiting toxicity; SAE = Serious adverse event.

Dose limiting toxicities

In Phases 1, the DLTs will be listed by participant using the DLT evaluable population.

Analyses of adverse events

In Phases 1 and 2, the AEs will be coded according to MedDRA. Adverse events and laboratory abnormalities will be graded according to NCI CTCAE version 5.0.

The number (%) of participants experiencing TEAEs by primary SOC and PT will be summarized by CTCAE grade (all grades and Grade ≥3) for the all treated population. Same table will be prepared for treatment-related TEAEs, AESIs, TEAEs leading to treatment discontinuation, serious TEAEs and TEAEs with fatal outcome. The post-treatment AEs will be analyzed separately.

Clinical laboratory evaluations

All the laboratory abnormalities will be graded according to NCI CTCAE version 5.0, when applicable. The number (%) of participants with laboratory abnormalities (ie, all grades and Grade ≥3) using the worst grade during the on-treatment period will be provided for the all treated population.

Immunogenicity

The findings from the analyses of immunogenicity for isatuximab and cemiplimab will be summarized.

9.4.3 Other analyses

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

Analysis of PK endpoints

Individual concentrations and PK parameters of isatuximab and cemiplimab will be summarized by descriptive statistics (such as mean, geometric mean, median, standard deviation, standard error of the mean, coefficient of variation, and minimum and maximum) under the responsibility of Sanofi, Pharmacokinetic, Dynamic & Metabolism department. Individual and mean profiles will be presented graphically.

Analysis of pharmacodynamic endpoints

Findings from pharmacodynamics markers will be descriptively summarized and tabulated.

9.5 INTERIM ANALYSES

The Statistical Analysis Plan will describe the planned interim analyses in greater detail. 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 the first 17, 12, 18, and 10 participants, respectively, in Phase 2 have been treated and followed-up for 24 weeks.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable ICH Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the participation in the post-dose PK assessment sub-study. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 14 (see Section 10.14).

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

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

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees structure

DMC (Data Monitoring Committee):

Independent from the Sponsor and Investigators, the DMC role will be to monitor the safety of the participants enrolled in the study (ie, exposed to study treatment and/or to study procedures) and to provide the Sponsor with appropriate recommendations in due time to ensure the safety of the participants. During this exercise, the DMC will also institute any measures that may be required for ensuring the integrity of the study results during the execution of its primary mission.

Study committee:

During Phase 1, the study committee (SC) will review clinical data approximately every 2 weeks. During Phase 1, composition of the SC will vary based on the matter discussed, but it will generally include Sponsor representatives and at least two Investigators with participants participating to Phase 1. For Phase 2, the SC will consist of Sponsor representatives and at least two Investigators participating in Phase 2 Stage 1 or Stage 2. A radiotherapist will be included in the SC meetings to discuss the radiotherapy options after Cycle 10. The SC meetings will occur on an as needed basis to review data and provide strategic recommendations on study medical decisions.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

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

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the end of the clinical study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The informed consent form will include a statement by which the participant allowing the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data in the eCRF (eg, participant's medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality rules).

10.1.9 Study and site closure

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

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 14 will be performed by the local laboratory.

- The results must be entered into a system provided by the Sponsor.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 14 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology[a]	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Blood chemistry[a]	Urea or Blood urea nitrogen (BUN)[b] Uric acid	Potassium Chloride Bicarbonate/carbon Dioxide (to be performed as clinically indicated)	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin Lactate dehydrogenase (LDH)
	Creatinine eGFR (MDRD) Glucose fasting	Sodium Magnesium Phosphate Calcium	Alanine aminotransferase (ALT)[b]/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase	Total protein Albumin Thyroid stimulating hormone (TSH), free T4[c], (baseline), every other cycle thereafter, end of treatment, during follow-up visits (60 and 90 days after last treatment)
Routine urinalysis	Semi-quantitative urinalysis (including RBC, protein, glucose, pH, ketones, bilirubin, leucocytes, nitrates, and specific gravity). Semi-quantitative analysis is required at baseline, end of treatment (EOT), during follow-up, and during the treatment period if hematuria is observed. Dipstick will be performed on Day 1 of each new cycle if clinically indicated. Subsequent urinalysis may be performed; in case of positive dipstick results, semi-quantitative analysis would be required.			
Other screening tests	Serum (at baseline) or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).(urine pregnancy test on Day 1 of each cycle, EOT and monthly up to 6 months following study treatment discontinuation) Coagulation: prothrombin time or international normalized ratio (INR)[b] and partial thromboplastin time (PTT) Blood typing interference test Only for participants with prior history of these infections, including for viral genomes (PCR). Serology[d] (HIV antibody, hepatitis B surface antigen [HBsAg], anti-HBc total and IgM, (HBV DNA testing by PCR in case of anti-HBc positive), anti-HBs, anti-HCV and HCV RNA) The results of each test must be entered into the CRF. **Definitions:** 1. Controlled human immunodeficiency virus (HIV) infection is defined as undetectable viral load and CD4+ >200 cells/mm^3. 2. Controlled hepatitis B virus (HBV) infection is defined as anti-HBV therapy started before initiation of IMP, and HBV viral load <2000 IU/mL (10^4 copies/mL). The anti-HBV therapy should continue throughout the treatment period.			

