AMENDED CLINICAL TRIAL MASTER PROTOCOL 03

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with head and neck squamous cell carcinoma (HNSCC)**
Protocol number:	**ACT16903**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with other anticancer therapies for the treatment of participants with HNSCC (Master Protocol)**
Acronym:	**Pegathor Head and Neck 204**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Substudy/substudies impacted by amendment	Date, version
Amended Master Clinical Trial Protocol 03	All	01, 02, 04, 05	22 December 2021, version 1 (electronic 4.0)
Amended Master Clinical Trial Protocol 02	All	01, 02, 04, 05	19 August 2021, version 1 (electronic 3.0)
Amended Master Clinical Trial Protocol 01	All	01, 04, 05	26 July 2021, version 1 (electronic 2.0)
Master Clinical Trial Protocol	All		11 June 2021, version 1 (electronic 1.0)

Amended protocol 03 (22 December 2021)

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Spanish (Agency for Medicine and Health Products [AEMPS]), Italian (Medicines Agency [AIFA]) and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page and 1.1 Synopsis	The following study name: “Pegasus Head and Neck 204” has been removed from the protocol title and the new study acronym “Pegathor Head and Neck 204” has been added on the cover page.	For consistency across the program
1.1 Synopsis	The priority of recruitment for participants eligible to both Cohort B1 and Cohort B2 has been specified.	To specify the priority of recruitment between both Cohorts B1 and B2

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3 Objectives and Endpoints: Table 2, 9.4.3.1 Time to response, and 9.4.3.2 Duration of response	Definitions of Time to response and Duration of response have been revised as follows: • Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by investigator per RECIST 1.1. • Duration of response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by investigator per RECIST 1.1 or death from any cause, whichever occurs first.	For clarification
1.1 Synopsis and 4.1 Overall Design	Under the definition of End of Treatment and Follow-up for participants who discontinue study treatment with PD, the following text “or until start of another anticancer therapy or final cohort cut-off, whichever comes first” has been removed.	For clarification
1.1 Synopsis, 4.1 Overall Design, and 9.4.3.4 Progression-free survival	The study cut-off date has been replaced by cohort cut-off for final analysis.	For clarification
1.1 Synopsis and 6.1.2.1 Premedication for SAR444245	Oral administration of diphenhydramine is now permitted, in addition to IV administration. Intravenous administration of acetaminophen is now permitted, in addition to oral administration.	To allow local approved dosing regimens to be followed
1.1 Synopsis, 6.1.2.1 Premedication for SAR444245, 10.12 Appendix 12: Table 8 Risk assessment	[redacted]	[redacted]
1.1 Synopsis and 9.4.3.5 Adverse Events	Analyses of adverse events (AEs) related to specific IMP have been removed as treatment-related treatment-emergent adverse events (TEAEs) will be analyzed overall, regardless of the drug.	To assess treatment-related AE of the regimen as whole (SAR444245 with other anticancer therapies)

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	The following text: “Tumor biopsy during treatment period should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous” has been removed from footnote “g”.	For clarification
1.3 Schedule of Activities (SoA), 5.2 Exclusion Criteria, 10.2 Appendix 2: Clinical laboratory tests, and 10.8 Appendix 8: Country-Specific Requirements	Requirement for human immunodeficiency virus (HIV), hepatitis B and C serologies has been added at screening for participants in Italy and specified in exclusion criteria E15 and E16, SoA in footnote “f”, laboratory tests and country-specific requirements sections.	To clarify that serology for HIV, hepatitis B and C should be tested at screening in Italian participants
1.3 Schedule of Activities (SoA),	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessments of any potential cardiotoxicity
8 Study Assessments and Procedures,	The following text has been added: “A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiogram and troponin level”.	
8.2 Safety assessments, 8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	Troponin has been added as an example of cardiac enzymes within additional evaluation to carry out when clinically indicated. The following text has also been added for evaluations during treatment and post treatment follow-up: “During treatment, or post treatment follow-up: Troponin will be performed at Cycle 4 Day 1. In case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, troponin elevation, etc.), Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation”.	
and 10.2 Appendix 2: Clinical laboratory tests	Troponin has been added to “other screening tests”.	

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) and 10.2 Appendix 2: Clinical laboratory tests	The following footnote ("k" in the SoA and "d" in Section 10.2): "Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated" has	For clarification
[redacted]		
1.5.1 All cohorts	In the footnote b, "after flush" has been changed to "(EOI) precisely ±5 minutes".	For clarity
2.2.1.2 Rationale for combining with cetuximab	The reference No. 9 was revised to support the benefit of SAR444245 in combination with cetuximab.	To update the reference for consistency
4.1 Overall design	For the cohort cut-off date for the final analysis, the following wording: "or all participants within a cohort have completed study" has been removed.	For consistency
4.3 Justification for dose	This section has been updated with the most recent data available from Phase 1 Hammer study.	To include all available data in support of the safety of the RP2D
5.1 Inclusion Criteria, 8.2.5 Pregnancy testing, 8.3.5 Pregnancy, and 10.2 Appendix 2: Clinical laboratory tests	In I05, the requirement for contraception for male participants has been changed from "at least 210 days [corresponding to time needed to eliminate study intervention(s) plus an additional 90 days (a spermatogenesis cycle)] after the last dose of study intervention" to "at least 3 days [corresponding to time needed to eliminate SAR444245] after the last dose of SAR444245".	To change measures for male participants as per Clinical Trials Facilitation and Coordination Group (CTFG) guideline on "recommendations related to contraception and pregnancy testing in clinical trials version 1.1" of 21 Sept 2020. As SAR444245 is not genotoxic, there is no need to extend the requirement for contraception to 90 days (3 months) for male participants, but to take into account the 5 half-lives of the study intervention before its elimination.

Section # and Name	Description of Change	Brief Rationale
	The recommended duration for continuing contraception after last dose of study intervention has been changed for female participants in Cohorts A1, A2, and B1 (SAR444245 plus pembrolizumab) from 180 days to 120 days, and 60 days in Cohort B2 (SAR444245 plus cetuximab), and the requirement of extension extra 30 days (1 month) has been removed.	None of the products in combination is genotoxic in this study, there is no need to extend the requirement for contraception to 30 days (1 month) corresponding to a menstrual cycle for female participants
5.2 Exclusion Criteria	E 18 has been changed from "Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention, including premedication to be administered in this study, as well as PEG or any pegylated drug" to "Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein".	To clarify that patients with known hypersensitivity to any excipient of the study interventions and hypersensitivity to any E. Coli-derived protein must be excluded
	E 23 has been changed from: "Participation in a concurrent clinical study in the treatment period" To "Current enrollment or past participation in a study of an investigational treatment or has used an investigational device within 28 days prior to the first dose of study treatment. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational treatment".	For clarification
5.4 Screen Failures	The following text: "A participant may be rescreened only once" has been added.	For clarity
6.1.3 Hydration guidelines for SAR444245 administration	[redacted]	For consistency

Section # and Name	Description of Change	Brief Rationale
6.2 Preparation/handling/storage/accountability	The text was revised as shown below: "Under no circumstances will the Investigator supply IMP to a third party (~~except for DTP shipment, for which a courier company has been approved by the Sponsor~~), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner".	For correction. Direct-to-patient shipment of investigational medicinal product (IMP) is not possible in this study
6.8.2 Prohibited concomitant medications and 10.12 Appendix 12: Risk assessment	The following sentence in Section 6.5.2 has been deleted: "Participants requiring medication(s) that are metabolized by the liver and have narrow therapeutic index require close monitoring (drug blood levels or other surrogate of drug exposure) when on study treatment. If a participant cannot be closely monitored, he/she should be removed from the trial." In Table 8, the row for drug-drug interactions has been deleted.	Based on new de-risking in-vitro data
7.1.1 Permanent discontinuation, 8.3 Adverse events (AEs), Serious adverse events (SAEs) and other safety reporting, 10.1.3 Informed consent process, and 10.11.1 Informed consent	"If allowed by local regulations" has been added after "legally authorized representative" to cover for country-specific regulations.	To allow flexibility per country specific regulations
8.1.1 Assessment of objective response using the most appropriate modality according to the nature of the measurable lesion(s)	Imaging of head has been added to baseline scans.	For consistency
8.2.2 Vital signs	For the collection of vital signs from Cycle 2 to Cycle 4, "at baseline" has been changed to "prior to IMP dosing". The following bullet point has been added: "From Cycle 5 and beyond, vital signs will be collected prior to IMP administration".	For clarification
8.3.1 Time period and frequency for collecting AE and SAE information	The instruction to stop collecting AE and SAE/AESI information should the participant initiate another anticancer therapy has been removed. All AEs and SAEs/AESIs are to be collected until 30 days and 90 days, respectively, following cessation of study treatment.	For consistency with Sanofi standards

Section # and Name	Description of Change	Brief Rationale
8.6 Biomarkers	The following sentence: "This method will only apply to samples from clinical sites not exhibiting feasibility constrains on handling/shipment" has been added for [redacted].	To improve flexibility in case local constrains exist
	Concerning collection of samples, the following text "will be stored for a period of up to 15 years after the last participant's last visit for potential re-analyses" has been changed to "may be used for further research if consent is provided (see Section 8.9)".	Harmonization per Sanofi standard terminology
8.9 Use of biological samples and data for future research and 10.5 Appendix 5: Genetics	The text was revised to state that the duration of storage for biological samples and relating data is up to 25 years. The duration of biological sample storage was previously given as a maximum of 15 years.	For consistency with the latest Sanofi standards
9.3 Populations for Analyses	The efficacy population definition was revised to "All participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment".	To characterize the efficacy excluding participants newly enrolled
9.4.3.6 Clinical laboratory evaluations and 9.4.5 Other safety analyse(s)	Descriptive statistics for laboratory variables and vital signs will be performed only when relevant. The following text was deleted: "These analyses will be performed using local measurements for laboratory variables".	These analyses will be done as needed following analyses of abnormalities according to NCI-CTCAE grade
9.4.5 Other safety analyse(s)	"ECG" was removed from quantitative analyses.	ECG data are not collected systematically during the treatment period
10.1.6 Dissemination of clinical study data	The text has been revised as follows: "Sanofi shares information about clinical trials and results on publicly accessible websites for each completed sub study and final study results".	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
10.1.9 Study and site start and closure	The wording has been revised to specify "provided by the Sponsor" after "study treatment".	For clarification
10.2 Appendix 2: Clinical laboratory tests	Regarding blood chemistry/hematology assessments, "D2" has been removed from the footnote "a" of Table 7.	For consistency

Section # and Name	Description of Change	Brief Rationale
10.9 Appendix 9: Response evaluation criteria in solid tumors (RECIST) 1.1	"Or progressive disease" has been removed from the sentence "Confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response or progressive disease".	To correct a typographical error
11. References	List of references has been updated.	For consistency
Throughout the document	Minor editorial corrections have been made. Abbreviations have been revised.	For consistency

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with other anticancer therapies for the treatment of participants with head and neck squamous cell carcinoma (HNSCC)

Brief title: A study of SAR444245 combined with other anticancer therapies for the treatment of participants with HNSCC (Master Protocol)

Rationale:

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

Most patients with locally advanced head and neck squamous cell carcinoma (HNSCC) present with a high risk of recurrence, and approximately 10% of HNSCC patients present with metastatic disease. The disease is associated with a low quality of life (QoL) and high suicide rate. Despite advances in surgery and radiotherapy, 5-year survival rates for patients [excluding Epstein Barr Virus (EBV)-related nasopharyngeal] with HNSCC across all stages remain 40%-50% for tumors caused by traditional carcinogens [Human Papilloma virus (HPV)-negative]. The median overall survival (OS) for patients with refractory/metastatic (R/M) disease is 10 to 13 months. Standard of care for R/M disease in the 1st line setting includes platinum-based doublet chemotherapy with pembrolizumab or cetuximab, or pembrolizumab monotherapy. In the 2nd line standard of care could be nivolumab monotherapy, pembrolizumab monotherapy, cetuximab, methotrexate, or a taxane, each of which is associated with response proportions of 10%-15%.

Mechanistically, SAR444245 could potentiate immuno-oncology agents that are intended to expand innate and adaptive immune cells. In addition, SAR444245 may enhance antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab utilizing NK cells as an important effector cells.

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with other anti-cancer therapies will result in a significant increase in the percentage of patients with HNSCC experiencing an objective response to establish safety and preliminary anti-tumor activity.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. This design is with the flexibility to open new treatment cohorts as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity.

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

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with other anti-cancer therapies in patients with HNSCC	• Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1)
Secondary	
• To assess the safety profile of SAR444245 when combined with other anti-cancer therapies	• Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (2)
• To assess other indicators of antitumor activity	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1 • Duration of Response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first • Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1) • Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of first documented disease progression determined by Investigator as per RECIST 1.1, or death due to any cause, whichever occurs first
• To assess the concentrations of SAR444245	• Plasma concentrations of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]

Overall design:

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with HNSCC.

Brief summary:

The study consists of a core phase for all cohorts, with a safety run-in and an expansion phase for specific cohorts. The results of an interim analysis after the core phase will decide if the expansion phase will be opened.

Table 1 provides an overview by study intervention and disease type of the different cohorts that will be assessed in the study. A graphical presentation of the study schema is shown in Figure 1.

Table 1 - Overview of study cohorts

Cohort	Study intervention	Disease
A1	SAR444245 + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
A2	SAR444245 + cetuximab + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
B1	SAR444245 + pembrolizumab	R/M HNSCC treated with PD1/PD-L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for R/M disease
B2	SAR444245 + cetuximab	R/M HNSCC treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease

CPS: combined positive score; HNSCC: Head and neck squamous cell carcinoma; PD1: Programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; R/M: Recurrent/metastatic.

Participants who are eligible for both Cohorts A1 (to receive SAR444245 and pembrolizumab) and A2 (to receive SAR444245, pembrolizumab and cetuximab) should be enrolled in Cohort A1 until Cohort A1 enrollment is completed.

Participants who are eligible for both Cohorts B1 (to receive SAR444245 and pembrolizumab) and B2 (to receive SAR444245 and cetuximab) should be enrolled in Cohort B1 until Cohort B1 enrollment is completed.

Further details guiding the enrolment in each cohort are provided in individual substudies.

Number of participants:

Overall, in the core phase (all cohorts), approximately 40 participants will be enrolled per cohort.

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

Intervention groups and duration:

The duration of the study for a participant will include:

- **Screening period**: up to 28 days.
- **Treatment Period**: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 6 or completion of Cycle 35.
- **End of Treatment and Follow-up.** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **end of treatment (EOT)**:

1. Participants who discontinue study treatment **without PD** or who **complete 35 cycles of treatment without PD** , will be followed for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments every 3 months ±7 days from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.

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

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Survival Phone Call Follow-Up will continue until death, participant request to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival follow-up at the discretion of the Sponsor at any prior timepoint.

After the cohort cut-off date for the primary objective response rate (ORR) analysis, participants can continue to receive IMP, if clinical benefit is observed, until permanent discontinuation criteria described in Section 7.1.1 are met, and will continue to undergo all assessments as per the SoA.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort last patient-in (LPI). After this cut-off date for the final analysis, the participants still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9.

Study intervention(s)

Investigational medicinal product

SAR444245

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: 24 µg/kg administered as an IV infusion over 30 mins every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles or until PD**.

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

See substudy protocols for other IMPs.

Noninvestigational medicinal products

Premedication for SAR444245

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

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

SAR444245 premedication may be optional after 4 cycles

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

Statistical considerations:

- **Analysis of primary endpoint:**
  - Objective response rate (ORR) and best overall response (BOR) will be summarized for the efficacy population with descriptive statistics. In addition, two-sided 90% confidence intervals (CI) for ORR will be computed using the Clopper-Pearson method.
- **Analysis of secondary efficacy endpoints:**
  - The time to response (TTR) will be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The duration of response (DoR) will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.
  - The clinical benefit rate (CBR) will be estimated by dividing the number of participants with clinical benefit by the number of participants in the efficacy population.
  - The progression free survival (PFS) will be summarized on the efficacy population using Kaplan-Meier methods. The median PFS times and associated 90% CI will be provided.
- **Analysis of secondary safety endpoints:**
  - Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class (SOC) and Preferred Term (PT) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5.0 (all grades and Grade ≥3) for the exposed population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to permanent partial intervention discontinuation (any of the IMP

components), TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interest (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) and participants who died by study period (treatment-emergent period, post-treatment period) and reasons for death will be summarized. Immune Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS) events will be graded using American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading and will be summarized separately.

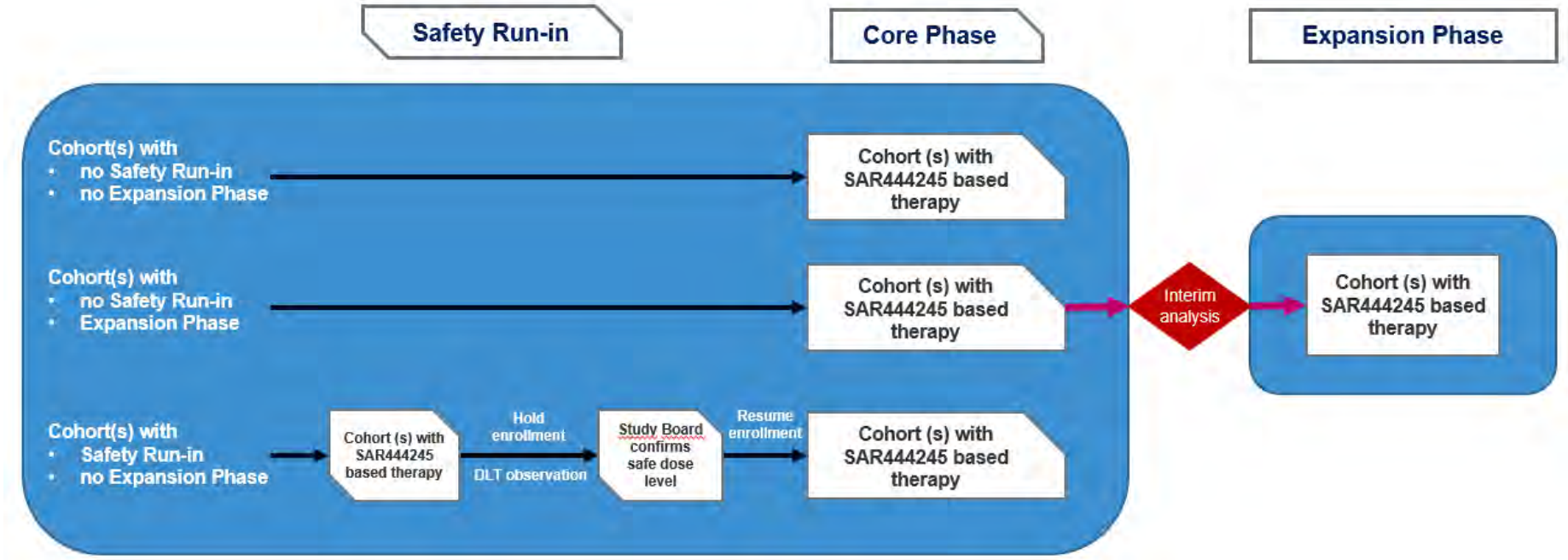
- Hematology and clinical chemistry results will be graded according to the NCI-CTCAE V5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided for the exposed population.