NOTES :

a Blood chemistry, hematology: assessments are not required to be repeated prior to Cycle 1 Day 1 if the screening laboratory assessments were performed within 3 days prior to first IMP administration and met entry criteria.

b All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis). INR = (PT test /PT normal) (international sensitivity index [ISI] value).

c Free T4: will be assessed if TSH is outside of the normal range.

d For patients with positive anti-HBc IgG and negative HBsAg and undetectable (under limit of quantification) HBV DNA at study entry (HBV carriers: past resolved infection, resolving acute infection or receiving antiviral treatment with controlled infection), specialist advice should be requested, close monitoring of viral reactivation (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or HBV DNA in patients with resolved infection) throughout and following the end of study treatment should be proposed (ALT, AST and HBV DNA at least every 3 months, up to 6 months after treatment discontinuation or initiation of further anticancer therapy).

In case of viral reactivation during study treatment (greater than 1log10 IU/mL increase in HBV DNA or reappearance of HBsAg or detection of HBV DNA in patients with resolved infection*), close monitoring of ALT, AST every month, up to study treatment discontinuation. HBV DNA to be done as per specialist advice.

In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2 and 3 months after end of vaccination.

* previous known history of acute or chronic hepatitis B or the presence of total anti-HBc with/without anti-HBs; HBsAg negative; undetectable serum HBV DNA; normal ALT levels.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition:

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, if they are symptomatic, require corrective treatment, lead to treatment discontinuation, or dose modification, fulfill a serious criterion, or the defined as an AESI).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" (eg, disease progression) will be reported as a DRE not as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition:

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

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a) **Results in death,**

b) **Is life-threatening,**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) **Requires inpatient hospitalization or prolongation of existing hospitalization,**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether "hospitalization" occurred, the AE should be considered serious.

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

d) **Results in persistent disability/incapacity,**

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

e) Is a congenital anomaly/birth defect,

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include second primary invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sanofi in lieu of completion of the Sanofi/AE/SAE CRF page.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of severity (grade)

The Investigator will make an assessment of severity (grade) for each AE and SAE reported during the study and assign it to one of the categories according to NCI CTCAE v.5.0.

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

Assessment of causality

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

Follow-up of AEs and SAEs

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

REPORTING OF SAES

SAE reporting to Monitoring team via an electronic data collection tool

- The primary mechanism for reporting an SAE to Monitoring team will be the electronic data collection tool.

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the monitoring team by fax or e-mail.

10.4 APPENDIX 4: RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC CEMIPLIMAB DRUG RELATED ADVERSE EVENTS

Table 15 - Colitis adverse event management

Colitis events CTCAE version 5.0	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Bowel obstruction Colitis Colitis microscopic	No change in dose	No change in dose	For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. Grade 1 diarrhea that persists for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate 4 times daily and budesonide 9 mg daily.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer.

Colitis events CTCAE version 5.0	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 2 Enterocolitis hemorrhagic GI perforation Necrotizing colitis Diarrhea: all participants who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	Delay or omit dose until ≤Grade 1 (See Section 6.5.2)	Delay or omit dose until ≤Grade 1 (See Section 6.5.2)	GI consultation and endoscopy is recommended to confirm or rule out colitis for Grade 2 diarrhea that persists >1 week or Grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). Grade 2 diarrhea should be treated with addition of oral diphenoxylate hydrochloride and atropine sulfate 4 times daily and budesonide 9 mg daily. Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. In participants with Grade 2 enterocolitis, cemiplimab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than 1 week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.	

Colitis events CTCAE version 5.0	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3 and Grade 4	Grade 3: delay or omit dose until ≤Grade 1 (See Section 6.5.2) Grade 4: discontinue treatment	Delay or omit dose until ≤Grade 1 (See Section 6.5.2) Discontinue if unable to reduce corticosteroid dose to <10 mg/day prednisone equivalent within 12 weeks of adverse event	Participants with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment): Rule out bowel perforation. Imaging with plain films or CT can be useful. Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. Treat with IV steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in participants with diffuse and severe ulceration and/or bleeding. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: Infliximab is contraindicated in participants with bowel perforation or sepsis. If symptoms persist despite the above treatment a surgical consult should be obtained.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, gastroenteritis or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer. If symptoms are persistent and/or severe, endoscopic evaluation should be considered.

Abbreviations: CT = Computed tomography; CTCAE = Common terminology criteria for adverse events; GI = Gastrointestinal; IV = Intravenous.

Table 16 - Endocrine adverse event management

Endocrine events CTCAE version 5.0	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1-2 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	No change in dose	No change in cemiplimab dose	Monitor thyroid function or other hormonal level tests and serum chemistries more frequently (every 3 to 6 weeks) until returned to baseline values. Replacement of thyroid hormone or thyroid suppression therapy as indicated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Grade 3-4 Hyperthyroidism Hypothyroidism Thyroid disorder Thyroiditis	Delay or omit dose until resolves to Grade ≤2 (see Section 6.5.2)	Delay or omit dose until on stable replacement dose as determined by resolution of symptoms and normalization of hormone levels (see Section 6.5.2)	Consider endocrine consultation. Rule out infection and sepsis with appropriate cultures and imaging. Replacement of thyroid hormone or thyroid suppression therapy as indicated.	
Grade 1-4 Adrenal insufficiency Hypophysitis Hypopituitarism Pan-hypopituitarism	Grade 1, 2: no change in dose, Grade 3, 4: delay or omit dose until resolves to Grade ≤2 (see Section 6.5.2)	Delay or omit dose until on stable replacement dose (see Section 6.5.2)	Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. If Grade 1-2 hypophysitis is considered, pituitary gland imaging should be considered (MRI with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended

Abbreviations: CTCAE = Common terminology criteria for adverse events; IV = Intravenous; MRI = Magnetic resonance imaging.

Table 17 - Pneumonitis adverse event management

Pneumonitis events CTCAE version 5.0Grade	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 1 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	No change in dose	Consider delay or omit dose (see Section 6.5.2). Cemiplimab may be continued with close monitoring.	Radiological findings should be followed on serial imaging studies at least every 3 weeks. Monitor for symptoms every 2 to 3 days. Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2)	Delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2)	To rule out other causes such as infection: Consider pulmonary consultation with bronchoscopy and biopsy/BAL. Consider pulmonary function tests Follow radiological findings on serial imaging studies every 1 to 3 days If the participant is determined to have study treatment-associated pneumonitis Monitor symptoms daily, consider hospitalization Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Treatment with cemiplimab may be resumed if the event improves to ≤Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply: First episode of pneumonitis: may decrease the dose to 1 mg/kg in subsequent cycles. Second episode of pneumonitis: Discontinue cemiplimab if upon re-challenge the participant develops a second episode of ≥Grade 2 pneumonitis.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection

Pneumonitis events CTCAE version 5.0Grade	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic considerations
Grade 3-4 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Grade 3: delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2) Grade 4: discontinue treatment	Discontinue cemiplimab	Consider pulmonary function tests with pulmonary consult. Bronchoscopy with biopsy and/or BAL is recommended. Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to Grade 1 or less, a high-dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. Add prophylactic antibiotics for opportunistic infections. If IV steroids followed by high-dose oral steroids does not reduce initial symptoms with 48 to 72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection

Abbreviations: BAL = Bronchoalveolar lavage; CTCAE = Common terminology criteria for adverse events; IV = Intravenous.

Table 18 - Renal adverse event management

Renal events CTCAE version 5.0 Grade	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic Considerations
Grade 1 Nephritis Nephritis autoimmune	No change in dose	Consider delay or omit dose if event does not improve with symptomatic treatment (see Section 6.5.2)	Provide symptomatic treatment. Monitor creatinine weekly: when it returns to baseline, resume routine creatinine monitoring per protocol.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.

Renal events CTCAE version 5.0 Grade	Isatuximab Dose Management	Cemiplimab Dose Management	Actions and Guidelines	Diagnostic Considerations
Grade 2 Renal failure	Delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2)	Consider delay or omit dose (see Section 6.5.2)	Systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued for at least 1 month. Consider prophylactic antibiotics for opportunistic infections. Consider renal biopsy. If elevations persist >7 days or worse, treat as Grade 4.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
Grade 3-4 Renal failure acute	Grade 3: delay or omit dose until resolves to Grade ≤1 (see Section 6.5.2) Grade 4: discontinue treatment	Discontinue cemiplimab	Renal consultation with consideration of ultrasound and/or biopsy as appropriate. Monitor creatinine daily. Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.

Abbreviations: CTCAE = Common terminology criteria for adverse events; irAEs = Immune-related adverse events.

Table 19 - Dermatologic adverse event management

Skin events CTCAE version 5.0	Isatuximab Dosing Managment	Cemiplimab Dosing Managemnt	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	No change in dose	Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruitics (eg, diphenhydramine HCl or hydroxyzine HCl) Treatment with oral steroids is at Investigator discretion for Grade 2 events.	All attempts should be made to rule out other causes such as metastatic disease, infectious, or allergic dermatitis.

Skin events CTCAE version 5.0	Isatuximab Dosing Managment	Cemiplimab Dosing Managemnt	Action and Guidelines	Diagnostic Considerations
Grade 3	No change in dose	Delay or omit dose until Grade ≤2 (see Section 6.5.2)	Consider dermatology consultation and biopsy for confirmation of diagnosis. Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once daily or dexamethasone 4 mg 4 times per day. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no less than 4 weeks.	
Grade 4	Delay or omit dose until Grade ≤3 (see Section 6.5.2)	Discontinue treatment	Dermatology consultation and consideration of biopsy and clinical dermatology photograph. Initiate with oral steroids with 1 mg/kg prednisone or equivalent. When symptoms improve to Grade ≤1, steroids taper should be started and continue over no less than 4 weeks.	

Abbreviations: CTCAE = Common terminology criteria for adverse events.