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

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

1.2 SCHEMA

Figure 1 - Overall study schema



DLT: dose limiting toxicity.
Safety run-in: prior core phase, participants in the substudy will be treated in a safety run-in to confirm safe dose level for the regimen
Core phase: substudy designed to treat participants only in a core phase or after safety run in.
Expansion phase: after the core phase to gather more safety data with the confirmed dose, the substudy may be expanded to enroll more participants and accumulate evidence of clinical activity.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent Inclusion/Exclusion criteria	X											
IRT contact	X	X			X	X	X					
Demography, medical/surgical and disease history	X											See Section 8
Full physical examination	X						X					
Directed physical examination		X	X	X	X	X		X				See Section 8.2.1
Body weight/Height[e]	X	X			X	X	X	X				
Vital signs	X	X	X	X	X	X	X	X				See Section 8.2.2
SpO_2	X	As clinically indicated										

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Performance status (ECOG)	X	X	X	X	X	X	X	X				
12-lead ECG	X	X	As clinically indicated									See Section 8.2.3
LVEF	X	As clinically indicated										See Section 8.2.3
Laboratory assessments												
Troponin	X	As clinically indicated				X (D1 Cycle 4)	As clinically indicated					See Section 8.2.3 & Section 10.2
Pregnancy test	X	X			X	X	X	X	X			See Section 8.2.5, Section 8.3.5 & Section 10.2
Blood chemistry/hematology	X	X	X	X	X	X	X	X				See Section 10.2
Coagulation	X	As clinically indicated										See Section 10.2
Urinalysis[k]	X	X				X	X	X				See Section 10.2

Evaluation[a]	**Screening/ baseline**	**Treatment period[b]**					**End of treatment**	**Observation period[c]**			**Survival phone call follow-up period[d]**	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Hepatitis serology CD4 counts & Viral Load	X[f]	As clinically indicated										See Section 10.2
HPV p16 status for participants with oropharyngeal cancer	X											
PK	See PK Flow-Chart in Section 1.5											
ADA	See PK Flow-Chart in Section 1.5											
Exploratory biomarkers												
PDy - Blood and tumor tissue collection[g]	See Biomarkers Flow-Chart Section 1.4											
Disease assessment												
CT/MRI[h]	X					X	X	X	X	X		See Section 8.1
Brain imaging[i]	X											See Section 8.1
IMP Administration (SAR444245 administration)		X			X	X						
AE/SAE assessment[j]	X	Continuously throughout treatment period						X				See Section 8.3

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Prior medication	(within 28 days prior to first dose)											
Concomitant medication		Continuously throughout treatment period										See Section 6.8
First subsequent anticancer therapy							X	X	X	X	X	
Survival status											X	

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

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

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

d **Survival Phone Call Follow-Up Period**: Participant who moves into the Survival Follow-up Period should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

f For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8).

g If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

h **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP or more frequently if clinically indicated in the first 45 weeks. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the **head, neck, chest and abdomen (pelvis is optional)** and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment and during treatment period until PD. After the first documentation of response or the first documentation of progression (if the participant is clinically stable) per RECIST 1.1, confirmatory imaging should be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy.

i **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease as per protocol tumor assessment schedule. In all other cases, the lesions must be treated. Two additional scans obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive systemic therapy during these 4 weeks stabilization at the treating physician's discretion, this systemic therapy will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

j **AE/SAE assessment**: Severity will be graded according to NCI-CTCAE v 5.0, ICANS and cytokine release syndrome (CRS) will be graded using ASTCT criteria integrated with central laboratory cytokine results (2).

k Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; ALK: anaplastic lymphoma kinase; ASTCT: American Society for Transplantation and Cellular Therapy; C: Cycle; CRF: case report form; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; HPV: Human Papilloma virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; IMP: investigational medicinal product; IRT: Interactive Response Technology; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common terminology criteria for adverse events; PD: progressive disease; PD L1: programmed cell death ligand 1; PDy = pharmacodynamic; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; [redacted]; SAE: serious adverse event; SpO_2: oxygen saturation.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHART

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

1.5.1 All cohorts

Cycle	Treatment Cycle 1				Treatment Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	**D1**		**D2**	**D8**	**D1**		
Time after start of SAR444245 dosing	**SOI**	**EOI**	**Any time**	**Any time**	**SOI**	**EOI**	
SAR444245 PK sample		P00[b]	P01			P00[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI).
b EOI samples must be taken at end of infusion (EOI) precisely ±5 minutes.
Abbreviations: ADA: anti-drug antibodies; D: day; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

2 INTRODUCTION

SAR444245 is a recombinant human IL-2 with a site-specific substitution of a non-native azido lysine amino acid residue which is bio-conjugated to a single linear 30 kDa PEG. SAR444245 is being developed as an immuno-oncology treatment to be administered every 2 weeks (Q2W) or less frequently (every 3 weeks [Q3W] in the present study) in patients with cancer. [redacted] The site-specific pegylation of IL-2 in SAR444245 provides a "non-alpha" pharmacologic profile for SAR444245 that is designed to prevent engagement of the high affinity IL-2Rα, while maintaining CD8+ T cell anti-tumor activity and resulting in an improved safety profile relative to aldesleukin. Aldesleukin is approved in the United States (US) for the following indications: the treatment of metastatic renal cell carcinoma (RCC) and metastatic melanoma, with the same or limited approval status in other countries. Its use has resulted in durable CR in some patients with anti-tumor effects via elevations in CD8+ T cells (naïve, effector, and memory T cells). However, widespread use of aldesleukin is limited by its low response rate, short half-life ($t_{1/2}$), and severe toxicities including primarily vascular leak syndrome (VLS), and CRS.

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

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

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models. The first-in-human clinical study with SAR444245 (TCD16843/HAMMER, hereafter referred to as HAMMER) demonstrated that treatment with SAR444245 leads to expansion of CD8+ T cells and NK cells (with higher IL-2 βγ receptor expression) with negligible IL-2Rα induced effect on immunosuppressive Treg cells expansion, vascular leak syndrome related eosinophils expansion and IL-5 release.

Most patients with locally advanced HNSCC present with a high risk of recurrence, and approximately 10% of HNSCC patients present with metastatic disease (4). Disease associated with a low QoL and high suicide rate. Despite advances in surgery and radiotherapy, 5-year survival rates for patients [excluding EBV-related nasopharyngeal] with HNSCC across all stages remain 40%-50% for tumors caused by traditional carcinogens [Human Papilloma Virus (HPV)-negative]. The median OS for patients with refractory/metastatic (R/M) disease is 10 to 13 months. Standard of care for R/M disease in the 1st line setting includes platinum-based doublet chemotherapy with pembrolizumab or cetuximab, or pembrolizumab monotherapy. In the 2nd line standard of care could be nivolumab monotherapy, pembrolizumab monotherapy, cetuximab, methotrexate, or a taxane, each of which is associated with response proportions of 10%-15%.

Mechanistically, SAR444245 could potentiate immuno-oncology agents that are intended to expand innate and adaptive immune cells. In addition, SAR444245 may enhance antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab utilizing NK cells as important effector cells.

2.2 BACKGROUND

2.2.1 Rationale for combining with other anti-tumor agents

2.2.1.1 Rationale for combining with checkpoint inhibitor

Based on preclinical pharmacology studies, SAR444245 is expected in the clinic to demonstrate synergistic anti-tumor activity when administered together with an antibody targeted to the PD-(L)1 pathway. The rationale for this approach is that T cell receptor (TCR) activation following engagement of tumor cell-presented antigens induces the surface expression of PD-1 on the activated T cell. Expression of programmed death-ligand 1 (PD-L1) on cancer cells induces PD-1 mediated silencing of TCR signaling and CD28 co-stimulation, effectively silencing the cytolytic activity of CD8+ T cells (5, 6). PD-1 inhibitory antibodies such as pembrolizumab have shown clinical efficacy by reinvigorating those cells.

SAR444245 is an ideal agent to combine with an anti-PD-1 antibody because it induces the polyclonal expansion of CD8+ T cells and their infiltration into tumors and inhibiting the PD-1 pathway prevents PD-L1 mediated silencing of those cells. These effects of combination treatment have been shown to be additive with increased anti-tumor activity in the syngeneic mouse CT-26 colon cancer model; a survival benefit was also demonstrated. Furthermore, studies using human mixed lymphocyte reactions to model TCR-mediated T cell responses to presented tumor antigens show that an anti-PD-1 antibody enhances interferon gamma (IFNγ) release from T cells, addition of SAR444245 on anti-PD-1 antibody further enhanced IFNγ production by T cells. It indicates the potential of this combination to enhance durable anti-tumor effects.

2.2.1.2 Rationale for combining with cetuximab

SAR444245 can activate NK cells thus leading to enhanced antibody-dependent cellular-mediated cytotoxicity (ADCC) in target cells.

Cetuximab is an IgG1 monoclonal antibody against the ligand binding domain of EGFR, which is abnormally activated in many epithelial cancers, including colon cancer and HNSCC (7). The mechanism of action of cetuximab include ADCC via NK cells (8), in addition to EGFR blockade.

A study that added SAR44425 into co-culture of human PBMC with EGFR expressing CA27 HNSCC cells and cetuximab, showed an enhanced cytotoxicity against cancer cells. It indicated that SAR444245 may improve anti-tumor efficacy of cetuximab (9).

2.2.2 Rationale for HNSCC and selected participant population

Squamous cell carcinoma of the head and neck (HNSCC) is the 9th leading cancer by incidence worldwide and constitutes 90% of all head and neck cancers (10). In the US, approximately 50 000 new cases of HNSCC and more than 10 000 deaths occur per year (11, 12, 13, 14). Squamous cell carcinoma of the head and neck (HNSCC) is a biologically diverse and genomically heterogeneous disease that arises from the squamous mucosal lining of the upper aerodigestive tract, including the lip and oral cavity, nasal cavity, paranasal sinuses, nasopharynx, oropharynx, larynx and hypopharynx (11, 15, 16, 17, 18).

A large number of patients with head and neck cancer initially present with locally advanced, Stage III/IV disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as “definitive” therapy, which typically combines chemoradiation and surgery and can result in DCR ranging between 33% and 86% of patients. Patients who progress after initial definitive therapy require subsequent treatment for recurrent (R) disease. Patients who initially present with metastatic (M) disease generally receive the same therapy as those with recurrent disease after definitive treatment.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

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

2.3.1.1 Aldesleukin experience

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

Aldesleukin is a human recombinant interleukin-2 which has been shown to possess the biological activities of human native IL-2 mediated through its binding with the high-affinity IL-2Rαβγ and intermediate-affinity IL-2Rβγ receptors. The widespread use of aldesleukin has been limited by its low response rate, a short $t_{1/2}$ that requires dosing three times per day, and toxicities (14), which include life-threatening and sometimes fatal VLS. Vascular leak syndrome is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. It results in hypotension and reduced organ perfusion which, if severe, can result in death. It may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

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

It was recognized early in clinical studies that eosinophilia appeared to mark the onset of VLS, with several reports of fast, dose-dependent elevation in eosinophils. Additional publications suggested a causal connection between the increase in peripheral IL-5 levels and identified ILC-2 as the source of this powerful chemoattractant and activator of eosinophils (15). Aldesleukin mediates activation of ILC-2s via interaction with the high affinity IL-2Rα chain that exists at low levels on ILC-2s.

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

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

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

High doses of aldesleukin (IL-2) were associated with decreased expression of enzymes of hepatic metabolism (16). As SAR444245 also exercises IL-2 activity, the Investigator should monitor clinical effects of narrow therapeutic index drugs that are hepatically metabolized.

2.3.1.2 SAR444245

2.3.1.2.1 Preclinical data

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

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

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

There are no preclinical data for tumor lysis syndrome (TLS) associated with the use of SAR444245, but it is known to occur when aldesleukin is combined with cisplatinum, vinblastine and dacarbazine (refer to Proleukin US label) (14). The participants at greatest risk of TLS are those with high tumor burden prior to treatment, elevated uric acid level, poor hydration or tumor infiltration of the kidney, or receiving intensive cytoreductive therapy.

Cytokine release syndrome (CRS) is a potentially life-threatening toxicity that has been described in the setting of immunotherapy with T cell engagement. It is characterized by a variety of symptoms including high fevers, hypotension, rigors and malaise, and may progress to cytokine storm (uncontrolled immune hyperactivation involving myriad cytokines) with more severe and potentially life-threatening manifestations. As SAR444245 mediates immune activation, it may induce AEs related to cytokine release (eg, fatigue, fever, chills, muscle pain, rash, nausea, symptoms of autoimmune disease). Furthermore, SAR444245-related increases of plasma monocyte chemoattractant protein-1 (MCP-1), IL-2, and IL-1RA were observed in non-human primates, indicating that SAR444245 administration may be associated with CRS.

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

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

2.3.1.2.2 Clinical studies

A Phase 1/2 first-in-human study (HAMMER) is currently ongoing in adult patients with advanced or metastatic solid tumors. Available safety information from this study has informed the selection of the dose (see details in Section 4.3).

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

2.3.1.3 NKTR-214 (bempegaldesleukin) clinical data

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

In the first-in-human Phase 1 study, NKTR-214 was administered as an outpatient regimen and was well tolerated. Twenty-eight patients with advanced or locally advanced solid tumor malignancies were enrolled in the study. Grade 3 treatment-related adverse events (TRAEs) were reported by 21.4% of patients; there were no Grade 4 TRAEs or any treatment related deaths. The most common TRAEs included fatigue (71%), flu-like symptoms (68%), pruritus (64%), hypotension (57%), rash (50%), decreased appetite (46%), arthralgia and cough (each 32%). The majority of these events coincided with the peak plasma concentrations of the active cytokine and resolved spontaneously or were mitigated by nonprescription oral or topical treatments. There was one reported immune-related adverse event (irAE) of hypothyroidism associated with NKTR-214, which was treated with replacement therapy. All Grade 3 hypotension events (18%) were rapidly reversed with IV fluid administration and did not require treatment discontinuation. NKTR-214-related hypotension was predictable, manageable, and reversible and the incidence of Grade 3 hypotension was reduced once hypotension risk mitigation strategies were implemented. The maximum tolerated dose (MTD) was determined to be 0.009 mg/kg Q3W. This new generation, IL-2Rβγ-biased IL2 could be safely administered as outpatient basis, and there was no report of capillary leak syndrome (CLS) or VLS (17).

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

(TILs), suggesting therapeutic potential for patients with poor prognostic risk factors for response to PD-1/PD-L1 blockade. These data demonstrated that NKTR-214 can be safely combined with a checkpoint inhibitor as dual immunotherapy for the treatment of a range of advanced solid tumors (18).

2.3.2 Benefit assessment

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

Local interleukin-2 (IL-2) treatment was introduced as a neoadjuvant immunobiotherapy applied before the surgical resection of the oral squamous cell carcinoma. Early data demonstrated highly variable response rates for local rhIL-2 administrations (6% to 65%) (19). Phase III trials involving the local administration of rhIL-2 to oral squamous cell carcinoma patients resulted in a significant increase in disease-free survival as well as increased OS (20).

SAR444245, as a “non-alpha” new generation IL-2 is expected to result in greater anti-tumor activity than aldesleukin that has already demonstrated clinical benefit. Furthermore, preliminary Phase 1 clinical data from another new generation IL-2, RO6874281, a fibroblast activation protein (FAP) targeting IL-2 variant, shows CR was achieved in a recurrent and heavily pretreated HNSCC patient, who discontinued from study treatment after 2 years on study (21).

2.3.3 Overall benefit: risk conclusion

SAR444245, with its site-specific pegylation, was designed to substantially reduce association with the IL-2 α receptor, while retaining stimulatory activity for cells expressing the moderate affinity IL-2 βγ receptor. These design features are anticipated to minimize safety liability associated with Proleukin by avoiding expansion of immunosuppressive immune cell populations (regulatory T cells) and off-target complications such as VLS, while still promoting expansion of immune populations that can support anti-tumor immune responses.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with this new generation IL-2 SAR444245 combined with other anticancer treatments are justified by the anticipated benefits that may be afforded to participants with HNSCC.

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

2.3.4.1 Risks in the context of COVID-19

2.3.4.1.1 Risks related to the patient population

Head and neck squamous cell carcinoma (HNSCC) is unique in its location in the upper aerodigestive tract, a known location that harbors SARS-Cov2, the causative virus in COVID-19.

Comorbidities coexist with head and neck cancers in 36.4%-88.9% and 65%-90% of cases diagnosed at an advanced stage. Being mostly heavy smokers, chronic obstructive pulmonary disease (COPD) is one of the most common comorbidities in this group of patients. All these factors significantly increase the risk of a severe outcome, including acute respiratory distress syndrome (ARDS), hospitalization in intensive care units (ICUs), mechanical ventilation, and even death. Sidaway et al. report 53.6% of cancer patients requiring mechanical ventilation and a 28.6% death rate in this category of patients, with most fatalities due to ARDS. Another specific aspect of HNSCC is immunosuppressive treatment, an effect that is associated with a compromised immunity state generated by cancer, thus increasing the risk of a worse outcome in case of infection with the new coronavirus (22, 23). In a systematic review and meta-analysis that evaluated the effect of oncological therapies on the course of Covid-19 disease, Yekedüz et al. identified chemotherapy as a risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection mortality without a consensus on safety in surgery, radiation therapy, target molecular therapy, and immunotherapy. A systematic review and meta-analysis by Wang et al. concluded that these therapies do not increase the risk of death in combination with Covid-19, chemotherapy being in this case also considered to be the only cancer therapy at risk. Cancer is considered due to its immunosuppressive status a risk factor in association with SARS-CoV-2 infection, the rate of possible severe complications, not only ARDS, considered to be 33%. SARS-CoV-2 has had effects on HNSCC management in choosing optimal treatment, taking into account that resources available in each department involved are essential. The multidisciplinary team has an essential role in evaluating the optimal option and is also involved in patient evaluation and follow-up during this pandemic period (24, 25).

In response to the pandemic, many institutions created consensus guidelines to aid in the management of patients. These include the European Society for Medical Oncology (ESMO) Guidelines (26) and the American Society of Clinical Oncology (ASCO) COVID-19 Patient Care Disease-specific Information (27).

Head and neck cancer treatment remains a high priority during this pandemic and patients should undergo standard of care treatment as soon as possible when system resources are available, and the risk of collateral exposure can be controlled or prevented.

Testing for SARS-CoV-2 infection during the screening phase should be at Investigator's discretion and should also follow local/international guidelines (eg, asymptomatic but high risk of infection patients, patients with symptoms that could be associated with SARS-CoV-2 infection).

During the study, if a participant is diagnosed with SARS-CoV-2, dose modification of study intervention should be based on the recommendations provided in Section 6.6. In addition, all Investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as:

- American society of clinical oncology (ASCO) (27).
- European Society for Medical Oncology (ESMO) (26).

2.3.4.1.2 Risks related to study treatment

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

2.3.4.1.3 Risks related to study related activity

It is important to minimize the risk of exposure of patients to COVID-19. In addition to the contingency measures described in Section 10.11, the following prevention and mitigation plans could be implemented at clinical sites:

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

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

Overall, the benefit-risk ratio is deemed acceptable in patients with HNSCC during COVID-19 pandemic.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the antitumor activity of SAR444245 in combination with other anti-cancer therapies in patients with HNSCC	• Objective response rate (ORR) defined as proportion of participants who have a confirmed complete response (CR) or partial response (PR) determined by Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (1)
Secondary	
• To assess the safety profile of SAR444245 when combined with other anti-cancer therapies	• Incidence of TEAEs, SAEs, laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (2)
• To assess other indicators of antitumor activity	• Time to response (TTR) defined as the time from the first administration of investigational medicinal product (IMP) to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed and determined by Investigator per RECIST 1.1
	• Duration of Response (DoR), defined as the time from first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed until documented progressive disease (PD) determined by Investigator per RECIST 1.1 or death from any cause, whichever occurs first
	• Clinical benefit rate (CBR) including confirmed CR or PR at any time or stable disease (SD) of at least 6 months (determined by investigator per RECIST 1.1)
	• Progression free survival (PFS), defined as the time from the date of first IMP administration to the date of first documented disease progression determined by Investigator as per RECIST 1.1, or death due to any cause, whichever occurs first
• To assess the concentrations of SAR444245	• Plasma concentrations of SAR444245
• To assess the immunogenicity of SAR444245	• Incidence of anti-drug antibodies (ADAs) against SAR444245

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]

3.1 APPROPRIATENESS OF MEASUREMENTS

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

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

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multi-cohort, un-controlled, non-randomized, open-label, multi-center study assessing the antitumor activity and safety of SAR444245 combined with other anticancer therapies in participants with HNSCC.

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. This design is with the flexibility to open new treatment cohorts as new treatment combinations become available and close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity.

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

The study consists of a core phase for all cohorts, with a safety run-in and an expansion phase for specific cohorts (see Figure 1). The results of an interim analysis after the core phase will decide if the expansion phase will be opened. Further details on study design are provided in each substudy. An overview of the study intervention and disease being treated for each cohort is provided in Table 3.

Table 3 - Overview of study cohorts

Cohort	Study intervention	Disease
A1	SAR444245 + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
A2	SAR444245 + cetuximab + pembrolizumab	R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1
B1	SAR444245 + pembrolizumab	R/M HNSCC treated with PD1/PD-L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for R/M disease
B2	SAR444245 + cetuximab	R/M HNSCC treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease

CPS: combined positive score; HNSCC: Head and neck squamous cell carcinoma; PD1: Programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; R/M: Recurrent/metastatic.

Participants who are eligible for both Cohorts A1 (to receive SAR444245 and pembrolizumab) and A2 (to receive SAR444245, pembrolizumab and cetuximab) should be enrolled in Cohort A1 until Cohort A1 enrollment is completed. Further details guiding the enrolment in each cohort are provided in the individual substudies.

Study Board

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

See further details in substudies for cohorts with safety run-in.

Special considerations pertaining to methodology

Interactive Response Technology will be used to control recruitment assignment per site and facilitate drug supply.

The duration of the study for a participant will include:

- **Screening period**: up to 28 days.
- **Treatment Period**: enrolled participants will receive continuous treatment until PD, unacceptable AE, other full permanent discontinuation criteria as described in Section 6, or completion of Cycle 35.
- **End of Treatment and Follow-up.** End of Treatment Visit will occur 30 days ±7 days from last IMP administration or prior to initiation of further therapy. Participants will then enter the **Observation period** and will be followed differently depending on the reason leading to **EOT**:

1. Participants who discontinue study treatment **without PD** or who **complete 35 cycles of treatment without PD**, will be followed for safety (as per Schedule of Activities [SoA]) and tumor imaging assessments every 3 months ±7 days from last IMP administration, until PD, start of another anticancer therapy, final cohort cut-off, whichever comes first, before moving to the Survival Phone Call Follow-Up Period.
2. Participants who discontinue study treatment **with PD** will be followed for safety in the Follow-Up Visit 1 occurring 3 months ±7 days from last IMP administration, before moving to the Survival Phone Call Follow-Up Period.

Participants who move into the **Survival Phone Call Follow-Up Period** will be contacted by telephone every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment with best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Survival Phone Call Follow-Up will continue until death, participant request to discontinue from follow-up, or final cohort cut-off, or upon cancellation of Survival follow-up at the discretion of the Sponsor at any prior timepoint.

After the cohort cut-off date for the primary ORR analysis, participants can continue to receive IMP, if clinical benefit is observed, until permanent discontinuation criteria described in Section 7.1.1 are met and will continue to undergo all assessments as per the SoA.

For each cohort, the cut-off date for the final analysis (ie, analysis of secondary objectives and update of primary objective) will be 3 years from cohort LPI. After this cut-off date for the final analysis, the participants still receiving study treatment in that specific cohort will be followed up as the cohorts after early termination described in Section 10.1.9.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with other anticancer therapies, will result in a significant increase in the percentage of trial participants with HNSCC experiencing an objective response.