Table 20 - Hepatitis adverse event management

Hepatitis CTCAE version 5.0	Isatuximab Dosing Management	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1, 2	No change in dose	Delay or omit dose if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters (see Section 6.5.2)	Monitor liver function tests more frequently until returned to baseline values	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug adverse event, infectious causes and/or myositis
Grade 3, 4	Delay or omit dose until Grade ≤2 (see Section 6.5.2)	Discontinue treatment if: AST or ALT ≥5 x ULN Bilirubin ≥3 x ULN	Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. Treat with high-dose IV glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade ≤1, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks. If AST/ALT levels do not decrease 48 hours after initiation of systemic	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug adverse event, infectious causes and/or myositis

Hepatitis CTCAE version 5.0	Isatuximab Dosing Management	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
			steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity. Several courses of steroids taper may be necessary as symptoms may worsen when the steroids dose is decreased.	

Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common terminology criteria for adverse events; ULN = Upper limit of normal.

Table 21 - Ophthalmology (uveitis) adverse event management

Uveitis CTCAE version 5.0	Isatuximab Dosing Management	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy	Evaluation by an ophthalmologist is strongly recommended Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitis	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (eg, glaucoma or cataracts)
Grade 2	No change in dose	Discontinue treatment if symptoms persist despite treatment with topical immunosuppressive therapy, and do not improve to Grade 1 within the retreatment period or requires systemic treatment		
Grade ≥3	Delay or omit dose until Grade ≤2 (see Section 6.5.2)	Discontinue treatment	Treatment with systemic corticosteroids such as prednisolone at a dose of 1 to 2 mg/kg/day. When symptoms improve to Grade ≤1, steroid taper should be started and continued over no less than 4 weeks	

Abbreviations: CTCAE = Common terminology criteria for adverse events.

Table 22 - Nausea and vomiting adverse event management

Nauea and Vomiting CTCAE version 5.0	Isatuximab Dosing Management	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1	No change in dose	No change in dose	Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institution practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.	
Grade 2	Delay or omit dose until ≤Grade 1 (see Section 6.5.2) Restart treatment at same dose level	Delay or omit dose until ≤Grade 1 (see Section 6.5.2) May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities for resolve.		
Grade 3	Delay or omit dose until ≤Grade 1 (see Section 6.5.2) Restart at same dose level.	Delay or omit until ≤Grade 1 (see Section 6.5.2) May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities for resolve. Discontinue if adverse event does not resolve within 12 weeks.		
Grade 4	Discontinue treatment			

Abbreviations: CTCAE = Common terminology criteria for adverse events.

10.5 APPENDIX 5: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy,
    - Documented bilateral salpingectomy,
    - Documented bilateral oophorectomy.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Reproductive potential

- A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTION GUIDANCE

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 23 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male participants must refrain from donating sperm for the duration of the study and for 6 months after study completion or the last dose of study intervention.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 23.

In addition, WOCBP must refrain from donating ova for the duration of the study and for 6 months after study completion or the last dose of study intervention.

Table 23 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly effective methods that are user independent
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the intervention period and for at least [X, corresponding to time needed to eliminate study intervention plus 30 days for study interventions with genotoxic potential] after the last dose of study intervention.

PREGNANCY TESTING:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.
- Additional pregnancy testing is required during the intervention period and after the last dose of study intervention during 6 months of the follow-up period.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

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

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.6 APPENDIX 6: DISEASE ASSESSMENT AND LUGANO CLASSIFICATION

Disease response will be assessed using the Lugano response criteria 2014. Response assessments should occur at Screening and every 12 weeks (±7 days) thereafter starting from C1D1 (1).

Table 24 - Revised Criteria for Response Assessment

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

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

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

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

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

Imaging timing should follow calendar days and should not be adjusted for delays in cycle. For participants who discontinue for reasons other than PD, assessments should continue until the participant has documented PD. The first assessment may be performed earlier than 12 weeks if in the opinion of the Investigator the participant is clinically progressing.

10.7 APPENDIX 7: MITIGATING THE ANTI-CD38 INTERFERENCE WITH SEROLOGIC TESTING

Advancing Transfusion and Cellular Therapies Worldwide

Association Bulletin #16-02

Date: January 15, 2016
To: AABB Members
From: [redacted]
Re: Mitigating the Anti-CD38 Interference with Serologic Testing

Summary

A new class of therapeutic agents for multiple myeloma, CD38 monoclonal antibodies, can result in interference with blood bank serologic tests and thereby cause delays in issuing Red Blood Cell (RBC) units to patients receiving these agents. To minimize these delays, hospitals should set up procedures to inform the transfusion service when patients start receiving these agents. Considerations for the transfusion service, both before and after initiation of anti-CD38 therapy, are detailed below.

The AABB Clinical Transfusion Medicine Committee has developed this bulletin to provide background information and guidance to members regarding anti-CD38 interference with serologic testing. The bulletin includes recommendations for its prevention and treatment.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, may include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin contains information and recommendations. No new standards are proposed.

Background

CD38 monoclonal antibodies are a new treatment for multiple myeloma

CD38, an integral membrane protein that is highly expressed on myeloma cells, has been identified as an effective target antigen for monoclonal antibody therapies. In November 2015, the first therapeutic CD38 monoclonal antibody [daratumumab (Darzalex, Janssen Biotech, Horsham, PA)] was approved by the Food and Drug Administration.[1] Other CD38 monoclonal antibodies are under development.