The design of the study is a non-randomized study where the experimental combinations will be assessed in separate cohorts, using historical data from agents combined with SAR444245 as a benchmark to show outstanding objective response rate. The ORR will be assessed using response evaluation criteria in solid tumors (RECIST) 1.1. The objective response will be assessed per Investigator as primary endpoint. Central imaging reading may be done retrospectively if significant activity is observed.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

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

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

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

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

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

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

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

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

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

Within the HAMMER study, all together there were 13 patients that experienced any grade of CRS (per CTCAE version 5). Only 1 Grade 4 CRS with Grade 3 hypertension, Grade 2 fever, and Grade 2/3 neurological symptoms (with 24 µg/kg Q3W, 2.6%) is reported among participants who received SAR444245 monotherapy (n=38). From participants who received SAR444245 pembrolizumab combination (n=20), grade 3 CRS (with 16 µg/kg Q3W) is observed in 1 participant (5.0%) with Grade 3 hypotension and Grade 2 fever.

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

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

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

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

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

In addition, preclinical studies using human whole blood to assess the induction of cytokines showed no change in cytokine profiles when administering SAR444245 with and without pembrolizumab. This study used SAR444245 concentration ranges that went significantly higher than current clinical dosages (0.2-4.5 µg/mL) and showed that SAR444245-induced cytokine release in human whole blood was not affected in the presence of pembrolizumab at Q3W schedule.

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

1. SAR444245 monotherapy up to 32 µg/kg Q3W, pembrolizumab combination up to 32 µg/kg Q3W and cetuximab combination 24 µg/kg Q3W are all cleared in HAMMER study.
2. Sustained relevant PDy effect in blood, higher at higher dose, was documented in participants; and
3. Observed safety data from the Hammer study suggests the combination of SAR444245 combined with anti-PD1 (eg, pembrolizumab) may not lead to significant overlapping toxicities.

4.4 END OF STUDY DEFINITION

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

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

Age

I 01. Participant must be ≥18 years of age (or country's legal age of majority if >18 years), at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Histologically or cytologically confirmed diagnosis of R/M HNSCC that is considered not amenable to further therapy with curative intent. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx (nasopharynx is excluded).

I 03. Measurable disease

At least 1 measurable lesion (not biopsied at baseline) per RECIST 1.1 criteria. Target lesion(s) may be located in a previously irradiated field if there is documented radiographic disease progression of such lesion(s).

I 04. Known HPV p16 status for oropharyngeal cancer.

Weight (not applicable)

I 05. **Sex**

All (male and female)

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

a) Male participants

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

- Refrain from donating or cryopreserving sperm.

PLUS either:

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

OR

- Must agree to use contraception/barrier as detailed below

- A male condom with female partner use of an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 (Section 10.4) of the protocol when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant, or during homosexual intercourse

b) Female participants

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

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 4 (Section 10.4) during the intervention period (to be effective before starting the intervention) and for at least 120 days (for Cohorts A1, A2 and B1) or 60 days (for Cohort B2) [corresponding to the time needed to eliminate any study intervention(s)] after the last dose of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- A WOCBP must have a negative highly sensitive pregnancy test (as required by local regulations) within 7 days before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 4 (Section 10.4).
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

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. Active brain metastases or leptomeningeal metastases.

- Patients with previously treated brain metastases are eligible provided they are clinically stable for at least 4 weeks with no evidence of new or enlarging brain metastases and have not received corticosteroids at least 2 weeks prior to first IMP administration (Note: participants with brain involvement due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval from the Sponsor).
- Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) are eligible but will require regular imaging of the brain as a site of disease.

E 04. History of allogenic tissue/solid organ transplant.

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

E 06. Last administration of prior antitumor therapy (chemotherapy, targeted agents, and immunotherapy) or any investigational treatment within 28 days or less than 5 times the half-life, whichever is shorter; major surgery or local intervention within 28 days prior to first IMP administration.

E 07. Comorbidity requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 2 weeks of IMP initiation. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder. Participants who require a brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

E 08. Antibiotic use (excluding topical antibiotics) ≤14 days prior to first dose of IMP, or any serious systemic fungal, bacterial, viral (excluding viral infection settings as described in E 15), or other infection that is not controlled.

E 09. Severe or unstable cardiac condition within 6 months prior to starting study treatment, such as congestive heart failure (New York Heart Association Class III or IV), cardiac bypass surgery or coronary artery stent placement, angioplasty, left ventricular ejection fraction (LVEF) below 50%, unstable angina, medically uncontrolled hypertension

(eg, ≥160 mmHg systolic or ≥100 mmHg diastolic), uncontrolled cardiac arrhythmia requiring medication (≥ Grade 2, according to NCI-CTCAE v5.0), or myocardial infarction.

E 10. Ongoing AEs caused by any prior anticancer therapy ≥ Grade 2 (NCI-CTCAE Version 5.0). Participants with Grade 2 peripheral neuropathy, or Grade 2 alopecia, are permitted. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

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

E 11. Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). The following are not exclusionary: vitiligo, childhood asthma that has resolved, psoriasis that does not require systemic treatment.

E 12. History of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current (non-infectious) pneumonitis / interstitial lung disease.

E 13. Participant who has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

E 14. Receipt of a live or live-attenuated virus vaccine within 28 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

E 15. Human immunodeficiency virus (HIV)-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease or known uncontrolled infection with HIV. HIV-infected participants must be on anti-retroviral therapy (ART) and have a well-controlled HIV infection/disease defined as:

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

HIV serology will be tested at screening for participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8).

E 16. Known uncontrolled hepatitis B infection, known untreated current hepatitis C infection, active tuberculosis, or severe infection requiring parenteral antibiotic treatment.

- To control HBV infection, participants with positive HBsAg should have started anti-HBV therapy before initiation of IMP. Antiviral therapy for HBV must be given for at least 4 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.
- Participants who are positive for anti-hepatitis B core antibody HBc, negative for hepatitis B surface antigen (HBsAg), and negative or positive for anti-hepatitis B surface antibody (HBs), and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.
- Participants with past or ongoing hepatitis C virus (HCV) infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention. Participants with positive HCV antibody and undetectable HCV RNA without anti-HCV therapy are eligible.

  Hepatitis B and C serology will be tested at screening for participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8).

E 17. Known second malignancy either progressing or requiring active treatment within the last 3 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

E 18. Known severe hypersensitivity (≥ Grade 3) to or contraindication for the use of any study intervention or components thereof, including premedication to be administered in this study, as well as PEG or any pegylated drug and E. coli-derived protein.

E 19. Participants with baseline oxygen saturation (SpO_2) ≤92% (without oxygen therapy).

Prior/concomitant therapy

E 20. Has received prior IL2-based anti-cancer treatment.

E 21. Is unable or unwilling to take premedication.

E 22. Participants under anti-hypertensive treatment who cannot temporarily (for at least 36 hours) withhold antihypertensive medications prior to each IMP dosing.

Prior/concurrent clinical study experience

E 23. Current enrollment or past participation in a study of an investigational treatment or has used an investigational device within 28 days prior to the first dose of study treatment.

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

Diagnostic assessments

Not applicable.

Organ and bone marrow function

E 24. Absolute neutrophil count <1500 /uL (1.5×10^9/L) (after at least one week off G-CSF).

E 25. Platelets <100 × 10^3 /µL (after at least 3 days without platelet transfusion).

E 26. Hemoglobin <9 g/dL (without packed red blood cell [pRBC] transfusion within prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

E 27. Total bilirubin >1.5 x upper limit of normal (ULN) unless direct bilirubin ≤ULN (participants with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)

E 28. Aspartate aminotransferase and/or alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases).

E 29. Estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m² (Modification of Diet in Renal Disease [MDRD] Formula, see Appendix 2).

E 30. International Normalized Ratio (INR) or Prothrombin Time (PT) or Activated Partial Thromboplastin Time (aPTT) >1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

Other exclusions

E 31. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 32. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 (country-specific requirements).

E 33. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 34. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 35. Any specific situation during study implementation/course that may raise ethics considerations

E 36. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

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

5.3.2 Caffeine, alcohol, and tobacco

No restrictions are required.

5.3.3 Activity

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

5.3.4 Hydration

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

5.4 SCREEN FAILURES

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

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

A participant who screen failed may be rescreened; in this situation, the rescreened participant should sign a new ICF. A participant may be rescreened only once.

Rescreened participants should be assigned a different participant number as for the initial screening.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 10.11.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants will receive study treatment until confirmed PD, unacceptable toxicity, other permanent discontinuation criteria as described in Section 6, or completion of Cycle 35 when applicable.

If a participant has immune unconfirmed progression of disease (iUPD) and is clinically stable, it is at the discretion of the Investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed (iCPD) at least 4 weeks, but no longer than 8 weeks from the date of the scan suggesting progression of disease (Section 10.10).

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.11.

6.1.1 Investigational medicinal products

Details of SAR444245 are shown in Table 4.

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

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

Table 4 - Overview of IMP administered

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

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

6.1.2 Noninvestigational medicinal products

6.1.2.1 Premedication for SAR444245

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

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

SAR444245 premedication may be optional after 4 cycles

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

6.1.3 Hydration guidelines for SAR444245 administration

[redacted]

6.1.4 Readiness for treatment of severe cytokine release syndrome

Doses of tocilizumab or alternative therapies per site practice in CRS management should be available at site at all times in the event that a participant requires rapid intervention for the treatment of severe CRS. Please refer to Section 6.5 of individual substudies protocols for detailed guidelines for the management of CRS.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

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

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

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

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

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

6.5 DOSE MODIFICATION

Please see respective substudies protocols.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

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

6.7 TREATMENT OF OVERDOSE

There is no specific antidote for overdose with SAR444245.

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

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

Procedures for treating symptoms and complications of immune-related adverse events are provided in Section 6.5 of individual substudies protocols.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 90 days).
3. Obtain a plasma sample for PK analysis right after the overdose event is identified (only if an overdose is identified within 5 days from start of overdose infusion).
4. Document appropriately in the e-CRF.

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

6.8 CONCOMITANT THERAPY

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

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

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

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

6.8.1 Acceptable concomitant medications

All treatments that the Investigator considers necessary for a participant’s welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the e-CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of route, and date will also be included on the e-CRF.

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

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

Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed (28).

6.8.2 Prohibited concomitant medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Investigational agents other than specified in this protocol.
- Radiotherapy for tumor control (please refer to Section 6.8.1 for allowed radiotherapy).
- Live or live-attenuated virus vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live-virus vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, seasonal flu (seasonal flu vaccines that do not contain live virus are permitted), nasal H1N1 flu, rabies, Bacillus Calmette-Guérin (BCG), and typhoid.
- Systemic glucocorticoids and other immunosuppressive therapies such as anti-TNF, anti-IL6, etc, except for:
  - Treatment of immune-mediated AEs when indicated (IRR, CRS, irAE, and ICANS, see individual substudies protocols in Section 6.5),
  - Treatment of any life-threatening emergency,
  - Physiologic replacement as long as they are not being administered for immunosuppressive intent, and
  - A brief course (≤7 days) of systemic corticosteroid for prophylaxis (eg, contrast dye allergy) or for the treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reactions caused by contact allergen).

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

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

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

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

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

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative (if allowed by local regulations). "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the patient's participation in the procedure(s) involved in the research.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Unacceptable AE.
  - Documented disease progression
  - Poor compliance to the study protocol.
  - Completion of 35 cycles when applicable
  - Other, such as concurrent illness, that prevents further administration of study intervention, or that in the Investigator's opinion, in the best interest of the participant
- In case of pregnancy occurrence.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for serial tumor assessment if permanent discontinuation is not due to PD, for safety assessment as per SoA (Section 1.3) and until resolution or stabilization of AE, and any other assessment as per SoA. Data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed are reported in the SoA.

7.1.1.1 Unacceptable adverse events leading to permanent intervention discontinuation

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

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

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

Decision criteria for discontinuation following immune-mediated AEs are described in Section 6.5 of individual substudies protocols (Guidelines for the management of IRR, CRS, ICANS, VLS).

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

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

Handling of participants after permanent intervention discontinuation

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

If possible, and after the permanent intervention discontinuation, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate. Tumor assessment should be repeated if not done at the last cycle. A biopsy (optional - special consent) may be performed if treatment is discontinued for disease progression following an initial response.

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

7.1.2 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.11). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.3 Rechallenge

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

Recommendations for rechallenge in the context of an epidemic/pandemic (eg, COVID-19), are included in the Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.11).

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 or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, see SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, 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 CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

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

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

7.3 LOST TO FOLLOW UP

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures are summarized in this section and their timing is presented in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- During the screening period, demography, medical/surgical, and disease history will be evaluated. Demography includes age, gender, race, and ethnicity. Medical/surgical history includes relevant history of previous pathologies and smoking status. Disease history includes stage at diagnosis and at study entry, and previous anti-tumor therapy (type, duration, reason for discontinuation and response to the therapy). In addition, results of driver gene mutation (such as *BRAFV600E* for participants with melanoma) are also to be collected.
- A comprehensive medical history will be assessed for any cardiovascular signs or symptoms prior to treatment, along with a baseline ECG, echocardiogram and troponin level.
- Regular blood samples will be collected from each participant throughout the duration of the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Details on blood sampling, including the estimated volume collected for each analysis are provided in the laboratory manual.
- For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.11.

8.1 EFFICACY ASSESSMENTS

The assessment of anti-tumor activity documented by objective response to the IMP is the primary endpoint for this study and is conducted as per schedule provided in the SoA. All participants treated must have at least one measurable lesion for inclusion.

Decision to pursue treatment will be based on the response evaluation made by the Investigator, however, measures of lesions will be collected in the e-CRF for a determination of response by the Sponsor. A partial or complete response must be confirmed on a second examination done at least 4 weeks apart, in order to be documented as a confirmed response to therapy. Confirmation of PD[redacted]may be done at the discretion of the Investigator when clinically indicated.

Investigators will obtain copies of the images and will provide them to Sponsor or other repository facility identified by the Sponsor for potential central review. Study sites must retain

tumor assessment images, as Sponsor may decide to collect these images for possible Independent Central Review in the future.

Assessment of tumor response will be conducted using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (see Section 10.9 according to the nature of the measurable lesions, as described below).

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

For participants with disease that is measured radiologically according to RECIST 1.1 criteria (Section 10.9) a CT or magnetic resonance imaging (MRI) for tumor assessment will be performed as detailed in Section 1.3. The choice of whether the imaging is by CT (preferred) or MRI is an Investigator decision. Once the choice of CT scan or MRI has been made, the same imaging technique should be used in a participant throughout the trial.

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

The initial CT/MRI tumor imaging will be performed within 28 days prior to C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On-study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP and if clinically indicated. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). Per the primary tumor assessment criteria, after the first documentation of response or the first documentation of progression (if the participant is clinically stable), confirmatory imaging may be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anticancer therapy.

At a minimum, all radiologically measurable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment.

For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Two additional imaging, obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive therapy during these 4 weeks stabilization at the treating physician's discretion, it will be considered as prior anticancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic

symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain imaging may be collected up to 42 days prior to enrollment.

RECIST 1.1 [redacted]

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

[redacted]

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological and skin systems. Height and weight will also be measured and recorded.

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

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively;

- Vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose.
- At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring (to be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting).

- **For the core phase participants**: from Cycle 2 to Cycle 4, study therapy will be administered for all patients in out-patient clinic with vital signs taken prior to dosing, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.
- From Cycle 5 and beyond, vital signs will be collected prior to IMP administration.

8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)

- Includes single 12-lead ECG, LVEF and troponin that will be performed at screening and troponin at Cycle 4 Day 1, then, as clinically indicated.
- At Cycle 1 Day 1, at pre-dose and at end of SAR444245 infusion, ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- LVEF evaluation will be done by echocardiography or multigated acquisition (MUGA), and any repeated assessment should be done with the same technology used at screening.
- Additional evaluations such as ECG, LVEF, Holter monitoring, cardiac enzymes (such as troponin) and consultation with a cardiologist should be done when clinically indicated.

- During treatment, or post treatment follow-up: Troponin will be performed at Cycle 4 Day 1. In case of a suspicion of a drug related cardiac event (eg, including signs/symptoms of cardiac disease, ECG and/or echo changes, troponin elevation, etc.), Investigators are encouraged to do ECG, echocardiography and/or cardiac biomarker tests, as medically indicated, including cardiology consultation.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The clinical safety laboratory assessments will be done in the local laboratory.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within Follow-Up Visit 1 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2) must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria I 05 for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
- Women of childbearing potential must have a negative urine pregnancy test result within 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 60 days (for Cohort B2) or 120 days (for Cohorts A1, A2 and B1) after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8. AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative if allowed by local regulations).

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

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

8.3.1 Time period and frequency for collecting AE and SAE information

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

All SAEs and AESIs will be collected throughout the study period, from the signing of the informed consent form (ICF) until **90 days** following last administration of study treatment.

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and AESIs (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Stabilization is

defined as an AE ongoing without any change for at least 3 months. Participants with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or starting of a new antineoplastic therapy, whichever occurs first.

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

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events (SAEs) that are considered expected will be specified in the reference safety information (IB for SAR444245).
  - Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, should be expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 60 days (for Cohort B2) or 120 days (for Cohorts A1, A2 and B1) following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates another anticancer therapy.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Cardiovascular and death events

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

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

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An adverse event of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.
The following events need to be reported as AESIs:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.3).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 10.4).
  Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose of IMP is defined as: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
  - An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

- An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) lab value that is greater than or equal to 3 times the ULN and an elevated total bilirubin lab value that is greater than or equal to 2 times the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 times the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

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

- Other project-specific AESIs
  - IRR Grade ≥2
  - CRS Grade ≥2
  - ICANS of any grade
  - VLS of any grade
  - SARS-CoV-2 infection/COVID-19 disease
  - Any immune-related AE Grade ≥3
  - Arrhythmia Grade ≥3

8.3.9 Guidelines for reporting product complaints

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

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

8.4 PHARMACOKINETICS

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

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

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

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

8.5 GENETICS AND/OR PHARMACOGENOMICS

[redacted]

8.6 BIOMARKERS

[redacted]

[redacted]

8.7 IMMUNOGENICITY ASSESSMENTS

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

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

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

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

8.8 HEALTH ECONOMICS

No health economics data will be collected.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

[redacted]

9 STATISTICAL CONSIDERATIONS

Please refer to substudies protocols for additional statistical considerations.

9.1 STATISTICAL HYPOTHESES

All cohorts of the study are designed to obtain antitumor activity, safety, PK, and PDy data on SAR444245 administered in combination with other anticancer therapies.

The study is designed to assess the clinical benefit of SAR444245 with other anticancer therapies in participants with HNSCC. As this study is not intended to explicitly test a hypothesis, calculations of power and Type I error were not considered in the study design. No formal testing procedure is planned.

9.2 SAMPLE SIZE DETERMINATION

Overall, in the core phase, the plan is to treat approximately 40 participants per cohort.

Core Phase

Table 5 lists estimated ORR and the corresponding 90% exact CIs by number of responders in each cohort.

Table 5 - Estimated objective response rate (ORR) and 90% CI for core phase

Number of responders (N=40)	ORR	90% CI for ORR (Clopper-Pearson)
6	15.0%	(6.7%, 27.5%)
7	17.5%	(8.5%, 30.4%)
8	20.0%	(10.4%, 33.2%)
9	22.5%	(12.3%, 36.0%)
10	25.0%	(14.2%, 38.7%)
11	27.5%	(16.3%, 41.4%)
13	32.5%	(20.4%, 46.6%)
15	37.5%	(24.7%, 51.7%)
17	42.5%	(29.2%, 56.7%)
19	47.5%	(33.8%, 61.5%)
24	60.0%	(45.8%, 73.1%)

With a sample size of 40 study participants in each cohort in the core phase, the probability of observing 1 or more instances of a specific AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

9.3 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - Populations for analyses

Population	Description
Exposed	Exposed population will include all participants who have given their informed consent and received at least one dose (even incomplete) of IMP (SAR444245 or other anticancer therapies).
Efficacy	Efficacy population will include all participants from the exposed population with at least one evaluable post-baseline tumor assessment or who permanently discontinued study treatment.
PK	The PK population will include all participants from the exposed population with at least 1 PK concentration available after the first dose of study intervention.
PDy	The PDy population will include all participants from the exposed population with at least 1 PDy parameter assessed after the first dose of study intervention.

9.4 STATISTICAL ANALYSES

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

9.4.1 General considerations

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

All efficacy analyses will be performed on the efficacy population and analyzed by cohort. Some cross-cohort summaries will be presented too. Results will be presented by core phase and overall phase (combining core phase and expansion phase, if expansion phase applies). Objective response rate, as well as PFS, DOR, and CBR will be derived using the local radiologist's/Investigator's assessment for all cohorts. Central imaging may be done retrospectively if significant activity is observed. The assessments for all cohorts will use RECIST 1.1.

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

The analysis period will be divided into 3 segments:

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

- The post-treatment period is defined as the time from the 31 days after the last administration of IMP.

9.4.2 Primary endpoint(s)

The BOR is the best overall response observed from the date of first IMP until disease progression, death, cut-off date or initiation of post-treatment anti-cancer therapy, whichever occurs first. The BOR will be summarized with descriptive statistics. The ORR is the primary endpoint defined as the percentage of participants from the analysis population with BOR is either CR or PR, assessed per Investigator. The ORR and the corresponding 90% confidence intervals calculated from Clopper-Pearson exact method will be also presented. All objective responses need to be confirmed by a subsequent assessment performed at least 4 weeks apart from the initial response observation.

9.4.3 Secondary endpoint(s)

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

9.4.3.1 Time to response

Time to response will be defined as the time from the first administration of IMP to the first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed.

Time to response will be descriptively summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.

9.4.3.2 Duration of response

The DoR will only be summarized on the subgroup of participants who have achieved confirmed objective response in the efficacy population.

The DoR will be defined as the time from the date of first tumor assessment at which the overall response was recorded as PR or CR that is subsequently confirmed to the date of first documentation of objective PD before the initiation of any post-treatment anti-cancer therapy or death due to any cause, whichever occurs first.

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

9.4.3.3 Clinical benefit rate

The CBR will be defined as the proportion of participants with clinical benefit (confirmed CR or PR as BOR, or stable disease (SD) lasting at least 6 months). Specifically, participants will be considered as clinical benefit responders if they achieve a CR or PR as BOR, or have an overall

response recorded as SD at 6 months (ie, 26 weeks or later from first IMP intake, allowing for the ±7 days visit window for tumor assessment scheduled at 27 weeks).

9.4.3.4 Progression-free survival

Progression-free survival is defined as the time from the date of first IMP to the date of the first documentation of objective progressive disease when relevant or death due to any cause, whichever occurs first.

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

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

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

9.4.3.5 Adverse events

All AEs will be categorized according to NCI-CTCAE v 5.0 and classified by SOC and Preferred Term (PT) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Immune Cell-Associated Neurotoxicity Syndrome and CRS events will be graded using ASTCT Consensus Grading and will be summarized separately.

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

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

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

Treatment-emergent adverse events:

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

- TEAEs.
- TEAEs of Grade ≥3
- Grade 5 TEAE (any TEAE with a fatal outcome during the on-treatment period)

- Serious TEAEs
- Serious treatment-related TEAEs
- TEAE leading to partial intervention discontinuation
- TEAE leading to full intervention discontinuation
- Treatment-related TEAEs
- Treatment-related TEAEs of Grade ≥3

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

The following deaths summaries will be generated:

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

9.4.3.6 Clinical laboratory evaluations

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

When relevant, for laboratory variables, descriptive statistics for results and changes from baseline will be provided for the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period.

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

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

For laboratory variables graded by NCI-CTCAE:

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

9.4.3.7 Other secondary endpoints

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

Plasma concentrations of SAR444245 will be summarized with descriptive statistics by each cohort.

9.4.4 Tertiary/exploratory endpoint(s)

9.4.4.1 Exploratory antitumor indicators

[redacted]

9.4.4.2 Biomarker endpoints

[redacted]

9.4.5 Other safety analyse(s)

All safety analyses will be made on the exposed population. When relevant, the summary statistics (including mean, median, standard error, minimum and maximum) of all vital signs (raw data and changes from baseline) will be calculated for baseline, last on treatment value and/or worst value.

9.4.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.11.

9.5 INTERIM ANALYSES

During the core phase, no formal interim analyses are planned. However, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Data Monitoring Committee (DMC). The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises.

In addition, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the study, eg, in each cohort, after 20 participants have undergone two post-baseline tumor assessments (approximately 18 weeks from the 20 participants are first treated) or have discontinued study treatment whichever is earlier.

For each cohort, the cut-off date for the final analysis will be 3 years from cohort last patient-in (LPI).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

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

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

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

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

10.1.2 Financial disclosure

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

10.1.3 Informed consent process

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

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

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

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 11: Contingency Measures for a regional or national emergency that is declared by a governmental agency (Section 10.11).

10.1.4 Data protection

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

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

Protection of participant data

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

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

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

Protection of data related to professionals involved in the study

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

- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Data Monitoring Committee

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

10.1.6 Dissemination of clinical study data

Study participants

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

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

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

Professionals involved in the study or in the drug development program

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

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or e-CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the e-CRF.
- Guidance on completion of CRFs will be provided in the relevant sponsor data management study document.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

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

10.1.9 Study and site start and closure

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

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

The Sponsor or designee reserves the right to close the study site or terminate the study or one or more cohorts at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio,
  - Discontinuation of further study intervention development.
- For cohort termination
  - Early evidence of lack of benefit.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor’s procedures, or GCP guidelines,
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator,
  - Total number of participants included earlier than expected.

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

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

10.1.10 Publication policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology[a]	Platelet count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Urea or Urea nitrogen
	Creatinine and eGFR (MDRD formula[b])
	Glucose
	Potassium
	Sodium
	Corrected Calcium
	Phosphate
	Chloride
	Magnesium
	Bicarbonate[c]
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
	Lactate dehydrogenase (LDH)
	Albumin
	Amylase
	Lipase
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Routine urinalysis[d]	• Specific gravity, pH, glucose, protein, blood, ketones, and leukocytes by dipstick. • Microscopic examination (if blood or protein is abnormal).

Laboratory assessments	Parameters
Other screening tests	• Follicle-stimulating hormone and estradiol may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). • Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[e.] • Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus antibody), Hepatitis B viral load, HCV RNA level, CD4 counts & HIV viral Load[f.] • Troponin • The results of each test must be entered into the e-CRF.

NOTES:

a Blood Chemistry/hematology should be done with an overnight fasting if possible (should not interfere with hydration requirements). It will be performed weekly on D1 pre-dose, D8 and D15 during Cycle 1, then on Day 1 of every cycle up to Cycle 12, then every other cycle during Treatment Phase. During the Observation Period, it will be performed at Follow-Up Visit 1. It can also be performed as clinically indicated. In case of Grade ≥3 liver function abnormal tests, additional tests will be repeated every 2-3 days until recovery to baseline value.

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

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

d Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

e Pregnancy Test: Women of childbearing potential must have a negative urine pregnancy test result within 72 hours prior to first IMP administration of each cycle, at EOT and every 30 (±7) days until 60 days (for Cohort B2) or 120 days (for Cohorts A1, A2 and B1) after the last dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

f Participants with known HIV infection under antiretroviral treatment should have HIV viral load & CD4+ count done at screening to confirm controlled infection. Participants with known HBV hepatitis under treatment must have viral load determined at baseline to document controlled infection. Participants with positive serology against HCV must have determination of HCV RNA levels. The need for additional testing due to positive test results will be at the discretion of the Investigator. HIV, hepatitis B and C serology will be tested at screening for participants in Germany and Italy (see Section 10.8).

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE definition

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

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2 Definition of SAE

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

A) Results in death.

B) Is life-threatening

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

C) Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

D) Results in persistent or significant disability/incapacity

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

E) Is a congenital anomaly/birth defect.

F) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm,
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc),
  - Development of drug dependence or drug abuse,
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
  - Bullous cutaneous eruptions.

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

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

AE and SAE recording

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

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

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

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than 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 IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send 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 the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

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

SAE reporting to the Sponsor via paper data collection tool

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

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below). A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

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

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

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

10.4.2 Contraception guidance

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

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

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

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

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

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

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

- Oral
- Intravaginal
- Transdermal
- Injectable

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

- Oral
- Injectable

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

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

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: GENETICS

[redacted]

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

Not applicable.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Amendment for Germany

Section 1.3 **Schedule of Activities (SoA)** (Section 1.3), Section 5.2 **Exclusion Criteria** (Section 5.2) and Section 10.2 **Clinical Laboratory tests** (Section 10.2)

In Germany, serology for HIV, hepatitis B and C will be tested at screening.

10.8.2 Amendment for Italy

Section 1.3 **Schedule of Activities (SoA)** (Section 1.3), Section 5.2 **Exclusion Criteria** (Section 5.2) and Section 10.2 **Clinical Laboratory tests** (Section 10.2)

In Italy, serology for HIV, hepatitis B and C will be tested at screening.

10.9 APPENDIX 9: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1

Confirmatory scans should be obtained **at least 4 weeks** following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline Version 1.1 (1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease**: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest X-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
- **Malignant lymph nodes**: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Target lesions**: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions**: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions**. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest X-ray**. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI**. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT**. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers**. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology**. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- **FDG-PET**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A "positive" FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR)**: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

- **Partial Response (PR)**: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)**: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD)**: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR)**: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD**: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD)**: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (1) are summarized in the table:

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

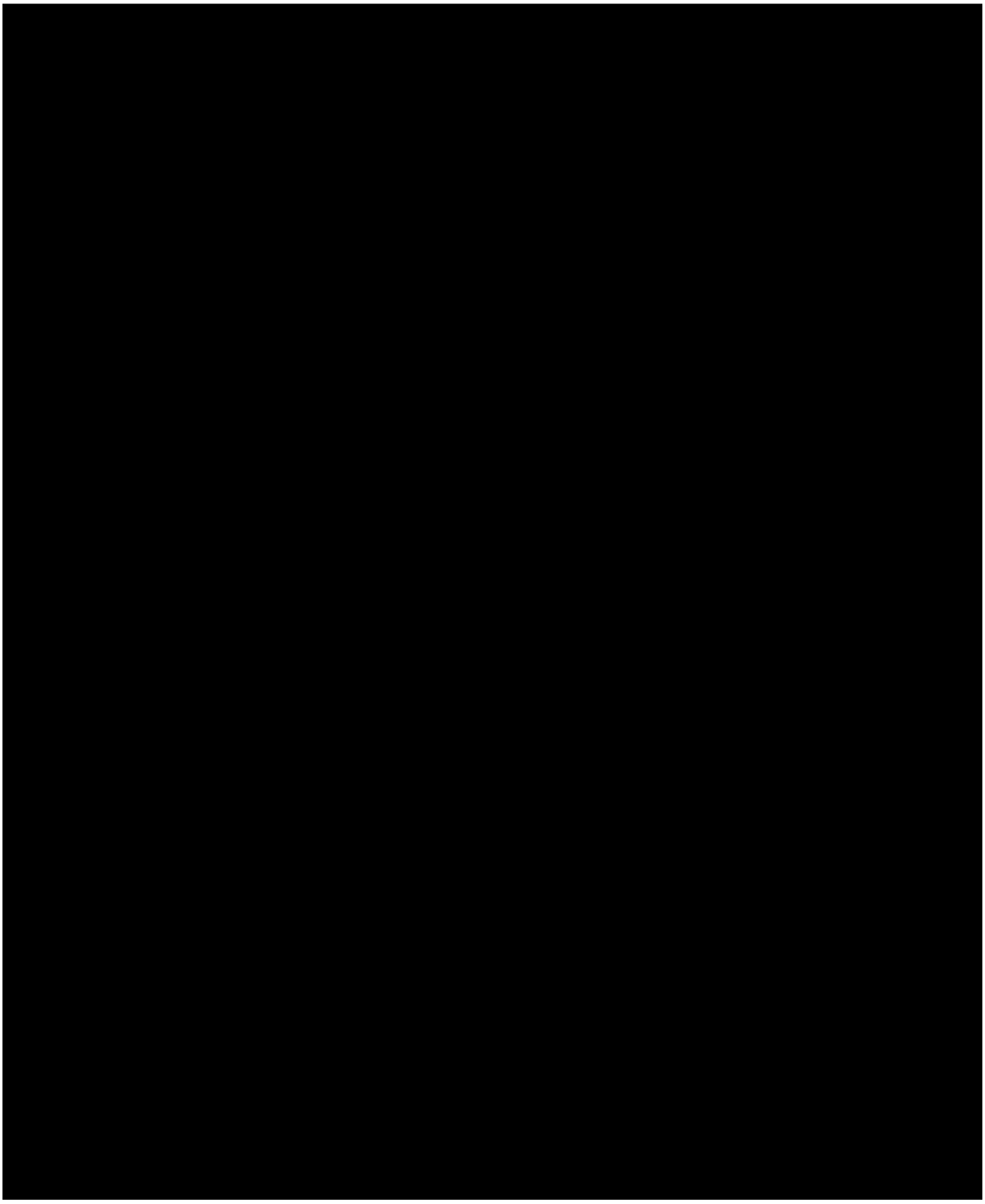
Target lesions	Non-target lesions	New lesions	Overall response	Best overall response when confirmation is required[a]
CR	CR	No	CR	>4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	>4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	

Target lesions	Non-target lesions	New lesions	Overall response	Best overall response when confirmation is required[a]
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once >4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR = Complete response; PD = Progressive disease; PR = Partial response; SD = Stable disease.
a In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

10.10 APPENDIX 10: [redacted]

[redacted]



[redacted]

10.10.1 Response and stable disease duration (RECIST 1.1 [redacted])

Response duration will be measured from the time measurement criteria for CR/PR[redacted] (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.10.2 Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion.”

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (1). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or SD and PD.

10.11 APPENDIX 11: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

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

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

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

10.11.1 Informed consent

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

10.11.2 Study procedures

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

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

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

10.11.3 Statistical analysis

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

10.11.4 Temporary discontinuation

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

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

Contingencies implemented due to emergency will be documented.

10.12 APPENDIX 12: RISK ASSESSMENT

The information shown in Table 8 reflects the clinical safety data available at the time of Edition 3 of the SAR444245 IB. Please always refer to the latest version of the IB for the most up-to-date safety data.

Table 8 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-associated reactions	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the THOR-707-101/HAMMER study have reported such AE as detailed in the IB.	SAR444245 Standard pre-medication Dose modification and treatment guidelines for SAR444245 infusion-associated reactions are provided in individual substudies.
Hypersensitivity, including anaphylaxis	SAR444245 Not observed in non-clinical toxicology studies. No reports of anaphylaxis in the HAMMER study to date.	Exclusion of participants with known hypersensitivity to or contraindication any components of SAR444245, PEG, or pegylated drugs.
Infections	SAR444245 Nonclinical data do not indicate higher risk for infections. Adverse events of infections have been reported in the HAMMER study and are presented in the SAR444245 IB.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Signs and symptoms of infection are monitored as part of TEAE.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Cytokine release syndrome	SAR444245 No major increases in cytokines have been reported in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Study to be conducted at sites experienced with CRS management, with bed available in ICU. Premedication with paracetamol, diphenhydramine (or equivalent medications). Hydration guidelines, including management of anti-hypertensive treatment around the time of infusion, are provided. Extensive post-dosing monitoring will be performed. Dose modification and treatment guidelines are provided in individual substudies.
Capillary leak syndrome (CLS) / Vascular leak syndrome (VLS)	SAR444245 Not observed in non-clinical toxicology studies. None reported in the HAMMER study.	Intensive monitoring in C1D1 and beyond in the first cycle. Participants are monitored for signs and symptoms of VLS. Dose modification and treatment guidelines are provided in individual substudies.
Hematological/bone marrow toxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, SAR444245-related changes in clinical pathology parameters were observed at all doses and were generally most prominent 3 days following each dose. Changes in hematology parameters included decreased or attenuated reticulocytes followed by decreases in red blood cell (RBC) mass at [redacted] mg/kg/dose, and increased WBCs (lymphocytes and monocytes) and transiently mildly decreased platelets at [redacted] mg/kg/dose. The increases in lymphocytes were attributed to the expected pharmacology of SAR444245 and correlated with the gross and microscopic findings of splenic and lymph node enlargement and increased lymphoid cellularity; there were no microscopic or clinical correlates for the decreases in platelets. Adverse events of bone marrow toxicity have been reported in the HAMMER study and are presented in the SAR444245 IB. Transient lymphopenia has also been observed.	Routine mitigation: Participants must have appropriate ANC and other organ/bone marrow function to be included. During treatment, regular hematology and biochemistry is examined. Dose modification/discontinuation of IMP for Grade 3/4 anemia, thrombocytopenia and/or neutropenia as per general guidelines for the management of TRAEs (see individual substudies).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hepatotoxicity	SAR444245 In 28-day repeat-dose study of IV SAR444245 in mice, males at [redacted]mg/kg/dose and females at[redacted] and[redacted] mg/kg/dose also had mild increases in AST and ALT activity that corresponded to a spectrum of microscopic findings in the liver including mononuclear cell infiltration, apoptosis, necrosis, mixed leukocyte inflammation, oval cell hyperplasia, and Kupffer cell hypertrophy. No such data are reported in 28-day Repeat-Dose Study of IV SAR444245 in non-human primates. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Patients with significant impaired liver functions are excluded. Monitor clinical signs and symptoms of hepatic impairment as part of TEAE. Monitor liver function parameters (AST, ALT, bilirubin & ALP) regularly from screening and throughout the study. Dose modification and treatment guidelines for liver enzyme increase are provide under immune-related reactions in individual substudies.
Nephrotoxicity	SAR444245 There are no non-clinical data indicating a potential for nephrotoxicity. One relevant serious adverse event (SAE) considered related to SAR444245 (Acute Kidney Injury) has been reported in the HAMMER study within a monotherapy cohort. Investigator's assessment is that it is related to the CRS occurring in the same patient. Sponsor's assessment was that the kidney injury was related to increased fluid losses from persistent fever.	Participants must have appropriate eGFR to be included. Monitor renal function parameters (BUN/urea & creatinine) regularly from screening and throughout the study. Dose modification and treatment guidelines for nephrotoxicity are provide under immune-related reactions in individual substudies.
Neurological AEs, including ICANS	SAR444245 Not observed in non-clinical toxicology studies. A minority of patients in the HAMMER study have reported such AE as detailed in the IB. One SAE of CRS (Grade 4 with 24 ug/kg monotherapy) associated with neurological manifestations [hypertension, chills/rigors, flushing, fever (maximum temperature: 102.8°F), as well as neurological symptomatology (loss of ability to follow commands, confusion, aphasia, and involuntary fist clinching)] was reported in the HAMMER study. The event resolved completely within 30 to 60 minutes after treatment with tocilizumab and steroid. This patient later discontinued the study.	Exclusion of participants with lymphomatous involvement of the central nervous system. Guidelines for the management of ICANS are provided in Table 10.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Cardiovascular effects, including QT interval prolongation	SAR444245 In 28-day repeat-dose study of IV SAR444245 in non-human primates, there were no SAR444245-related changes to the PR or QRS intervals or the heart rate (HR) corrected QTca interval. There was a SAR444245-related, dose dependent, non-adverse higher HR at doses of [redacted] mg/kg/dose beginning on Day 1 compared to the control dose group and persisting through each respective dose following applicable telemetry recording sessions, with recovery. There was also an expected physiologic inverse relationship in the respiration rate (RR) intervals as well as the raw QT intervals, which correlated to the changes in HR, and were also considered to be non-adverse. There were increases in individual females of troponin I minimal post first dose. There were marked decreases in females and males. These changes correlated with findings of mononuclear cell infiltrates and/or myocardial degeneration. All changes however, recovered by the end of a 28 day or 42/44 day treatment free period. A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Routine mitigation: Selection of qualified investigative centers with availability of intensive critical care/equipment. Exclusion of patients with severe or unstable cardiac condition within 6 months prior to starting study treatment. ECG, LVEF, and vital sign monitoring and coagulation tests performed at screening and thereafter as clinically indicated. Monitoring will depend on site assessment of participant's symptoms.
Immune-mediated Adverse Events	SAR444245 A minority of patients in the HAMMER study have reported such AE as detailed in the IB.	Exclusion of participants with: Active, known, or suspected autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). Close monitoring for endocrine abnormalities and other potentially autoimmune phenomena will be performed. Dose modification and treatment guidelines for under immune-related reactions are provided in individual substudies.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	SAR444245 No studies have been conducted with SAR444245 on fertility or general reproductive performance.	Exclusion of participants who are pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial as per inclusion criterion I05. Guidance on highly effective contraceptive methods is provided in the protocol. Pregnancy tests are to be performed regularly as described in Section 8.2.5.
Use in children	The safety and efficacy of the study interventions in children below 18 years of age have not yet been established.	
Participants over 75 years of age	SAR444245 At this stage of development, no safety data are available for this population.	No specific mitigation strategy for this population.
Clinically significant medication errors	With the increased complexity of the design of oncology clinical trials, medication errors need to be considered. Although their occurrence is estimated to be low (eg, chemotherapy errors occur at a rate of about one to four per 1000 orders), their impact may be high. According to the report on medication safety in cancer clinical trials, the processes in which the errors originated were prescribing (47%), administering (10%), dispensing (6%), and monitoring (5%). Prescribing errors typically arise from not following an institutional procedure or the protocol (39%, most likely due to the protocol procedures differing from existing standards of care), followed by the written order (30%), and poor communication involving both the healthcare team and the patient (26%) (29, 30, 31).	Strict adherence to the protocol. Adequate and verified training of staff at investigational sites.
Overdose and its treatment	There is no specific antidote for overdose with SAR444245.	Strict adherence to the protocol; Adequate and verified training of staff at investigational sites. See Section 6.7.
Study procedures		
Biopsies of tumor tissue are expected during the trial.		Strict adherence to the guidance in the protocol

10.13 APPENDIX 13: ASTCT ASSESSMENT FOR ICANS AND CRS

Table 9 - Encephalopathy assessment ICE tool for ICANS Grading

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

Source: (2).

Table 10 - ASTCT ICANS consensus grading for adults

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

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

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

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

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

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

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; EEG = Electroencephalogram; ICANS = Immune effector cell-associated neurotoxicity syndrome; ICE = Immune Effector Cell-Associated Encephalopathy; ICP = Intracranial pressure;
N/A = Not applicable.
Source: (2).