CD38 monoclonal antibodies interfere with blood bank serologic tests

CD38 is weakly expressed on red cells. Anti-CD38 binds to CD38 on reagent RBCs, causing panreactivity in vitro.[2, 3] Plasma samples from anti-CD38-treated patients consistently cause positive reactions in indirect antiglobulin tests (IATs), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches. Agglutination due to anti-CD38 may occur in all media (eg, saline, low ionic strength saline, polyethylene glycol), and with all IAT methods (eg, gel, tube, solid phase). Agglutination reactions caused by anti- CD38 are usually weak (1+), but stronger reactions (up to 4+) may be seen in solid-phase testing. However, anti-CD38 does NOT interfere with ABO/RhD typing or with immediate-spin crossmatches.

Other notes on anti-CD38 serologic interference:

- Adsorptions using either untreated or ZZAP-treated cells fail to eliminate the interference.
- Anti-CD38 variably interferes with direct antiglobulin tests (DATs) and antibody identification panel autocontrols.
- Some rare Lu(a–b–) cells are not reactive in the presence of anti-CD38, potentially giving the false impression that the patient has a Lutheran-related antibody[4, 5].
- Positive IATs can be observed for up to six months after anti-CD38 is discontinued[1, 3].
- Anti-CD38 may cause a small decrease in hemoglobin in vivo (~1 g/dL), but severe hemolysis has not been observed among treated patients[3, 6].

Anti-CD38 interference can cause delays in issuing RBCs

If the transfusion service is unaware that a patient has received anti-CD38, the following scenario may occur when the patient's sample is tested:

1. ABO/RhD typing: no issues.
2. Antibody detection (screening) test: all cells positive.
3. Antibody identification panel: all cells positive (autocontrol may be negative).
4. DAT: positive or negative.
5. AHG crossmatches: positive with all RBC units tested.
6. Adsorptions: panreactivity cannot be eliminated.

This leads to delays in issuing RBCs to the patient. In some cases, the anti-CD38 interference could mask the presence of a clinically significant alloantibody.

Recommendations

To avoid problems with transfusion, hospitals should set up procedures to inform the transfusion service whenever any patient is scheduled to begin taking anti-CD38.

BEFORE a patient begins taking anti-CD38:

- A baseline type and screen should be performed.
- In addition, a baseline phenotype or genotype is recommended.

AFTER a patient begins taking anti-CD38:

- ABO/RhD typing can be performed normally.
- For antibody detection (screening) and identification, dithiothreitol (DTT)-treated cells can be used to eliminate the interference[2, 7].
  - Because DTT treatment destroys Kell antigens, K-negative units should be provided unless the patient is known to be K-positive.
  - Antibodies against other DTT-sensitive blood group antigens (anti-k, anti-Yt^a, anti-Do^a/Do^b, etc) will not be detectable when the antibody screen with DTT-treated cells is performed; such antibodies are encountered infrequently, however.

Crossmatch

- For patients with a negative antibody screen using DTT-treated cells, an electronic or immediate-spin crossmatch with ABO/RhD-compatible, K-matched units may be performed.
- For patients with known alloantibodies, phenotypically or genotypically matched RBC units may be provided[6, 8].
  - As some typing antisera require the use of AHG, phenotyping should be performed before the patient receives anti-CD38.
  - Genotyping can be performed either before or after the patient receives anti-CD38.
  - AHG crossmatches with phenotypically or genotypically matched units will still be incompatible.
  - Some clinically significant antibodies may be missed with the use of uncrossmatched phenotypically or genotypically matched units, although this will occur infrequently.
- Alternatively, an AHG crossmatch may be performed using DTT-treated donor cells.
- If an emergency transfusion is required, uncrossmatched ABO/RhD-compatible RBCs may be given per local blood bank practices.

Future/alternative approaches to mitigating the anti-CD38 interference

It is possible to neutralize anti-CD38 in plasma and eliminate the interference using either recombinant soluble human CD38 or daratumumab idiotype antibody[2, 3]. Neither reagent is widely available at this time, and additional validation would be needed. In principle, soluble CD38 could be used to neutralize any anti-CD38, while different idiotype antibodies would be needed to neutralize different CD38 therapeutic antibodies. Finally, antigen-typed cord cells have been used for the antibody screen as an alternative to DTT-treated cells[9].

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10.8 APPENDIX 8: GENETICS

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to IMP and related diseases. They may also be used to develop tests/assays including diagnostic tests related to IMP administration. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire exome (as appropriate).

DNA samples will be analyzed for immune genetic markers (such as FcγRIII polymorphism). Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

DNA samples may be analyzed for additional analyses if it is hypothesized that this may help resolve issues with the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to IMP or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on study intervention or study interventions of this class or indication continues but no longer than 5 years or other period as per local requirements.