Table 11 - ASTCT CRS consensus grading

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

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

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

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

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

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=Bi-level positive airway pressure CPAP= Continuous Positive Airway Pressure; CRS=Cytokine release syndrome.
Source: (2)

10.14 APPENDIX 14: ABBREVIATIONS

ADA: Anti-drug antibody
ADCC: antibody-dependent cellular-mediated cytotoxicity
ADL: activities of daily living
AE: adverse events
AESI: adverse event of special interest
ALT: alanine aminotransferase
ASCO: American Society of Clinical Oncology
AST: aspartate aminotransferase
ASTCT: American Society for Transplantation and Cellular Therapy
BOR: best overall response
CBR: clinical benefit rate
CI: confidence interval
CLS: capillary leak syndrome
CR: complete response
CRF: case report form
CRS: cytokine release syndrome
CSFs: colony-stimulating factors
[redacted]

DMC:	Data Monitoring Committee
DoR:	duration of response
EBV:	Epstein Barr Virus
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
e-CRF:	electronic case report form
EGFR:	epidermal growth factor receptor
EOT:	end of treatment
ESMO:	European Society for Medical Oncology
FDA:	Food and Drug Administration
HCV:	hepatitis C virus
HIV:	Human immunodeficiency virus
HNSCC:	head and neck squamous cell carcinoma
HPV:	Human Papilloma virus
IAR:	infusion-associated reaction
IB:	Investigator's Brochure
ICANS:	immune cell-associated neurotoxicity syndrome
ICF:	informed consent form
IFNγ:	interferon gamma
IL:	interleukin
ILC:	innate lymphoid cell
IMP:	investigational medicinal product
irAE:	immune-related adverse event
IRR:	infusion-related reaction
LPI:	last patient-in, last patient-in
LVEF:	left ventricular ejection fraction
MCP-1:	monocyte chemoattractant protein-1
MRI:	magnetic resonance imaging
MTD:	Maximum Tolerated Dose
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NHP:	non-human primates
NK:	natural killer
ORR:	objective response rate
[redacted]	
OTC:	over-the-counter
PD:	progressive disease
PD-L1:	programmed death-ligand 1
PDy:	pharmacodynamic
PFS:	progression free survival
PK:	pharmacokinetic
PO:	oral route
PR:	partial response
PT:	preferred term
Q2W:	every 2 weeks
Q3W:	every 3 weeks
QoL:	quality of life

RCC:	renal cell carcinoma
[redacted]	
RP2D:	recommended Phase 2 dose
SAE:	serious adverse events
SAP:	statistical analysis plan
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SB:	Study Board
SD:	stable disease
SoA:	Schedule of Activities
SpO2:	oxygen saturation
TCR:	T cell receptor
TEAEs:	treatment-emergent adverse events
TLS:	tumor lysis syndrome
TTR:	time to response
ULN:	upper limit of normal
US:	United States
VLS:	vascular leak syndrome
WOCBP:	woman of childbearing potential

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (26 July 2021)

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 overall rationale for the amendment is to respond to the Health Authorities (Food and Drug Administration, [FDA]) requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Updated to mark ECG at C1D1.	Regulatory Authority (FDA) request
Section 1.5.1 All Cohorts	The frequency of sampling for PK and ADA has been increased to obtain data every cycle for the first 3 cycles, every other cycle for 4 samples, then every 4th cycle.	Regulatory Authority (FDA) request

Section # and Name	Description of Change	Brief Rationale
Section 4.3 Justification for Dose	Updated based on most recent data.	Regulatory Authority (FDA) request
Section 8.2.3 Electrocardiograms	The following text has been added: "At Cycle Day 1, at pre-dose and at end of SAR444245 infusion, ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals."	Regulatory Authority (FDA) request

Amended protocol 02 (19 August 2021)

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

The main rationale for this amendment is the decision to add a new study cohort (Cohort A2, Substudy protocol 02) to explore the triplet combination of SAR444245 + cetuximab + pembrolizumab in R/M HNSCC treatment-naïve participants for R/M disease. A new substudy protocol (Substudy 02) has been therefore created. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	In the rationale, the following text "for non-alpha IL-2 SAR444245 combined with other anticancer therapies" has been deleted.	For correction and readability
Section 1.1 Synopsis and Section 4.1 Overall Design	A brief description of study phases has been added. Table 1 and Table 3 have been newly added. Subsequent tables have been renumbered. The priority of recruitment for participants eligible to both Cohort A1 and Cohort A2 has been also specified.	To ensure clarity on study conduct and participants recruitment
Section 1.2 Schema and Section 4.1 Overall Design	The name "Study Committee" has been changed to "Study Board". Details describing its composition and role have been provided.	To ensure clarity and avoid confusion with any Independent Committee

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA), Section 5.2 Exclusion Criteria, Section 10.2 Clinical laboratory tests, and Section 10.8 Country-Specific Requirements	Requirement for human immunodeficiency virus (HIV), hepatitis B and C serologies has been added at screening for participants in Germany and specified in exclusion criteria E15 and E16, SoA in a new footnote "f" (subsequent footnotes have been resequenced), laboratory tests and country-specific requirements sections. The following text "in any countries where mandatory as per local requirements" has been removed from footnote "e" of Section 10.2.	To align with standard German Health Authorities requirements
Section 5.2 Exclusion Criteria	The E04 "History of allogenic or solid organ transplant" has been revised to "History of allogenic tissue/solid organ transplant".	For clarification
Section 8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	The following text: "and left ventricular ejection fraction (LVEF)" has been added to the naming of the section. Regarding ECG measurement, "At Cycle Day 1" was changed to "At Cycle 1 Day 1".	For correction and clarification
Throughout the document	Minor editorial corrections have been made.	For consistency

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Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 03 (SUBSTUDY 01)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treatment-naïve participants for R/M disease, programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ≥1**
Protocol number:	**ACT16903-S01**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of R/M HNSCC treatment-naïve participants for R/M disease, PD-L1 CPS ≥1**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	IND156423
EudraCT:	2021-002105-99
NCT:	NCT05061420
WHO:	U1111-1251-5073

Date: 22-Dec-2021 Total number of pages: 64

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03 (Substudy 01)	All	22 December 2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02 (Substudy 01)	All	19 August 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 01)	All	26 July 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 01)	All	11 June 2021, version 1 (electronic 1.0)

Amended protocol 03 (22 December 2021)

This amended protocol (Amendment 03) 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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Spanish (Agency for Medicine and Health Products [AEMPS]), Italian (Medicines Agency [AIFA]) and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA applicable for this substudy has been provided with procedures taken from the master protocol.	For clarity and consistency
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessments of any potential cardiotoxicity
1.4 Biomarker flow-chart and 1.5 Pharmacokinetic flow-chart	Complete biomarker and pharmacokinetic flow-charts applicable for this substudy have been provided with procedures taken from the master protocol.	For clarity and consistency
6.5.3 General guidelines for the management of treatment-related adverse events	As the Study Board does not intervene for this substudy, any reference to it has been removed.	For consistency

Section # and Name	Description of Change	Brief Rationale
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS) and 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	The following statement “or alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following an issue with tocilizumab availability
6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 6 under Grade 4, “signs of” has been removed before “diffuse cerebral edema on neuroimaging”.	Change made for consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus and correction
10.1 Appendix 1: Regulatory, ethical, and study oversight considerations	A new subsection 10.1.6 entitled “Dissemination of clinical study data” has been added with the following text: “Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study”.	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
10.11 Appendix 11: Abbreviations	List of abbreviations has been revised.	For consistency
11 References	List of references has been updated.	For consistency
Throughout the document	Minor editorial corrections were made.	For consistency

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LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy A1-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treatment-naïve participants for R/M disease, PD-L1 CPS ≥1

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of R/M HNSCC treatment-naïve participants for R/M disease, PD-L1 CPS ≥1

Rationale:

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

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with pembrolizumab will result in a significant increase in the percentage of patients with HNSCC experiencing an objective response.

Objectives and endpoints

Please refer to the master protocol for description of objectives and endpoints.

Overall design:

Please refer to the master protocol.

Brief summary:

Cohort A1: This substudy will include participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 Combined Positive Score (CPS) ≥1 and will assess SAR444245 combined with pembrolizumab.

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

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in Cohort A1.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration.

Study intervention(s)

Cohort A1: R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1, SAR444245 + pembrolizumab

Dosing sequence: [redacted]

Investigational medicinal product(s)

Pembrolizumab

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

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

SAR444245

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: 24 μg/kg administered as an IV infusion over 30 mins every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles.**

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

Non-investigational medicinal products

Please refer to the master protocol.

Statistical considerations:

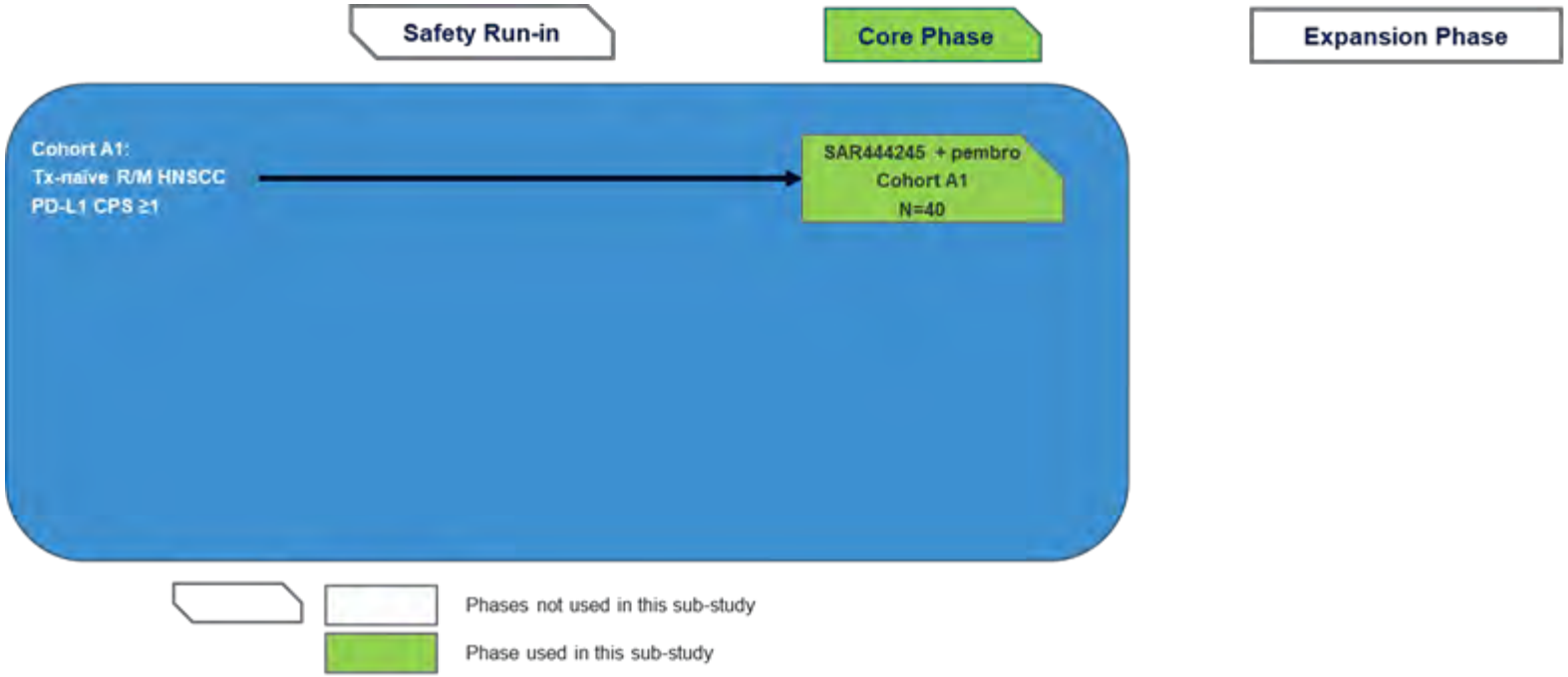
Please refer to the master protocol for description of common statistical considerations.

For Cohort A1, the cohort cut-off for the primary objective response rate (ORR) endpoint analyses is estimated to be approximately 9 months from the date of the last participant's first infusion in the core phase (to document that last participant response is maintained for 6 months in the core phase).

Data Monitoring: Yes

1.2 SCHEMA

Figure 1 - Overall substudy schema



CPS: Combined Positive Score; HNSCC: head and neck squamous cell carcinoma; PD-L1: programmed death ligand 1; pembro: pembrolizumab; Tx: treatment; R/M: recurrent/metastatic.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Elements of the schedule of activities (SoA) common to all cohorts are detailed in the master protocol. Cohort A1-specific evaluations are presented in this table.

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent Inclusion/Exclusion criteria	X											
IRT contact	X	X			X	X	X					
Demography, medical/surgical and disease history	X											See Section 8 of master protocol
Full physical examination	X						X					
Directed physical examination		X	X	X	X	X		X				See Section 8.2.1 of master protocol

Evaluation[a]	**Screening/ baseline**	**Treatment period[b]**					**End of treatment**	**Observation period[c]**			**Survival phone call follow-up period[d]**	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Body weight/Height[e]	X	X			X	X	X	X				
Vital signs	X	X	X	X	X	X	X	X				See Section 8.2.2 & Section 8.2.2 of master protocol
SpO_2	X	As clinically indicated										
Performance status (ECOG)	X	X	X	X	X	X	X	X				
12-lead ECG	X	X	As clinically indicated									See Section 8.2.3 of master protocol
LVEF	X	As clinically indicated										See Section 8.2.3 of master protocol

Evaluation[a]	**Screening/ baseline**	**Treatment period[b]**					**End of treatment**	**Observation period[c]**			**Survival phone call follow-up period[d]**	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Laboratory assessments												
Troponin	X	As clinically indicated				X (D1 Cycle 4)	As clinically indicated					See Section 8.2.3 & Section 10.2 of master protocol
Pregnancy test	X	X			X	X	X	X	X			See Section 8.2.5, Section 8.3.5 & Section 10.2 of master protocol
Blood chemistry/hematology	X	X	X	X	X	X	X	X				See Section 10.2 and Section 10.2 of master protocol

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
T3, FT4, TSH, and cortisol	X				X	X	X	X				See Section 10.2
Coagulation	X	As clinically indicated										See Section 10.2 of master protocol
Urinalysis[k]	X	X				X	X	X				See Section 10.2 of master protocol
Hepatitis serology CD4 counts & Viral Load	X[f]	As clinically indicated										See Section 10.2 of master protocol
HPV p16 status for participants with oropharyngeal cancer	X											

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
PK	See PK Flow-Chart in Section 1.5											
ADA	See PK Flow-Chart in Section 1.5											
Exploratory biomarkers												
PDy - Blood and tumor tissue collection[g]	See Biomarkers Flow-Chart in Section 1.4											
Disease assessment												
CT/MRI[h]	X					X	X	X	X	X		See Section 8.1 of master protocol
Brain imaging[i]	X											See Section 8.1 of master protocol

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
IMP Administration (SAR444245 administration)		X			X	X						
Pembrolizumab Administration		X			X	X						
AE/SAE assessment[i]	X	Continuously throughout treatment period						X				See Section 8.3 of master protocol
Prior medication	(within 28 days prior to first dose)											
Concomitant medication		Continuously throughout treatment period										See Section 6.8 of master protocol

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
First subsequent anticancer therapy							X	X	X	X	X	
Survival status											X	

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

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

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

d **Survival Phone Call Follow-Up Period**: Participant who moves into the Survival Follow-up Period should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

f For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8 of master protocol).

g If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

h **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP or more frequently if clinically indicated in the first 45 weeks. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the **head, neck, chest and abdomen (pelvis is optional)** and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment and during treatment period until PD. After the first documentation of response or the first documentation of progression (if the participant is clinically stable) per RECIST 1.1, confirmatory imaging should be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy.

i **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease as per protocol tumor assessment schedule. In all other cases, the lesions must be treated. Two additional scans obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive systemic therapy during these 4 weeks stabilization at the treating physician's discretion, this systemic therapy will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

j **AE/SAE assessment**: Severity will be graded according to NCI-CTCAE v 5.0, ICANS and cytokine release syndrome (CRS) will be graded using ASTCT criteria integrated with central laboratory cytokine results (1).

k Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; C: Cycle; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; FT4: free thyroxine; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; HPV: Human Papilloma virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; IMP: investigational medicinal product; IRT: Interactive Response Technology; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common terminology criteria for adverse events; PD: progressive disease; PDy: pharmacodynamic; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SpO_2: oxygen saturation; T3: triiodothyronine; TSH: thyroid stimulating hormone.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHART

Cycle	Treatment Cycle 1				Treatment Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	**D1**		**D2**	**D8**	**D1**		
Time after start of SAR444245 dosing	**SOI**	**EOI**	**Any time**	**Any time**	**SOI**	**EOI**	
SAR444245 PK sample		P00[b]	P01			P00[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI).
b EOI samples must be taken at end of infusion (EOI) precisely ±5 minutes.
Abbreviations: ADA: anti-drug antibodies; D: day; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort A1 (participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 CPS ≥1), for the combination of SAR444245 with pembrolizumab.

Please refer to the master protocol for an introduction for ACT16903 study.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+ T cells in murine and NHP models while anti-PD-1 antibody prevents T cell suppression through the PD-1/PD-L1 pathway. The combination of anti-PD-1 treatment with SAR444245 was tested in a syngeneic mouse Ct-26 colon cancer model and demonstrated enhanced anti-tumor activity and prolonged survival compared to each monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

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

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (6, 8, 9, 10). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (11, 12).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (13, 14, 15, 16, 17, 18, 19). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (7, 16, 18, 19, 20). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo. Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab Investigator's brochure [IB]).

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

2.2.2 Rationale for HNSCC and selected participant population

Please refer to the master protocol.

2.2.3 Current standard of care in HNSCC

2.2.3.1 PD1/PD-L1 inhibitor monotherapy or in combination with chemotherapy as first line therapy

Anti-PD-1 therapy has recently been approved in the first line R/M setting. The Phase 3 KEYNOTE-048 trial investigated pembrolizumab as 1st line therapy for the treatment of patients with R/M HNSCC (21, 22). This study randomized 882 patients to receive treatment in one of three arms: pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin or carboplatin and 5-FU) or the EXTREME regimen (cetuximab plus cisplatin or carboplatin and 5-FU).

Pembrolizumab monotherapy significantly prolonged OS in patients with a CPS ≥1 (12.3 versus 10.3 months, respectively; HR 0.78 with 95% confidence interval [CI] 0.64-0.96), and, in all patients irrespective of CPS, was non-inferior to standard of care (SOC) chemotherapy plus cetuximab with a non-inferiority boundary of 1.2. Although patients treated with pembrolizumab monotherapy had a lower ORR compared to patients treated with SOC (23% versus 36% for CPS ≥20, 19% versus 35% for CPS ≥1), duration of response (DOR) in patients treated with pembrolizumab monotherapy was longer compared to SOC for patients with CPS ≥1 (20.9 versus 4.5 months). Overall, treatment with pembrolizumab monotherapy demonstrated a favorable safety profile with lower incidence of any grade, Grade 3-4, and Grade 5 treatment-related adverse events (TRAEs). Moreover, pembrolizumab plus platinum-based chemotherapy versus EXTREME significantly prolonged OS in the total patient population (13.0 versus 10.7 months, respectively; HR 0.77 [95% CI: 0.63-0.93]). There was a similar incidence of TRAEs and no unexpected toxicity due to addition of chemotherapy to checkpoint blockade.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

Risk assessment of SAR444245 combined with pembrolizumab results from anticipated risks for SAR444245 and from the label information for pembrolizumab, taking into account potential overlapping risks. The available safety data for pembrolizumab, along with proposed mitigation strategies are summarized below and also provided in Table 9.

2.3.1.1 Pembrolizumab

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

The use of pembrolizumab may cause infusion-related reactions (IRRs) (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome [CRS]). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

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

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

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

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

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

2.3.1.2 SAR444245 combined with pembrolizumab

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

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

2.3.2 Benefit assessment

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

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

2.3.3 Overall benefit: risk conclusion

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

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

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

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

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of objectives and endpoints.

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 CPS ≥1 and will assess SAR444245 combined with pembrolizumab.

Overall, approximately 40 participants will be enrolled and treated in Cohort A1.

The maximum number of cycles allowed in this Cohort A1 substudy is 35 cycles.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with the anti-PD1 antibody pembrolizumab, will result in a significant increase in the percentage of trial participants with HNSCC experiencing an objective response.

This regimen has been already tested and dose confirmed in first in human HAMMER study, therefore this substudy is designed to treat participants only in a core phase.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5-fold exposure range (refer to the pembrolizumab IB) (23).

- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications.
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

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

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort A1-specific criteria.

5.1 INCLUSION CRITERIA

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

Type of participant and disease characteristics

I 01. PD-L1 expression CPS as determined preferably using a locally approved assay (with an absolute value provided to Sponsor) at local laboratory (for details on PD-L1 assay, please refer to lab manual)

- PD-L1 expression CPS ≥1 (with an absolute value provided to Sponsor).

I 02. Provision of tumor tissue:

- **Mandatory baseline biopsy in Core Phase** (minimum **5 slides with 4-5 micron thickness for the first 20 participants who have signed ICF, excluding screening failure participants, minimum 10 slides with 4-5 micron thickness for subsequent participants**). Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - location of the tumor not amenable to biopsy due to significant risk, OR
  - less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment.

I 03. Prior anticancer therapy

- Have not received prior systemic therapy for **R/M disease**. Participants who received systemic therapy as part of multimodal treatment for locally advanced disease are eligible if the systemic therapy was completed at least 6 months prior to enrollment.

5.2 EXCLUSION CRITERIA

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

Prior/concomitant therapy

E 01. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD-1/PD-L1 in the experimental arm but have written confirmation they have not received anti-PD-1/PD-L1 are allowed).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING [ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION]

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

The maximum number of cycles allowed in this Cohort A1 substudy is 35 cycles.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245, and pembrolizumab administered as described in Section 4.1. Details of each IMP component to be administered are shown in Table 1.

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

Table 1 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	25 mg/mL
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	IMP	IMP
Packaging and labeling	See master protocol	Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	NA	Keytruda

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

6.1.2 Non-investigational medicinal product

Please refer to the master protocol.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

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

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

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

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

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

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

6.5.2 Cycle delay

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

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

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

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

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

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

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

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

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

Recommended guidelines for the management of specific AEs including irAE, CRS, Vascular Leak Syndrome (VLS) and IRRs are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

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

6.5.4.1 Infusion-related reactions (IRR)

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

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

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

infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 2.

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

Guidelines for the management of SAR444245 IRR events are provided in Table 3. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 2 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids, • Antihistamines, • NSAIDs, • Acetaminophen, • Narcotics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; urgent intervention indicated	• Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • Epinephrine*, • IV fluids, • Antihistamines, • NSAIDs, • Acetaminophen, • Narcotics, • Oxygen, • Pressors, • Corticosteroids. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

Table 3 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

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

NCI CTCAE Grade	Treatment
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; urgent intervention indicated	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

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

6.5.4.2 Anaphylaxis

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

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

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

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

Monitoring of vital signs is detailed in Safety Assessments (Section 8.2.2).

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 4. If any grade of CRS is suspected, sites should make every effort to draw an additional blood sample for cytokines levels (by central laboratory) prior to the administration of tocilizumab or alternative therapies per site practice in CRS management, as well as C-reactive protein (CRP) and ferritin (by local laboratory).

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

Guidelines for management of CRS according to severity grading are provided in Table 4. ASTCT CRS consensus grading scale is provided in Section 10.13 of the master protocol.

Table 4 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Increase monitoring of vital signs, cardiac and other organ functions closely as medically indicated until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask	If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 4, permanently discontinue SAR444245. If CRS Grade 3 or Grade 4, initiate IV corticosteroids (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In

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

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
b Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or alternative therapies per site practice in CRS management or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.
d Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

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

6.5.4.4 Immune-related adverse events

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

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. For suspected irAEs, adequate evaluation should be performed to confirm etiology or exclude neoplastic, infectious, metabolic, toxin, or other etiologic causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 5. Of note, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

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

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

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 5 the combination of SAR444245 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 5 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

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

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

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

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

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

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

6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the

ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.13 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab or alternative therapies per site practice in CRS management should only be used in the context of CRS, as outlined in Table 6. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 6 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	Delay SAR444245[a]. Initiate treatment with IV corticosteroids as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	If Grade 3 ICANS, delay SAR444245. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. If Grade 4 ICANS, permanently discontinue SAR444245. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS If there is no clinical improvement within 24 to 72 hours, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants weighing ≥30 kg, total dose should not exceed 800 mg) or alternative therapies per site practice in CRS management should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant clinical specialists should be involved whenever indicated.

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

6.5.4.6 Vascular Leak Syndrome (VLS)

Vascular leak syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic, shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 7. These guidelines are not comprehensive and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (29).

Table 7 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	Delay SAR444245. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, permanently discontinue SAR444245. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
	marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

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

There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical examinations

Please refer to the master protocol.

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively;
  - Vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose.
  - At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring (to be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting).
- **For the core phase participants**: from Cycle 2 to Cycle 4 study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.

8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)

Please refer to the master protocol.

8.2.4 Clinical safety laboratory assessments

Please refer to the master protocol.

8.2.5 Pregnancy testing

Please refer to the master protocol.

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

Please refer to the master protocol.

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

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort A1 irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

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

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Not applicable.

8.3.8 Adverse event of special interest

Please refer to the master protocol.

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

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

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

Sample size:

The plan is to treat a total of 40 participants in Cohort A1. Please refer to the master protocol for details on sample size.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.5 INTERIM ANALYSES

In the core phase, periodic Data Monitoring Committees (DMCs) are planned (details are in the master protocol).

The cohort cut-off for the primary ORR endpoint analysis corresponds to approximately 9 months from the date of the last participant's first infusion (to document that last participant response is maintained for 6 months).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort A1-specific evaluations are presented in Table 8.

Table 8 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

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

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

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Please refer to the master protocol.

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

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245, available information about pembrolizumab is shown in Table 9.

Table 9 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and CRS.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion associated reactions are provided in Table 2.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Hepatotoxicity	Pembrolizumab Pembrolizumab can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent	Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 5.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of pembrolizumab in 0.3% (9) of patients. All patients who were withheld reinitiated pembrolizumab after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.	
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 5.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 5.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 5.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.7.

10.11 APPENDIX 11: ABBREVIATIONS

AEs: adverse events
AESIs: adverse events of special interest
ASTCT: American Society for Transplantation and Cellular Therapy
CI: confidence interval
COVID-19: Coronavirus disease 2019
CPS: Combined Positive Score
CR: complete response
CRS: cytokine release syndrome
CTLA-4: cytotoxic T-lymphocyte-associated protein 4
e-CRF: electronic case report form
EOT: end of treatment
FDA: Food and Drug Administration

HNSCC:	head and neck squamous cell carcinoma
IB:	Investigator's brochure
ICANS:	Immune cell-associated neurotoxicity syndrome
ICU:	intensive care unit
Ig:	immunoglobulin
IMP:	investigational medicinal product
irAEs:	immune-related AEs
IRR:	infusion-related reactions
IV:	intravenous
LVEF:	left ventricular ejection fraction
NCI-CTCAE:	National Cancer Institute- Common Terminology Criteria for Adverse Event
NSCLC:	non-small cell lung cancer
PBPK:	physiologically-based PK
PD1:	programmed cell death-1
PD-L1:	programmed cell death-ligand 1
PD-L2:	programmed cell death ligand 2
PK:	pharmacokinetic
Q2W:	every 2 weeks
Q3W:	every 3 weeks
R/M:	recurrent and/or metastatic
SAEs:	serious adverse events
SoA:	schedule of activities
SOC:	standard of care
TEAE:	treatment-emergent adverse event
TIL:	tumor infiltrating lymphocytes
TRAEs:	treatment-related adverse events
VLS:	Vascular Leak Syndrome

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (26 July 2021)

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 overall rationale for the amendment is to respond to the Health Authorities (Food and Drug Administration, [FDA]) requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4 Guidelines for the management of specific adverse events	For clarity and brevity, command language has been used in the toxicity management sections.	Regulatory Authorities (FDA) request
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 3 the following text has been revised: Under Grade 3 and Grade 4: - "prematurely" deleted from "prematurely permanently discontinued". - "clearly attributable" deleted from "If IRR is clearly attributable to SAR444245" as the table title already indicates treatment with regards to SAR444245 IRRs. Under Grade 2, Grade 3 and Grade 4: "if applicable" deleted in the sentence that reads "SAR444245 infusion should be interrupted if applicable".	Regulatory Authorities (FDA) request
	In Table 2 and Table 3, the following text "requires therapy or infusion interruption" has changed to "Therapy or infusion interruption indicated', and "pressor or ventilator support indicated" has been changed to "urgent intervention indicated".	For consistency with Common terminology criteria for adverse events (CTCAE) guidelines (version 5)
Section 6.5.4.1 Infusion-related reactions (IRR) and Section 10.10 Risk assessment (Table 9)	The text "SAR444245 infusion-associated reaction" was changed to "SAR444245 infusion-related reaction".	For consistency
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 4 the following text "If subsequent administration is tolerated, increasing the SAR444245 dose to [redacted] µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor" has been removed for Grade 3.	Regulatory Authorities (FDA) request
	For Grade 3, the following sentence has been changed from "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1 at [redacted] µg/kg or permanently discontinued, as clinically indicated" to "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated". For Grade 4 "as clinically indicated" has been removed from the subtitle. The following sentence has been added: "Monitoring of vital signs is detailed in Section 8.2.2" for clarity.	For consistency and clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 6 the following text has been added under Grade 3 ICANS: "Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days."	Regulatory Authorities (FDA) request
	The following text "diffuse cerebral edema" has been revised to "signs of diffuse cerebral edema".	For consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus
Sections 8.2.1 Physical examinations, Section 8.2.2 Vital signs, Section 8.2.3 Electrocardiograms, Section 8.2.4 Clinical safety laboratory assessments, and Section 8.2.5 Pregnancy testing	Sections newly inserted.	For clarity
Section 8.2.2 Vital signs	Details regarding monitoring of vital signs provided in the Master protocol have been added.	Regulatory Authorities (FDA) request
Section 10.10: Appendix 10: Risk assessment	In Table 9 assessment under hepatoxicity for pembrolizumab was revised to be aligned with the last version of USPI warnings and precautions for pembrolizumab.	Regulatory Authorities (FDA) request
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

Amended protocol 02 (19 August 2021)

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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to add a new study cohort (Cohort A2, substudy protocol 02) and clarify the priority of recruitment of participants between Cohorts A1 and A2 (see Master protocol). Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Columns indicating D8 (±1) and D15 (±1) for treatment cycle 2 and treatment cycle 3 and beyond were removed.	Change made for correction
	"IMP Administration (SAR444245 Administration)" has been changed to "SAR444245 Administration" with a reference to the master protocol.	Change made for clarification
Section 5.1 Inclusion criteria	In I06 "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment"	Harmonization per program level approach
Section 6.5.2 Cycle delay, and Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following text regarding the treatment resumption after cycle delay has been deleted: "or is stable and manageable through supportive/medical therapy".	Change made for correction
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The name "Study Committee" has been changed to "Study Board".	Change made to ensure clarity and avoid confusion with any Independent Committee
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 3 under Grade 3 and Grade 4, the following text "Interrupt SAR444245 infusion" has been removed.	Change made for clarification
Section 8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	The following text: "and left ventricular ejection fraction (LVEF)" has been added to the naming of the section.	Change made for clarification
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

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Approve & eSign	[redacted] Clinical [redacted]

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AMENDED CLINICAL TRIAL PROTOCOL 01 (SUBSTUDY 02)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab and cetuximab for the treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treatment-naïve participants for R/M disease, programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ≥1**
Protocol number:	**ACT16903-S02**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab and cetuximab for the treatment of R/M HNSCC treatment-naïve participants for R/M disease, PD-L1 CPS ≥1**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

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Date: 22-Dec-2021 Total number of pages: 74

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01 (Substudy 02)	All	22 December 2021, version 1 (electronic 1.0)
Clinical Trial Protocol (Substudy 02)	All	19 August 2021, version 1 (electronic 1.0)

Amended protocol 01 (22 December 2021)

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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Spanish (Agency for Medicine and Health Products [AEMPS]), Italian (Medicines Agency [AIFA]) and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design, and 9.3 Populations for Analyses	The definition of DLT-evaluable participants has been updated to "all participants in the safety run-in part who have been treated and observed for at least 21 days. Any participant who experienced a DLT ~~at any time~~ during the first 21 days will also be DLT-evaluable."	Per harmonization across program
1.3 Schedule of activities (SoA)	Table of SoA for this substudy has been updated with procedures taken from the master protocol. Footnotes have been added and abbreviation list has been updated.	For clarity and consistency
	For electrolytes, "weekly under treatment and then at the EOT, at FU visit 1" has been removed, and a cross has been presented for appropriate times instead.	For clarification
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessments of any potential cardiotoxicity

Section # and Name	Description of Change	Brief Rationale
1.4 Biomarker flow-chart and 1.5 Pharmacokinetic flow-chart	Complete biomarker and pharmacokinetic flow-charts applicable for this substudy have been provided with procedures taken from the master protocol.	For clarity and consistency
1.4 Biomarker flowchart: footnote c, 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS) and 6.5.4.6 Immune Cell-Associated Neurotoxicity Syndrome	[redacted]	[redacted]
1.5.1 A2 Cohort	The cetuximab PK sample identification labelling has been changed from “P00” to “SC00” at start of infusion (SOI) and from “P01” to “SC01” at end of infusion (EOI). The cetuximab PK sample identification labelling “SC02” has been provided at D3 of cycle 1 for participants in the safety run-in who have a Day 3 visit.	Change made for correction and clarity
1.3 Schedule of activities (SoA): footnote f, 5.1 Inclusion Criteria: I03 and 10.7.1 Amendment for Germany	The following country-specific requirement has been added: “German participants will not be enrolled in Cohort A2 substudy 02”.	To specify that German participants cannot be included in this substudy
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	Information on cytokine-release syndrome (CRS) reported with cetuximab and recommended guidelines for management have been added. A column mentioning "Recommended Cetuximab dose modifications and supportive care guidelines" has been added to Table 9.	To add recommended guidelines for management of CRS reported with cetuximab
6.5.4.6 Immune Cell-Associated Neurotoxicity Syndrome	In Table 12 under Grade 4, “signs of” has been removed before “diffuse cerebral edema on neuroimaging”.	Change made for consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus and correction
10.1 Appendix 1: Regulatory, ethical, and study oversight considerations	A new subsection 10.1.6 entitled “Dissemination of clinical study data” has been added with the following text: “Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study”.	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
10.10 Appendix 10: Risk assessment	The following wording has been added: “For pembrolizumab and cetuximab, the information below is per currently available USPI and EU SmPC. Please always refer to the latest version of the SAR444245 IB and pembrolizumab and/or cetuximab local label for the most up-to-date safety data”.	To refer to the latest version of IB or local label for the safety data
10.11 Appendix 11: Abbreviations	List of abbreviations has been revised.	For consistency
11 References	List of references has been updated.	For consistency
Throughout the document	Minor editorial corrections were made.	For consistency

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy A2-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab and cetuximab for the treatment of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treatment-naïve participants for R/M disease, programmed cell death-ligand 1 (PD-L1) combined positive score (CPS) ≥1

Brief title: A study of SAR444245 combined with pembrolizumab and cetuximab for the treatment of R/M HNSCC treatment-naïve participants for R/M disease, PD-L1 CPS ≥1

Rationale:

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

Collectively, the combination of SAR444245 with pembrolizumab and cetuximab is supported by: a) increase in natural killers (NK) cells by SAR444245 b) the ability of cytokines such as IL-2 to improve the antibody-dependent cellular cytotoxicity (ADCC) response of cetuximab and c) addition of an anti-PD-1 to prevent PD-1/L-1 inhibition of infiltrating cytotoxic immune cells.

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with pembrolizumab and cetuximab will result in a significant increase in the percentage of patients with HNSCC experiencing an objective response.

Objectives and endpoints

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

Table 1 - Objectives and endpoints

Objectives	Endpoints
Secondary	
To confirm the dose of SAR444245 when combined with cetuximab and pembrolizumab	Incidence of dose-limiting toxicities (DLT)
To assess the concentrations of cetuximab	Concentrations of cetuximab

Overall design:

Please refer to the master protocol.

Brief summary:

Cohort A2: This substudy will include participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 CPS ≥1 and will assess SAR444245 combined with pembrolizumab and cetuximab.

A safety run-in will confirm the dose of SAR444245 when combined with pembrolizumab and cetuximab in a sample of at least 6 participants. After recruitment of the first 10 participants, enrollment will be paused if a total of at least 6 participants are evaluable for dose-limiting toxicities (DLT). Safety data for these participants will be reviewed by the Study Board (SB) comprising the Investigators or designees participating in the safety run-in part of the trial and the Sponsor clinical team members. DLT-evaluable participants include all participants in the safety run-in part who have been treated and observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. If no safety concerns are identified by the SB, participant enrollment will continue.

If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from Study Board. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants.

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an IV infusion over 30 minutes every 3 weeks (Q3W) on Day 1 of each cycle (21 days per cycle). Overall safety monitoring will be performed throughout the study. If recommended by the SB, SAR444245 dose may be reduced to [redacted]µg/kg or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

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

Dose limiting toxicity: Selected events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to study drugs. Please refer to the full list of events in Section 4.1. Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the Study Board will determine if the dose of SAR444245 needs to be reduced to [redacted] µg/kg or another lower dose level, in agreement with the Sponsor.

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

Number of participants:

Overall, approximately 40 participants will be enrolled and treated at the confirmed safe dose in Cohort A2.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration.

Study intervention(s)

Cohort A2: R/M HNSCC treatment-naïve for R/M disease, PD-L1 CPS ≥1, SAR444245 + pembrolizumab + cetuximab

Dosing sequence: [redacted]

Investigational medicinal product(s)

Pembrolizumab

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

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

Cetuximab

- **Formulation**:
  - a clear, colorless solution for injection provided as 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL in a single-dose vial

  or

  - 100 mg/20 mL or 500 mg/100 mL

  or

  - any other cetuximab formulation approved locally.
- **Route of administration:** IV infusion.
- **Dose regimen**: cetuximab will be given on Cycle 1 Day 1 as an initial loading dose of 400 mg/m^2 infused over 120 minutes (maximum infusion rate 10 mg/min or as per local practice and labels) followed by weekly 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for all subsequent doses starting with the Cycle 1 Day 8 administration, **until progressive disease (PD)**.

SAR444245

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: IV infusion.
- **Dose regimen**: 24 µg/kg (or reduced to [redacted]µg/kg Q3W or another lower dose level recommended by Study Board) administered as an IV infusion over 30 mins every 3 weeks on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles.**

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

Non-investigational medicinal products

Please refer to the master protocol for SAR444245 premedication.

Premedication for cetuximab

All participants who will receive cetuximab should be pre-medicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab, or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions (IR).

When SAR444245 and cetuximab are given on the same day, participants who have received diphenhydramine as cetuximab premedication may skip the diphenhydramine as SAR444245 premedication.

Statistical considerations:

Please refer to the master protocol for description of common statistical considerations. Cohort A2 specific analysis:

- **Analysis of other secondary endpoints:**

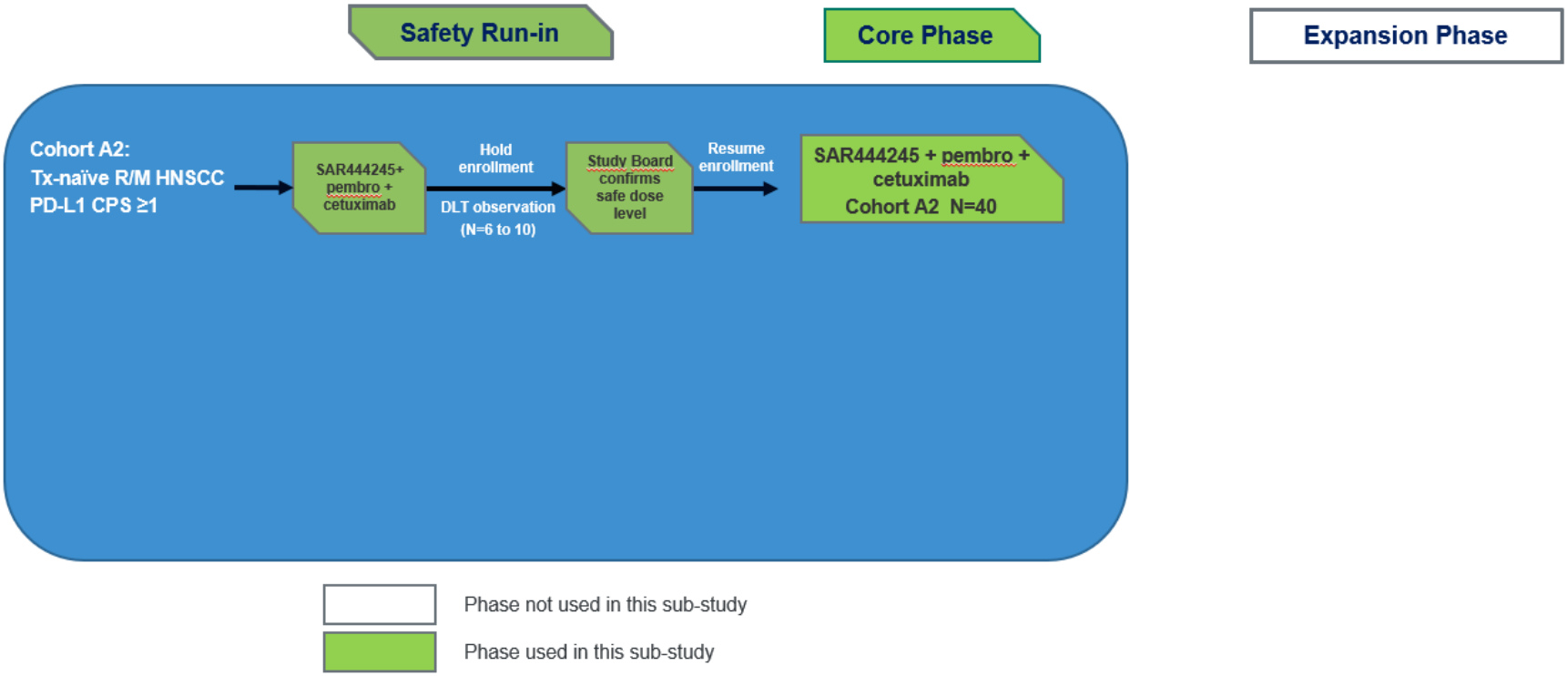
Plasma concentrations of cetuximab will be summarized with descriptive statistics.

For Cohort A2, the cohort cut-off for the primary objective response rate (ORR) endpoint analyses is estimated to be approximately 9 months from the date of the last participant's first infusion in the core phase (to document that last participant response is maintained for 6 months in the core phase).

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Overall Substudy schema



CPS: Combined Positive Score; HNSCC: head and neck squamous cell carcinoma; N: number of participants; PD-L1: programmed death ligand 1; pembro: pembrolizumab; Tx: treatment; R/M: recurrent/metastatic.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Elements of the schedule of activities (SoA) common to all cohorts are detailed in the master protocol. Cohort A2-specific evaluations are presented in this table.