10.9 APPENDIX 9: MODIFICATION OF DIET IN RENAL DISEASE (MDRD) EQUATION

$$\text{Glomerular filtration rate (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African-American}).$$

10.10 APPENDIX 10: DEFINITION OF LINE OF THERAPY

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

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

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

(See: https://www.cibmtr.org/DATAMANAGEMENT/TRAININGREFERENCE/MANUALS/DATAMANAGEMENT/DOCUMENTS/APPENDIX%20T_PRE-HCT%20TREATMENT%20FOR%20LYMPHOMA.PDF)

10.11 APPENDIX 11: COUNTRY-SPECIFIC REQUIREMENTS

10.11.1 Amendment for France

Section 5.1 Inclusion Criteria (I01.)

I 01. Age: Participant must be ≥18 years of age inclusive at the time of signing the informed consent.

10.12 APPENDIX 12: ABBREVIATIONS

5PS:	5-point scale
ABC:	activated B cell-like
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
AITL:	angioimmunoblastic T-cell lymphoma
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
AUC:	area under the curve
CD38:	cluster of differentiation CD38
cHL:	classic Hodgkin's lymphoma
CLL:	chronic lymphocytic leukemia
CONSORT:	Consolidated Standards of Reporting Trials
CR:	complete remission
CSR:	clinical study report
CT:	computed tomography
CTCAE:	common terminology criteria for adverse events
CTLA-4:	cytotic T-lymphocyte-associated protein 4
DCR:	disease control rate
DDI:	drug-drug interaction
DLBCL:	diffuse large B-cell lymphoma
DLCO:	diffusing capacity of the lungs for carbon monoxide
DLT:	dose limiting toxicity
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DoR:	duration of response
DRE:	disease related event
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOI:	end of infusion
EOT:	end of treatment
FDA:	Food and Drug Administration
FDG:	Fluorodeoxyglucose
FFPE:	formalin-fixed paraffin-embedded
FL:	follicular lymphoma
GCB:	germinal center B cell-like
HBc:	hepatitis B core antigen
HBsAg:	surface antigen of the hepatitis B
HBV:	hepatitis B virus
HCV:	hepatitis C virus

HGLT:	high group level term
HIV:	human immunodeficiency virus
HL:	Hodgkin's lymphoma
HSCT:	hematopioetic stem cell transplantation
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Committee of Harmonization
Ig:	immunoglobulin
IHC:	immunohistochemistry
IMP:	investigational medicinal product
INR:	international normalized ratio
IR:	infusion reaction
irAE:	immune-related adverse event
LLT:	low level term
LVEF:	left ventricular ejection fraction
mAb:	monoclonal antibodies
MDRD:	modified diet in renal disease formula
MedDRA:	Medical Dictionary for Regulatory Activities
MM:	multiple myeloma
MRI:	magnetic resonance imaging
NCI:	National Cancer Institute
NIMP:	noninvestigational medicinal product
NK:	natural killer
NLPHL:	nodular lymphocyte predominant Hodgkin's lymphoma
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
PCR:	polymerase chain reaction
PD:	progressive disease
PD-L1:	programmed cell death-ligand 1
PD-L2:	programmed cell death-ligand 2
PET:	positron emission tomography
PFS:	progression-free survival
PK:	pharmacokinetic
PP:	polypropylene
PR:	partial response
PT:	preferred term/prothrombin time (depends on contex)
PTCL:	peripheral T-cell lymphoma
Q2W:	once every 2 weeks
Q3W:	every 3 weeks
RNA:	ribonucleic acid
RNT:	relative nominal time
RP2D:	Recommended Phase 2 dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	study committee
SD:	stable disease

SoA: schedule of activities
SOC: system organ class
SUSAR: suspected unexpected serious adverse reaction
SUV: standardized uptake value
TEAE: treatment-emergent adverse event
tFL: transformed follicular lymphoma
TLS: tumor lysis syndrome
TSH: thyroid stimulating hormone
ULN: upper limit of normal
WOCBP: woman of child-bearing potential