Evaluation[a]	**Screening /baseline**	**Treatment period**[b]											**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1					**Treatment Cycle 2**			**Treatment Cycle 3 and beyond**			**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3**[l]	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent Inclusion/Exclusion criteria	X																	
IRT contact	X	X					X			X			X					
Demography, medical/surgical and disease history	X																	See Section 8 of master protocol
Full physical examination	X												X					
Directed physical examination		X	X	X	X	X	X			X				X				See Section 8.2.1 of master protocol
Body weight/Height[e]	X	X					X			X			X	X				

Evaluation[a]	Screening /baseline	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1					Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[l]**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X				See Section 8.2.2 of master protocol & Section 8.2.2
SpO_2	X	As clinically indicated																
Hospitalization[m]		X																
Performance status (ECOG)	X	X			X	X	X			X			X	X				
12-lead ECG	X	X	As clinically indicated															See Section 8.2.3 of master protocol
LVEF	X	As clinically indicated																See Section 8.2.3 of master protocol
Laboratory assessments																		
Troponin	X	As clinically indicated								X (D1 Cycle 4)			As clinically indicated					See Section 8.2.3 & Section 10.2 of master protocol
Pregnancy test	X	X					X			X			X	X	X			See Section 8.2.5, Section 8.3.5 & Section 10.2 of master protocol
Blood chemistry/ hematology	X	X			X	X	X	X	X	X	X	X	X	X				See Section 10.2 of master protocol
Electrolytes	X	X			X	X	X	X	X	X	X	X	X	X	as clinically indicated			

Evaluation[a]	Screening /baseline	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1					Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[l]**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
T3, FT4, TSH, and cortisol	X						X			X			X	X				See Section 10.2
Coagulation	X	As clinically indicated																See Section 10.2 of master protocol
Urinalysis[k]	X	X								X			X	X				See Section 10.2 of master protocol
Hepatitis serology CD4 counts & Viral Load	X[f]	As clinically indicated																See Section 10.2 of master protocol
HPV p16 status for participants with oropharyngeal cancer	X																	
PK	See PK Flow-Chart in Section 1.5																	
ADA	See PK Flow-Chart in Section 1.5																	
Exploratory biomarkers																		
PDy - Blood and tumor tissue collection[g]	See Section 1.4																	

Evaluation[a]	Screening /baseline	Treatment period[b]											End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1					Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D2**	**D3[l]**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Disease assessment																		
CT/MRI[h]	X									X			X	X	X	X		See Section 8.1 of master protocol
Brain imaging[i]	X																	See Section 8.1 of master protocol
SAR444245 administration		X					X			X								
Cetuximab administration		X			X[n]	X[n]	X	X[n]	X[n]	X	X[n]	X[n]						
Pembrolizumab administration		X					X			X								
AE/SAE assessment[j]	X	Continuously throughout treatment period												X				See Section 8.3 of master protocol
Prior medication	X (within 28 days prior to first dose)																	
Concomitant medication		Continuously throughout treatment period																See Section 6.8 of master protocol
First subsequent anticancer therapy													X	X	X	X	X	
Survival status																	X	

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

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

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

d **Survival Phone Call Follow-Up Period**: Participant who moves into the Survival Follow-up Period should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

f For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany (See wording specific to Germany in Section 10.7.1) and Italy (see details and specific instructions in Section 10.2 and Section 10.8 of master protocol).

g If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

h **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP or more frequently if clinically indicated in the first 45 weeks. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the **head, neck, chest and abdomen (pelvis is optional)** and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment and during treatment period until PD. After the first documentation of response or the first documentation of progression (if the participant is clinically stable) per RECIST 1.1, confirmatory imaging should be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy.

i **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease as per protocol tumor assessment schedule. In all other cases, the lesions must be treated. Two additional scans obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive systemic therapy during these 4 weeks stabilization at the treating physician's discretion, this systemic therapy will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

j **AE/SAE assessment**: Severity will be graded according to NCI-CTCAE v 5.0, ICANS and cytokine release syndrome (CRS) will be graded using ASTCT criteria integrated with central laboratory cytokine results (1).

k Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

l Visit and assessments on C1D3 are only for participants in the safety run-in.

m Only for safety run-in participants.

n Cetuximab dosing only.

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; C: Cycle; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; FT4: free thyroxine; FU: follow-up; HPV: Human Papilloma virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; IMP: investigational medicinal product; IRT: Interactive Response Technology; LVEF; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common terminology criteria for adverse events; PD: progressive disease; PDy: pharmacodynamic; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SpO_2: oxygen saturation; T3: triiodothyronine; TSH: thyroid stimulating hormone.

1.4 BIOMARKER FLOWCHART

Cohort A2-specific samplings are presented in the table below:

1.5 PHARMACOKINETIC FLOWCHART

1.5.1 A2 Cohort

Cycle	Treatment Cycle 1					Treatment Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	**D1**		**D2**	**D3**[c]	**D8**	**D1**		
Time after start of SAR444245 dosing	**SOI**	**EOI**	**Any time**	**Any time**	**Any time**	**SOI**	**EOI**	
SAR444245 PK sample		P00[b]	P01				P00[b]	
SAR444245 ADA sample	AB00[a]				AB01	AB00[a]		ABF00
Time after start of dosing cetuximab	**SOI**	**EOI**	**D2**	**D3**[c]	**D8**	**SOI**	**EOI**	
Cetuximab PK sample	SC00[a]	SC01[b]		SC02[a]		SC00[a]	SC01[b]	

a Samples collected strictly before start of infusion (SOI).
b EOI samples must be taken at end of infusion (EOI) precisely ±5 minutes.
c Day 3 sampling only for participants in the safety run-in who have a Day 3 visit.
Abbreviations: ADA: anti-drug antibodies; D: day; EOI: end of infusion; EOT: end of treatment; PK: pharmacokinetic; SOI: start of infusion.

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort A2 (participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 CPS ≥1), for the combination of SAR444245 with pembrolizumab and cetuximab.

Please refer to the master protocol for an introduction for ACT16903 study.

2.1 STUDY RATIONALE

2.1.1 Cohort A2: triplet combination of SAR444245, pembrolizumab and cetuximab

Clinical data from the on-going monotherapy dose escalation of SAR444245 has indicated a peripheral increase in the number of NK cells. NK cells are an important effector cells which mediate ADCC for immunoglobulin G1 (IgG1) antibodies such as cetuximab. Furthermore, in vitro data have shown that NK-cell-mediated lysis of head and neck tumor cells is significantly enhanced by the combination of cetuximab therapy with immune stimulatory cytokines, including IL-2 (2). This was demonstrated in SAR444245 in vitro studies, where NK cells pretreated with SAR444245 and then co-cultured with the Epithelial Growth Factor Receptor (EGFR)-expressing CAL27 cancer cells improved the ADCC function of cetuximab in a dose-dependent fashion. Cetuximab can prime the immune system for anti-PD-1 therapy by recruiting cytotoxic cell effectors of both the innate and adaptive immune systems to the intratumoral space (3). Additionally, associated negative feedback loops lead to upregulation of PD-1/PD-L1-mediated immunosuppression of active cytotoxic cell types, an issue that could be overcome successfully via combination therapy with anti-PD-1. Collectively, the combination of SAR444245 with pembrolizumab and cetuximab is supported by: a) increase in NK cells by SAR444245 b) the ability of cytokines such as IL-2 to improve the ADCC response of cetuximab and c) addition of an anti-PD-1 to prevent PD-1/L-1 inhibition of infiltrating cytotoxic immune cells.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

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

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (4). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (5, 6).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (7, 8)

The structure of murine PD1 has been resolved (9). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (8, 10, 11, 12). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (13, 14).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (15, 16, 17, 18, 19, 20, 21). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (9, 18, 20, 21, 22). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (20). Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab Investigator's brochure [IB]).

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

2.2.2 Cetuximab

Cetuximab is an IgG1 monoclonal antibody against the ligand binding domain of EGFR, which is abnormally activated in many epithelial cancers including colorectal cancer (23). The mechanism of action of cetuximab appears to include antibody dependent cell mediated cytotoxicity (24) in addition to EGFR blockade, which may contribute to its efficacy and may be further exploited. Erbitux (Cetuximab) is indicated for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil. It is also indicated for the treatment of R/M squamous cell carcinoma of the head and neck.

2.2.3 Rationale for HNSCC and selected participant population

Please refer to the master protocol.

2.2.4 Current standard of care in HNSCC

2.2.4.1 PD1/PD-L1 inhibitor monotherapy or in combination with chemotherapy as first line therapy

Anti-PD-1 therapy has recently been approved in the first line R/M setting. The Phase 3 KEYNOTE-048 trial investigated pembrolizumab as 1st line therapy for the treatment of patients with R/M HNSCC (25, 26). This study randomized 882 patients to receive treatment in one of three arms: pembrolizumab monotherapy, pembrolizumab plus chemotherapy (cisplatin or carboplatin and 5-FU) or the EXTREME regimen (cetuximab plus cisplatin or carboplatin and 5-FU).

Pembrolizumab monotherapy significantly prolonged OS in patients with a CPS ≥1 (12.3 versus 10.3 months, respectively; HR 0.78 with 95% confidence interval [CI] 0.64-0.96), and, in all patients irrespective of CPS, was non-inferior to standard of care (SOC) chemotherapy plus cetuximab with a non-inferiority boundary of 1.2. Although patients treated with pembrolizumab monotherapy had a lower ORR compared to patients treated with SOC (23% versus 36% for CPS ≥20, 19% versus 35% for CPS ≥1), duration of response (DOR) in patients treated with pembrolizumab monotherapy was longer compared to SOC for patients with CPS ≥1 (20.9 versus 4.5 months). Overall, treatment with pembrolizumab monotherapy demonstrated a favorable safety profile with lower incidence of any grade, Grade 3-4, and Grade 5 treatment-related adverse events (TRAEs). Moreover, pembrolizumab plus platinum-based chemotherapy versus EXTREME significantly prolonged OS in the total patient population (13.0 versus 10.7 months, respectively; HR 0.77 [95% CI: 0.63-0.93]). There was a similar incidence of TRAEs and no unexpected toxicity due to addition of chemotherapy to checkpoint blockade.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

Risk assessment of SAR444245 combined with pembrolizumab and cetuximab results from anticipated risks for SAR444245 and from the label information for Keytruda® (pembrolizumab) and Erbitux® (cetuximab), taking into account potential overlapping risks. The available safety data for pembrolizumab and cetuximab, along with proposed mitigation strategies are summarized below and also provided in Table 16.

2.3.1.1 Pembrolizumab

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

The use of pembrolizumab may cause infusion-related reactions (IRRs) (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome [CRS]). Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy (common). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated AEs are designated as important identified risk for pembrolizumab (27).

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

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

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

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

2.3.1.2 Cetuximab

The important identified risks for cetuximab include, but are not limited to: IRs (including anaphylaxis on the first dose); interstitial lung disease (ILD), severe adverse skin reactions (with increased risk of secondary bacterial infection), electrolyte disturbances (hypomagnesemia, hypokalemia, hypocalcemia) cardiac AEs (including cardiopulmonary arrest/sudden death), and eye disorders (including ulcerative keratitis).

The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The following precautions and warnings are to be acknowledged:

Cetuximab can cause serious and fatal IRs. Infusion reactions (IRs) of any grade occurred in 8.4% of patients who received cetuximab across clinical trials. Grades 3 and 4 IRs occurred in 2.2% of patients. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of immunoglobulin E (IgE) antibodies directed against galactose-α-1,3-galactose (alpha-gal). Approximately 90% of severe IRs occurred with the first infusion despite premedication with antihistamines. Infusion reactions (IRs) may occur during or several hours following completion of the infusion. Premedication with a histamine-1 (H1) receptor antagonist is recommended together with monitor patients for at least 1 hour following each infusion.

Cardiopulmonary arrest or sudden death have occurred in 2%-3% patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil cetuximab. A history of coronary artery disease, congestive heart failure, or arrhythmias and abnormal serum electrolytes may be predisposing factors.

Interstitial lung disease that may be fatal has occurred in <0.5% of patients receiving cetuximab in clinical trials.

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of patients across clinical trials. Grades 3 or 4 acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping treatment in

most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis).

Cetuximab can cause hypomagnesemia which occurred in 55% patients in various clinical trials, including Grades 3 and 4 in 6% to 17%. Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating treatment. It is recommended to monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of treatment and to replete electrolytes as necessary.

Based on animal data and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys resulted in an increased incidence of embryo-lethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development.

Please refer to the country-approved cetuximab labeling (eg, USPI, SmPC) for more detailed prescribing information.

2.3.1.3 SAR444245 combined with pembrolizumab and cetuximab

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

As all three substances are biologic agents, they may have the propensity to induce IRR that may have higher rate of occurrence and severity when SAR444245 with pembrolizumab or cetuximab are used in combination.

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

Data from the combination in Phase 2 study pembrolizumab plus cetuximab in R/M HNSCC are very promising, with a manageable safety profile and encouraging ORR (28).

2.3.2 Benefit assessment

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

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

Preclinical and preliminary clinical data indicates that SAR444245 expands NK cells which are important effector cells mediating ADCC for IgG1 antibodies such as cetuximab. In vitro experiments show that SAR444245 improved the ADCC function of cetuximab in a dose-dependent fashion.

Head and neck squamous cell carcinoma is a tumor type that benefits from immune checkpoint inhibitor (ICI) and cetuximab treatment. The companion ICI (anti-PD1) pembrolizumab and cetuximab to be combined with SAR444245 in this study is approved to treat various disease settings of HNSCC either as a monotherapy or in combination with chemotherapy.

2.3.3 Overall benefit: risk conclusion

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

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

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

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was explored by 2 groups who did not find a clinically meaningful signal (29, 30).

3 OBJECTIVES AND ENDPOINTS

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

Table 2 - Objectives and endpoints

Objectives	Endpoints
Secondary	
To confirm the dose of SAR444245 when combined with cetuximab and pembrolizumab	Incidence of dose-limiting toxicities (DLT)
To assess the concentrations of cetuximab	Concentrations of cetuximab

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include participants with HNSCC who are treatment-naïve for R/M disease, PD-L1 CPS ≥1 and will assess SAR444245 combined with pembrolizumab and cetuximab.

Overall, approximately 40 participants will be enrolled and treated at the confirmed safe dose in Cohort A2.

The maximum number of cycles allowed in this Cohort A2 substudy is 35 cycles for SAR444245 and pembrolizumab, and until PD for cetuximab.

A safety run-in will confirm the dose of SAR444245 when combined with pembrolizumab and cetuximab in a sample of at least 6 participants. After recruitment of the first 10 participants, enrollment will be paused if a total of at least 6 participants are evaluable for DLT. Safety data for these participants will be reviewed by the Study Board comprising the Investigators or designees participating in the safety run-in part of the trial and the Sponsor clinical team members DLT-evaluable participants include all participants in the safety run-in part who have been treated and observed for at least 21 days. Any participant who experienced a DLT during the first 21 days will also be DLT-evaluable. If no safety concerns are identified by the Study Board, participant enrollment will continue.

If after recruiting the first 10 participants there are fewer than 6 participants evaluable for DLT, more participants will be enrolled to ensure at least 6 DLT evaluable participants after agreement from Study Board. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants.

The SAR444245 dose to be confirmed is 24 µg/kg, administered as an IV infusion over 30 minutes every 3 weeks on Day 1 of each cycle (21 days per cycle). Overall safety monitoring will be performed throughout the study. If recommended by the Study Board, SAR444245 dose may be reduced to [redacted] µg/kg or another lower dose level which will be explored following the same process described in the safety run-in for 24 µg/kg dose level.

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

0.35 indicate dose de-escalation. The interval with the largest UPM is the winning interval and implies the corresponding dose escalation/de-escalation decision. For the safety run-in part of the study, mTPI2 rules (see Table 3) will be applied as follows, unless decided otherwise by the Study Board:

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

Table 3 - Dose escalation rule of the modified toxicity probability interval-2 method

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

E: Escalate to the next higher dose, S: Stay at the current dose, D: De-escalate to the next lower dose, DU: De-escalate to the next lower dose and the current dose will never be used again because unacceptable high toxicity.

Dose limiting toxicity: The following events occurring during the DLT observation period (21 days of first cycle) are considered as DLT unless due to disease progression or to a cause obviously unrelated to study drugs. Please refer to the list of events as below. Based on the occurrence of DLT and overall assessment of safety data supplemented with data from other SAR444245 studies, the Study Board will determine if the dose of SAR444245 needs to be reduced to [redacted] µg/kg Q3W or another lower dose level, in agreement with the Sponsor.

Hematologic abnormalities:

- Grade 4 neutropenia for ≥7 consecutive days
- Grade 3 or 4 neutropenia complicated by fever (temperature of >38.3°C [101°F] or a sustained temperature of ≥38.0°C [100.4°F] for more than 1 hour) or microbiologically or radiographically documented infection.
- Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding requiring clinical intervention.

Non-hematologic abnormalities:

- Grade 3 or above alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with a bilirubin >2 times upper limit of normal (ULN) with no evidence of cholestasis or another cause such as viral infection or other drugs
- Grade 3 or above Vascular Leak Syndrome (VLS)
- Grade 3 or above hypotension
- Grade 3 or above cytokine release syndrome
- Other Grade 3 or above AE except:
  - Grade 3 fatigue that resolves within 1 week
  - Grade 3 nausea, vomiting, or diarrhea that resolves within 72 hours with antiemetics and standard supportive care measures
- Any Grade 3 non-hematologic laboratory value

Exceptions:

- Grade 3 electrolyte abnormalities that are not clinically complicated and resolve within 72 hours with conventional medical interventions.
- Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.

- Any Grade 4 non-hematologic laboratory value.

Other abnormalities:

- Any death not clearly due to the underlying disease or extraneous causes.
- Any toxicity requiring permanent discontinuation of the study drug(s).
- More than 1 missing dose of cetuximab due to toxicity.

Participants who are treated at the confirmed safe dose in the safety run-in of Cohort A2 will be included in the total number of participants for Cohort A2.

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

Study Board

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with pembrolizumab and cetuximab, will result in a significant increase in the percentage of trial participants with HNSCC experiencing an objective response.

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

The design of the study is an open-label study where the experimental combination will be assessed in a single cohort to show outstanding ORR. The ORR will be assessed using RECIST 1.1 for participants with R/M HNSCC.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

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

4.3.3 Cetuximab dose

This study proposes to evaluate the clinical benefit of 24 µg/kg SAR444245 Q3W combined with pembrolizumab at the dose of 200 mg every 3 weeks (Q3W) and the approved dose of 400 mg/m² cetuximab as an IV infusion on day 1 of the study followed by subsequent doses of 250 mg/m² cetuximab IV QW.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort A2-specific criteria.

5.1 INCLUSION CRITERIA

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

Type of participant and disease characteristics

I 01. PD-L1 expression CPS as determined (with an absolute value provided to Sponsor) at local laboratory (for details on PD-L1 assay, please refer to lab manual)

- PD-L1 expression CPS ≥1 (with an absolute value provided to Sponsor).

I 02. Provision of tumor tissue:

- **Mandatory baseline biopsy in Core Phase** (minimum **5 slides with 4-5 micron thickness for the first 20 participants who have signed ICF (excluding screening failure participants), minimum 10 slides with 4-5 micron thickness for subsequent participants**). Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - location of the tumor not amenable to biopsy due to significant risk, OR
  - less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment.

I 03. Prior anticancer therapy

- Have not received prior systemic therapy for **R/M disease**. Participants who received systemic therapy as part of multimodal treatment for locally advanced disease are eligible if the systemic therapy was completed at least 6 months prior to enrollment (See wording specific to Germany in Section 10.7.1).

5.2 EXCLUSION CRITERIA

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

E 01. Electrolytes (magnesium, calcium, and potassium) outside the normal ranges.

Prior/concomitant therapy

E 02. Prior treatment with an agent (approved or investigational) that blocks the PD-1/PD-L1 pathway (participants who joined a study with an anti-PD-1/PD-L1 in the experimental arm but have written confirmation they have not received anti-PD-1/PD-L1 are allowed).

E 03. Prior treatment with cetuximab (prior cetuximab allowed if used for the treatment of locally advanced disease, with no PD for at least 4 months from completion of prior cetuximab therapy).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING [ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION]

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

The maximum number of cycles allowed in this Cohort A2 substudy is 35 cycles for SAR444245 and pembrolizumab, and until PD for cetuximab.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245, cetuximab and pembrolizumab administered as described in Section 4.1. Details of each IMP component to be administered are shown in Table 4.

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

Table 4 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab	Cetuximab
Type	See master protocol	Biologic	Biologic
Dose formulation	See master protocol	Solution for infusion	Solution for infusion
Unit dose strength(s)	See master protocol	25 mg/mL	100 mg/ 50 mL (2 mg/mL)
Dosage level(s)[a]	24 µg/kg Q3W (or reduced to [redacted] µg/kg Q3W or another lower dose level recommended by Study Board)	200 mg Q3W	400 mg/m^2 C1D1 and QW 250 mg/m^2 at C1D8 and subsequent administrations
Route of administration	See master protocol	IV infusion	IV infusion
Use	See master protocol	Treatment of cancer (combination)	Treatment of cancer (combination)
IMP or NIMP	IMP	IMP	IMP

Intervention name	SAR444245	Pembrolizumab	Cetuximab
Packaging and labeling	See master protocol	Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.	Supplied as 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL in a single-dose vial or 100 mg/20 mL or 500 mg/100 mL or any other formulation approved locally.
Current/Former name(s) or alias(es)	NA	Keytruda	Erbitux

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the electronic case report form (e-CRF). For SAR444245 and pembrolizumab, study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes -5 min/+10 min).

6.1.2 Non-investigational medicinal product

Please refer to the master protocol for SAR444245 premedication.

Premedication for cetuximab

All participants who will receive cetuximab should be pre-medicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab, or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior IRs.

When SAR444245 and cetuximab are given on the same day, participants who have received diphenhydramine as cetuximab premedication may skip the diphenhydramine as SAR444245 premedication

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 is permitted according to the guidelines described in this section. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Dose modifications for cetuximab are permitted, and modification of dose levels in case of dose reduction is described in Table 5.