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

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

10.13.1 Amended protocol 01 (19 September 2019)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to include clarifications requested by the French Health Authority (ANSM). Other modifications or editorial changes are included to correct inconsistencies and improve operational feasibility.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol Summary: Study Objectives: Primary endpoints Section 3: Objectives and endpoints Section 5.1: Inclusion criteria Section 8.1.1: FDG-PET-CT/CT	5-point scale per the Lugano classification changed to “Lugano criteria” regarding the response criteria.”	Original wording in primary objective was clarified and corrected because the response criteria based on the 2014 Lugano criteria are not only based on the 5-point scale resulting of the PET-CT assessment for FDG-avid lymphoma but also on CT assessment for non FDG-avid lymphoma.
Protocol Summary: Data Monitoring Committee Section 10.1.5: Committees structure	Clarified that data monitoring committee to provide recommendations to the Sponsor.	For clarification
Section 1.3 Schedule of Activities	Time window for cycles adjusted.	Adjusted according to cycles, as time window is different.
Section 1.3 Schedule of Activities: Physical examination	Screening period updated from 7 days to 14 days prior to first dose.	To maintain consistency with the protocol body.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities: Urinalysis	"As clinically indicated" area extended to include C1D1.	To maintain consistency with other laboratory testing schedules.
Section 1.3 Schedule of Activities Freshly collected Tumor Biopsy for biomarker analyses Section 8.6 Pharmacodynamics	Specified that on treatment biopsy on C2D1 to be obtained within 7 days prior to IMP administration on C2D1 as opposed to ±7 days earlier.	In order to obtain the tumor biopsy prior to the start of the Cycle 2.
Section 1.3: Schedule of Activities: Radiotherapy	Added footnote to clarify "no fly zone", 2 Gy × 2 fractions in 2 consecutive days (eg, Monday and Tuesday) will be administered once a week every 3 weeks for 3 times (treatment lasts for a total of 9 week), starting in the same week when isatuximab and cemiplimab are administered.	The second radiotherapy schedule option was added in the SoA as already stated in the initial protocol Section 6.1.4.
Section 1.3: Schedule of Activities: Urine or Serum Pregnancy Test Section 8.2.6.7: Pregnancy test Section 10.2: Clinical laboratory tests Section 10.5: Contraceptive guidance and collection of pregnancy information	Amended to indicate that females of child-bearing potential will be required to be tested for pregnancy monthly for 6 months after discontinuation of study treatment.	Change due to re estimation of isatuximab plasma half-life
Section 1.4.2: Intervention period: from Cycle 2 and beyond (Sparse sampling); footnote "d" Section 7: Discontinuation of study intervention and participant discontinuation/withdrawal Section 8.9: Immunogenicity assessments	Clarification added about ADA sampling done systematically at FUP 90 (±7) days rather than depending on result of last sample collected during last treatment.	To specify that isatuximab ADA samples are systematically collected at FUP 90 (±7) days and to simplify monitoring of immunogenicity.
Protocol Summary Section 2.3.4: Preventive measures to minimize risk from the combination Section 6.1.2: Non Investigational Medicinal Products Section 6.1.2.5: Montelukast	Montelukast 10 mg orally added as primary prophylactic treatment.	Montelukast 10 mg orally or equivalent was added as a premedication based on recent references (25, 26, 27) that this addition may decrease incidence and respiratory symptoms of IR.
Protocol Summary Section 2.3.4: Preventive measures to minimize risk from the combination Section 6.1.2: Non Investigational Medicinal Products Section 6.1.2.5: Montelukast	Premedication requirements were modified.	Change based on data from completed and ongoing studies to allow patients with Grade ≤2 infusion reactions (IRs) to omit premedications at Investigators' discretion.
Section 2.2.2 Cemiplimab	US FDA approval for cemiplimab added	Updated as per the latest information available.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.4: Preventive measures to minimize risk from the combination	Deleted “mild” hypersensitivity reactions from the below statement “In the event of mild or moderate hypersensitivity reaction, the isatuximab infusion should be interrupted and may be subsequently resumed after recovery, at a slower infusion rate, under close monitoring and with supportive care as needed.”	To maintain consistency with the protocol body Section 6.5.5, transient reaction; infusion interruption or intervention not indicated in mild hypersensitivity reactions.
Section 2.3.4: Preventive measures to minimize risk from the combination	Primary prophylactic treatment time changed from 15 to 30 minutes prior to isatuximab infusion to 30 to 60 minutes prior to the isatuximab infusion	To maintain consistency with the protocol body for the premedication in Section 6.1.2
Section 2.3.4: Preventive measures to minimize risk from the combination Section 5.2 Exclusion criteria E05	“Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder” was removed from Section 2.3.4 and E05. Specified that the exclusion of patients with comorbidity requiring corticosteroid therapy refers to systemic corticosteroid therapy only	For clarification as participants with active, known or suspected autoimmune disorder are ineligible as per E07.
Section 4.3: Justification for dose	Re-estimation of isatuximab half-life of 28 days is included	Re-estimation of isatuximab half-life of 28 days.
Section 5.1: Inclusion criteria I01 Section 10.11.1: Amendment for France	The lower limit of age for patient inclusion in France will be 18 years old, inclusive.	Clarification based on feedback received from French Health Authorities (ANSM).
Section 5.1: Inclusion criteria I03:	Inclusion criteria 03 modified to add that if the only measurable lesion is previously irradiated; the lesion should also be FDG-avid.	FDG-avid lesions previously irradiated can be used as measurable lesion as the disease assessment is based on FDG-PET-CT and no impact on the assessment is expected in this case.
Section 5.1: Inclusion criteria I10:	Male and female participants to start using contraceptive measures 2 weeks before study intervention.	Clarification based on feedback received from French Health Authorities (ANSM)
Section 5.2: Exclusion criteria E13	Specified primary mediastinal large B-cell lymphoma to be more specific	For clarification
Section 5.2: Exclusion criteria E26	Modified from “No anti-cancer therapy including radiotherapy or auto-HSCT between failure of anti-PD-1/PD-L1 therapy and initiation of IMP” to “Participants with anti-cancer therapy including radiotherapy or auto-HSCT between failure of anti-PD-1/PD-L1 therapy and initiation of IMP”.	To make it consistent with other exclusion criteria and for better readability.
Section 5.2: Exclusion criteria E28	Exclusion criteria 28 replaced with “Not applicable. Removed by Protocol Amendment 01”	Criteria removed.
Section 5.2: Exclusion criteria E30	Inadequate organ and bone marrow function was modified from at the Screening visit to prior to IMP administration.	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.4 Concomitant therapy	Clarified exceptions for use of systemic corticosteroids (including management of irAEs).	Previous guidance on prohibited use of corticosteroids was inconsistent with management guidelines.
Section 6.5.2: Dose delay and dose omission	Treatment windows clarified with ±1 day during Cycle 1, ±2 days during Q2W, and ±3 days for Q3W and Q4W cycles.	The original wording describing the dose delay was confusing, therefore wordings was clarified to indicate that the treatment window is ±3 days for both the 4 week administration cycles (Cycle 1 to Cycle 6) and the 3 week administration cycles (Cycle 7 and beyond).
Section 6.5.3: Dose modifications Table 3 Isatuximab and cemiplimab dose modification guidelines	Management of Grade 4 hematological AEs added.	This text was removed from original protocol in error and is being reinstated.
Section 7: Discontinuation of study intervention and participant discontinuation/withdrawal	Added following text “The cycle duration is 28 days from Cycle 1 to Cycle 6 then 21 days from Cycle 7 to Cycle 30”.	For clarity
Section 7: Discontinuation of study intervention and participant discontinuation/withdrawal	Participants who discontinued the study treatment without PD are followed every 90 days instead of every month.	To maintain consistency with the protocol body.
Section 7: Discontinuation of study intervention and participant discontinuation/withdrawal	Participants who are still on study treatment after study cut-off date: will continue to receive study treatment if they benefit, and will undergo planned study procedures (except PK and ADA) until confirmation of PD, or start with another anti-cancer therapy, or treatment period ended, whichever comes first, added in the body of the protocol according to the synopsis.	To maintain consistency with body of the protocol and the synopsis.
Section 8.1.2 Bone Marrow Biopsy and Aspirate	Language added to specify that if the FDG-PET-CT is negative in the bone marrow site then biopsy/aspirate is performed to identify involvement as per the investigator’s judgment and based on other factors consistent with advanced stage or poor prognosis	For more clarity
Section 8.2.2 Vital Signs	Vital signs monitoring during isatuximab infusion was modified	To simplify monitoring of vital signs during the isatuximab infusion, and clarification when it is clinically indicated
Section.8.2.6.7: Pregnancy Test Appendix 10.5: Contraceptive Guidance and Collection of Pregnancy information	Clarified that pregnancy testing must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit. This will be applicable to all countries.	Per French Health Authorities (ANSM) request, the current protocol is unclear to investigators whether the more frequent tests are a legal requirement in France according to the phrase “in countries where required by local regulations”. In order to meet the legal requirement, ANSM is requesting to indicate that pregnancy testing (urine or serum) must be performed on Day 1 of each cycle prior to the study treatment and at the EOT visit. This will be applicable to all countries.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.5: Pregnancy	Changed pregnancy follow-up guidance from 6 months after the last administration of study treatment to no longer than 6 to 8 weeks following the estimated delivery date.	Typographical error
Appendix 10.4: From Table 16 to Table 23	CTCAE version changed from 4.03 to 5.0.	Typographical error. To maintain consistency in the protocol body.
Appendix 10.4: Table 18 Renal adverse event management	Deleted text regarding discontinuation of Cemiplimab if unable to reduce corticosteroid dose for irAEs to ≤10 mg.	To avoid repetition, cemiplimab discontinuation is already in the column cemiplimab management.
Appendix 10.4: Table 18 Renal adverse event management	For patients with Grade 3-4 renal events, under Isatuximab Dose Management, “Grade 3: discontinue treatment” is corrected to “Grade 4: discontinue treatment” (as Grade 3 is already noted as “delay or omit dose until resolves to Grade ≤1”)	Typographical error
Appendix 10.10: definition of line of therapy	Clarification was added regarding the definition of line of therapy.	To clarify the definition of line of therapy, a reference to Center for International Blood and Morrow Transplant Research (CIBMRT) website added (cibmrt.org).
Throughout the document	Minor editorial, typographical error corrections, and document formatting revisions have been made throughout the document.	Minor changes, therefore have not been summarized.

Abbreviations: ADA = Anti-drug antibody; AEs = adverse events; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; EOT = End of Treatment; FDG = Fluorodeoxyglucose; FUP = Follow-up; HSCT = Hematopoetic stem cell transplant; IMP = Investigational medicinal product; IR = Infusion reaction; PD = Progressive disease; PD-L1 = Programmed cell death-ligand 1; PET = Positron emission tomography; PK = Pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; SOA = Schedule of Activities.

10.14 APPENDIX 14: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

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

Contingency procedures are suggested below and in Section 6, Section 6.5.2, Section 7.1, Section 8, Section 9.3, and Section 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening and administration of study intervention may be temporarily delayed.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data. For example, patient interview for medical history/prior medications could be performed by phone, local safety labs and some efficacy assessments could be performed off-site/at the participant's home (eg, home nursing) if agreed by patient and permissible per local regulations.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely, if needed (eg, ±14 days for visits).

Contingencies implemented due to emergency will be documented.

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

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension).

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