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

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

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

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

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

6.5.2 Cycle delay and dose omission

The treatment window is ±3 days for each of the Q3W IMP administrations. The treatment window is ±1 day for cetuximab administration on Day 8 and Day 15 of each cycle.

A cycle is deemed to have been delayed if the treatment is administered ≥4 days beyond the theoretical day of Q3W IMP administration. The participant may receive the next dose after recovery from the toxicity as described in Section 6.5.3. After cycle delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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

- For Q3W IMP administration: If toxicity occurs and the participant does not recover on the day of planned administration; restart of study IMPs could occur only on the initiation of the subsequent cycle.
- For cetuximab Day 8 and Day 15 administration in each cycle: if toxicity occurs and the patient does not recover on the day of planned infusion or within the following 3 days, infusion may be omitted.
- In case of cycle delay or dose omissions for the recovery of toxicity, the following rules should be followed for restart or discontinuation of the treatment:
  - In case of a cycle delay up to 14 days or a dose omission, it is per Investigator's decision to restart the study treatment.
  - After a cycle delay of >14 days and ≤84 days, or 2 to 4 consecutive dose omissions, it is per Investigator's decision to restart the study treatment or the IMP that is omitted, if a clear benefit from treatment is observed and after consultation with the Sponsor.
  - The study treatment must be permanently discontinued if the cycle delay is longer than 84 days.
  - For any delayed cetuximab treatment, do not repeat the initial dose of 400 mg/m². At the restart of cetuximab treatment, all subsequent infusions will be at the appropriate dose level according to Table 5.
- Cycle delay or dose omission may be considered may be interrupted for situations other than TEAEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled delay or dose omission, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for this delay or dose omission should be documented in the participant's study record.

Modification of dose levels in case of dose reduction

Dose reduction steps for cetuximab are shown in Table 5. One or several doses of cetuximab can be omitted.

Table 5 - Dose levels for cetuximab dose reduction

Starting dose	Dose level 1	Dose level 2
400 mg/m² then 250 mg/m²	200 mg/m² (20% decrease)	150 mg/m² (20% decrease)

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

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

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

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

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

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

Recommended guidelines for the management of specific AEs including irAE, CRS, VLS and IRR are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

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

6.5.4.1 Infusion-related reactions

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-related infusion reaction are provided in Table 6.

Table 6 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

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

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v 5.0 (CTCAE) at http://ctep.cancer.gov.

Participants who experience cetuximab-related infusion reactions should have cetuximab reduced according to Table 7 and continue to receive antihistamine premedication prior to administration. Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it should remain decreased for all subsequent infusions. If the participant experiences a second infusion reaction at the decreased rate, cetuximab should be permanently discontinued. If any Grade 3-4 infusion reaction occurs, cetuximab treatment should be discontinued immediately and permanently.

Severe infusion-related reactions, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a CRS. Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions.

Table 7 - Cetuximab Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Dose modification
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop cetuximab infusion and administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; urgent intervention indicated	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. Permanently discontinue Cetuximab. The participant can continue treatment with pembrolizumab or SAR444245.

Abbreviations: CTCAE = Common terminology criteria for adverse events; IRR = Infusion related reaction; NCI = National Cancer Institute.

Guidelines for the management of SAR444245 IRR events are provided in Table 8. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 8 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	If IRR happens during infusion, continuation of SAR444245[a] infusion is per Investigator's judgment following close direct monitoring of the participant's clinical status. SAR444245 infusion may be interrupted at any time if deemed necessary. If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE definition. If IRR happens after completion of infusion, increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Interrupt SAR444245 infusion. If symptoms resolve within 1 hour of interrupting drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the participant will be premedicated for the next scheduled dose according to Section 6.1.2.1 of the master protocol. Give the next infusion at half the infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; urgent intervention indicated	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

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

6.5.4.2 Anaphylaxis

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

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines in (14, 31, 32).

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

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

Monitoring of vital signs is detailed in Safety Assessments (Section 8.2.2).

Cetuximab may be associated with CRS. Cytokine-release syndrome typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. Cytokine-release syndrome is normally most severe in relation to the first infusion of cetuximab. Cetuximab related IRRs, including CRS, are discussed in Section 6.5.4.1 of the protocol. Please refer to Table 7 for Cetuximab IRR dose modifications and treatment guidelines.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 9. If any grade of CRS is suspected, sites should make every effort to draw an additional blood sample for cytokines levels (by central laboratory) prior to the administration of tocilizumab or alternative therapies per site practice in CRS management, as well as C-reactive protein (CRP) and ferritin (by local laboratory).

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

Guidelines for management of CRS according to severity grading are provided in Table 9. ASTCT CRS consensus grading scale is provided in Section 10.13 of the master protocol.

Table 9 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Increase monitoring of vital signs, cardiac and other organ functions closely as medically indicated until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.	Stop cetuximab infusion and administer intravenous fluids, bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once the event has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask	If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at ■ µg/kg or permanently discontinued, as clinically indicated.	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Cetuximab should be permanently discontinued. The participant can continue treatment with SAR444245.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 4, permanently discontinue SAR444245. If CRS Grade 3 or Grade 4, initiate IV corticosteroids (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed. CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS.	

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
	If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, initiate management for persistent or worsening CRS. Re-evaluation for other contributing conditions will be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants weighing ≥30 kg) or alternative therapies per site practice in CRS management should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension, fever and other manifestations is observed after the first dose of tocilizumab, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab or alternative therapies per site practice in CRS management and steroids, alternative options will be discussed with clinical site specialists.	

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

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

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

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

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

6.5.4.4 Immune-related adverse events

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

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. For suspected irAEs, adequate evaluation should be performed to confirm etiology or exclude neoplastic, infectious, metabolic, toxin, or other etiologic causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and/or cetuximab and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 10. Of note, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

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

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 10, the combination of SAR444245, pembrolizumab and cetuximab may be restarted at the discretion of the Investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 10 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

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

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold[a]	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue[b]		
Diarrhea/Colitis	Grade 2 or 3	Withhold[a]	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		
AST or ALT elevation or Increased Bilirubin	Grade 2[c]	Withhold[a]	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).
	Grade 3[d] or 4[e]	Permanently discontinue[b]	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
Type 1 Diabetes Mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[a,f]	Initiate insulin replacement therapy for participants with T1DM. Administer antihyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2 Grade 3 or 4	Withhold[a] Withhold[a] or permanently discontinue[b,f]	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
Hyperthyroidism	Grade 2 Grade 3 or 4	Continue Withhold[a] or permanently discontinue[b,f]	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per SOC	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Neurological Toxicities	Grade 2 Grade 3 or 4	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[b]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS Confirmed SJS, TEN, or DRESS	Withhold[a] Permanently discontinue[b]	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab and SAR444245	Corticosteroid and/or other therapies	Monitoring and follow-up
All Other irAEs	Persistent Grade 2	Withhold[a]	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold[a] or discontinue based on the event[g]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue[b]		

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

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

6.5.4.5 Dermatologic toxicity

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis.

The dosing of cetuximab will be omitted 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. If acneiform rash improves during this time, then the dose of cetuximab should be reduced as indicated in Table 11. The dose modification guidelines in Table 5 should be followed for dermatologic toxicities other than acneiform rash.

If acneiform rash does not improve during this time, cetuximab will be permanently discontinued.

Participants who have omitted cetuximab therapy for more than 2 consecutive infusions due to acneiform rash, and upon resolution of the toxicity are still felt to be benefiting from cetuximab treatment may resume cetuximab with Sponsor approval.

Table 11 - Cetuximab dose modification for dermatologic toxicities

Dermatologic toxicities and infectious sequelae (eg, acneiform rash, mucocutaneous disease)	Recommended IMP dose modification
1st occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, continue at the same dose of 250 mg/m^2. If no improvement, discontinue cetuximab.
2nd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at dose level 1. If no improvement, discontinue cetuximab.
3rd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at dose level 2. If no improvement, discontinue cetuximab.
4th occurrence; Grade 3 or 4	Permanently discontinue cetuximab.

6.5.4.6 Immune Cell-Associated Neurotoxicity Syndrome

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.13 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab or alternative therapies per site practice in CRS management should only be used in the context of CRS, as outlined in Table 12. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 12 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	Delay SAR444245[a]. Initiate treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that	If Grade 3 ICANS, delay SAR444245. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor.

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention. Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Table 9. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. If Grade 4 ICANS, permanently discontinue SAR444245. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Table 9. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS If there is no clinical improvement within 24 to 72 hours, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants weighing ≥30 kg, total dose should not exceed 800 mg) should be considered or alternative therapies per site practice in CRS management, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant clinical specialists should be involved whenever indicated.

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

6.5.4.7 Vascular Leak Syndrome (VLS)

Vascular leak syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic, shock with multiple-organ failure. Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 13. These guidelines are not comprehensive, and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (13).

Table 13 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	Delay SAR444245 .Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, permanently discontinue SAR444245. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

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

Definition of pembrolizumab overdose is provided in Section 8.3.8.

There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab or cetuximab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical examinations

Please refer to the master protocol.

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively:
  - **For the safety run-in participants** vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose.
- **For the core phase participants**: from Cycle 2 to Cycle 4 study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.

8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)

Please refer to the master protocol.

8.2.4 Clinical safety laboratory assessments

Please refer to the master protocol.

8.2.5 Pregnancy testing

Please refer to the master protocol.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information

Please refer to the master protocol. For participants in Cohort A2 irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

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

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Not applicable.

8.3.8 Adverse event of special interest

Please refer to the master protocol.

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

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

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol for description of common PK evaluations, substudy specific evaluations are summarized below.

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

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

Sample size:

For Cohort A2 the study will start with a **safety run-in** to confirm the dose of SAR444245 when combined with pembrolizumab and cetuximab in a sample of at least 6 participants.

The plan is to treat a total of 40 participants at the confirmed safe dose in Cohort A2. Participants who are enrolled in the safety run-in and treated at the confirmed safe dose will be included in the total number of participants for this cohort.

Please refer to the master protocol for details on sample size.

9.3 POPULATIONS FOR ANALYSES

The following additional population for analyses is defined for Cohort A2. Please refer to the master protocol for populations common to all cohorts.

Table 14 - Populations for analyses

Population	Description
DLT-evaluable	DLT-evaluable population include all participants in safety run-in part who have been treated and observed for least 21 days. Any participants who have experienced a DLT during DLT observation period will also be DLT-evaluable.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

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

9.4.3.1 Adverse events

Incidence of DLTs will be summarized by dose levels (if applicable) for DLT-evaluable population in the safety run-in part.

9.4.3.2 Other secondary endpoints

Plasma concentrations of cetuximab will be summarized with descriptive statistics.

9.4.4 Tertiary/exploratory endpoint(s)

Please refer to the master protocol.

9.5 INTERIM ANALYSES

No formal interim analyses are planned. However, the following analyses will be performed:

- At the end of the safety run-in for Cohort A2 regimen, the occurrence of DLT and other safety data will be reviewed by the Study Board to decide about continuation of the dose of SAR444245 of 24 µg/kg or dose reduction.
- After the dose is confirmed by the Study Board, the cumulative safety data for each study intervention across cohorts will be reviewed periodically by the Data Monitoring Committee. The enrollment will not be paused or stopped during the safety monitoring unless severe safety concern arises.

Further details on Data Monitoring Committee are provided in the master protocol.

The cohort cut-off for the primary ORR endpoint analysis corresponds to approximately 9 months from the date of the last participant's first infusion (to document that last participant response is maintained for 6 months).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort A2-specific evaluations are presented in Table 15.

Table 15 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Clinical chemistry[a]	See master protocol
Endocrine function tests[b]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

a For participants in Cohorts A2 electrolytes to be done weekly under treatment and then at the end of treatment, at FU visit 1 and as clinically indicated. Additional electrolytes monitoring for Cohort A2, outside the visits, maybe done according the local standard institutional care.

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

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

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

10.7.1 Amendment for Germany

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

German participants will not be enrolled in Cohort A2 substudy 02.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Please refer to the master protocol.

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

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245. Available information about pembrolizumab and cetuximab is shown in Table 16. For pembrolizumab and cetuximab, the information below is per currently available USPI and EU SmPC.

Please always refer to the latest version of the SAR444245 IB and pembrolizumab and/or cetuximab local label for the most up-to-date safety data.

Table 16 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome. Cetuximab Cetuximab can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal). Consider testing patients for alpha-gal IgE antibodies using FDA-cleared methods prior to initiating cetuximab. Negative results for alpha-gal antibodies do not rule out the risk of severe infusion reactions. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion associated reactions are provided in Table 6. Cetuximab Premedicate with a histamine-1(H1) receptor antagonist as recommended. Monitor patients for at least 1 hour following each cetuximab infusion, in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue cetuximab based on severity. Immediately interrupt cetuximab and permanently discontinue cetuximab for serious IRRs. Advise patients that the risk of serious infusion reactions may be increased in patients who have had a tick bite or red meat allergy. Advise patients to contact their healthcare provider and to report signs and symptoms of infusion reactions, including late onset infusion reactions, such as fever, chills, or breathing problems.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab. Also, see specific instructions for cetuximab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.
Cytokine release syndrome	Pembrolizumab Not specifically reported.	Dose modification and treatment guidelines are provided in Section 6.5.4.3.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hepatotoxicity	Pembrolizumab Pembrolizumab can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of pembrolizumab in 0.3% (9) of patients. All patients who were withheld reinitiated pembrolizumab after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients. Cetuximab Increase in liver enzymes is very common.	Exclusion of participants with impaired liver functions: Aspartate aminotransferase and/or alanine aminotransferase >2.5 × ULN (or >5 × ULN for participants with liver metastases). Monitor clinical signs and symptoms of hepatic impairment as part of TEAE. Monitor liver function parameters (AST, ALT, bilirubin, & alkaline phosphatase [ALP]) regularly from screening and throughout the study. Pembrolizumab dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Table 10.
Electrolyte abnormalities (including Hypomagnesemia)	Cetuximab Cetuximab can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving cetuximab in Study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%. In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No Electrolyte abnormalities (including Hypomagnesemia) and accompanying electrolyte abnormalities can occur days to months after initiating cetuximab.	Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of cetuximab. Replete electrolytes as necessary.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury.	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Table 10.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Table 10.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Cardiovascular effects, including QT interval prolongation & cardiopulmonary arrest	Pembrolizumab Combination with chemotherapy, common: hypertension, cardiac arrhythmia (including atrial fibrillation) Cetuximab Cetuximab can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients treated with radiation therapy and cetuximab in BONNER. BONNER (NCT00004227) was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced HNSCC being treated with cetuximab in combination with radiation therapy. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. In EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of 219 patients treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.	Carefully consider use of cetuximab with radiation therapy or platinum-based therapy with fluorouracil in patients with SCCHN with a history of coronary artery disease, congestive heart failure, or arrhythmias. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab administration (see Hypomagnesemia and Accompanying Electrolyte Abnormalities). Advise patients of the risk of cardiopulmonary arrest or sudden death and to report any history of coronary artery disease, congestive heart failure, or arrhythmias.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Table 10.
Pulmonary effects	Cetuximab Cetuximab can cause interstitial lung disease (ILD). ILD, including 1 fatality, occurred in less than 0.5% of 1570 patients receiving cetuximab in clinical trials.	Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue cetuximab for confirmed ILD. Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Dermatological effects	Cetuximab: Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of the 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping cetuximab in most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed in patients who received cetuximab. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). Cutaneous adverse reactions (including rash, pruritus and nail changes) are the most common adverse reaction (incidence greater than 25%).	Pembrolizumab: Refer to immune-related adverse events. Cetuximab: Monitor patients receiving cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during cetuximab therapy. Withhold, reduce dose or permanently discontinue cetuximab based on severity of acneiform rash or mucocutaneous disease. Advise patients to limit sun exposure during cetuximab treatment and for 2 months after the last dose of cetuximab. Advise patients to notify their healthcare provider of any sign of acne-like rash, (which can include itchy, dry, scaly, or cracking skin and inflammation, infection or swelling at the base of the nails or loss of the nails), conjunctivitis, blepharitis, or decreased vision.
Risks related to special populations		
Reproductive toxicity	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab. Cetuximab Based on animal data and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Human IgG is known to cross the placental barrier; therefore, cetuximab may be transmitted from the mother to the developing fetus. Advise pregnant women of the potential	Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with cetuximab and for 2 months after the last dose of cetuximab. Verify pregnancy status in females of reproductive potential prior to initiating cetuximab.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15-20% respectively. Pregnant cynomolgus monkeys were administered cetuximab intravenously once weekly during the period of organogenesis (gestation day [GD] 20-48) at dose levels 0.4 to 4 times the recommended dose of cetuximab based on body surface area (BSA). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams on GD 49. While no fetal malformations occurred in offspring, there was an increased incidence of embryolethality and abortions at doses approximately 1 to 4 times the recommended dose of cetuximab based on BSA. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development), and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling.	
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.7

10.11 APPENDIX 11: ABBREVIATIONS

ADCC: antibody-dependent cellular cytotoxicity
AEs: adverse events
AESIs: adverse events of special interest
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ASTCT: American Society for Transplantation and Cellular Therapy
CI: confidence interval
COVID-19: Coronavirus disease 2019
CPS: Combined Positive Score
CR: complete response

CRS:	cytokine release syndrome
CTLA-4:	cytotoxic T-lymphocyte-associated protein 4
DLT:	dose-limiting toxicities
e-CRF:	electronic case report form
EGFR:	Epithelial Growth Factor Receptor
EOT:	end-of-treatment
HNSCC:	head and neck squamous cell carcinoma
IB:	Investigator's brochure
ICANS:	immune cell-associated neurotoxicity syndrome
ICU:	intensive care unit
Ig:	immunoglobulin
IgE:	immunoglobulin E
IgG1:	immunoglobulin G1
ILD:	interstitial lung disease
IMP:	investigational medicinal product
IR:	infusion reaction
irAEs:	immune-related AEs
IRR:	infusion-related reactions
IV:	intravenous
LVEF:	left ventricular ejection fraction
mTPI2:	modified toxicity probability interval 2
NCI-CTCAE:	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK:	natural killers
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
PBPK:	physiologically-based PK
PD:	progressive disease
PD1:	programmed cell death-1
PD-L1:	programmed cell death-ligand 1
PD-L2:	programmed cell death ligand 2
PK:	pharmacokinetic
Q2W:	every 2 weeks
Q3W:	every 3 weeks
R/M:	recurrent/metastatic
SAEs:	serious adverse events
SB:	Study Board
SmPC:	Summary of Product Characteristics
SoA:	schedule of activities
SOC:	standard of care
TEAE:	treatment-emergent adverse event
TIL:	tumor infiltrating lymphocytes
TRAEs:	treatment-related adverse events
ULN:	upper limit of normal
USPI:	United States Package Insert
VLS:	Vascular Leak Syndrome

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

11 REFERENCES

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Signature Page for VV-CLIN-0624549 v1.0
act16903-16-1-1-amended-protocol01-substudy02

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 03 (SUBSTUDY 04)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants in 2nd/3rd line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)**
Protocol number:	**ACT16903-S04**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with pembrolizumab for the treatment of participants in 2nd/3rd line R/M HNSCC**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	IND156423
EudraCT:	2021-002105-99
NCT:	NCT05061420
WHO:	U1111-1251-5073

Date: 22-Dec-2021 Total number of pages: 62

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03 (Substudy 04)	All	22 December 2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02 (Substudy 04)	All	19 August 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 04)	All	26 July 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 04)	All	11 June 2021, version 1 (electronic 1.0)

Amended protocol 03 (22 December 2021)

This amended protocol (Amendment 03) 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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Spanish (Agency for Medicine and Health Products [AEMPS]), Italian (Medicines Agency [AIFA]) and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol.	For clarity and consistency
	The row indicating “electrolytes” has been removed.	For clarity and consistency
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessments of any potential cardiotoxicity
1.4 Biomarker flow-chart and 1.5 Pharmacokinetic flow-chart	Complete biomarker and pharmacokinetic flow-charts applicable for this substudy have been provided with procedures taken from the master protocol.	For clarity and consistency
6.5.3 General guidelines for the management of treatment-related adverse events	As the Study Board does not intervene for this substudy, any reference to it has been removed.	For consistency

Section # and Name	Description of Change	Brief Rationale
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS) and 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	The following statement “or alternative therapies per site practice in CRS management” has been added to “tocilizumab”.	For flexibility following an issue with tocilizumab availability
6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 6 under Grade 4, “signs of” has been removed before “diffuse cerebral edema on neuroimaging”.	Change made for consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus and correction
10.1 Appendix 1: Regulatory, ethical, and study oversight considerations	A new subsection 10.1.6 entitled “Dissemination of clinical study data” has been added with the following text: “Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study”.	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
10.11 Appendix 11: Abbreviations	List of abbreviations has been revised.	For consistency
11 References	List of references has been updated.	For consistency
Throughout the document	Minor editorial corrections were made.	For consistency

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy B1-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with pembrolizumab for the treatment of participants in 2nd/3rd line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

Brief title: A study of SAR444245 combined with pembrolizumab for the treatment of participants in 2nd/3rd line R/M HNSCC

Rationale:

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

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with pembrolizumab will result in a significant increase in the percentage of participants with R/M HNSCC previously treated with PD1/PD-L1-based regimen & platinum-based regimen experiencing an objective response.

Objectives and endpoints

Please refer to the master protocol.

Overall design:

Please refer to the master protocol.

Brief summary:

Cohort B1: This substudy will include participants with R/M HNSCC previously treated with PD1/PD-L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for recurrent and/or metastatic (R/M) disease and will assess SAR444245 combined with pembrolizumab.

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

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in the core phase of Cohort B1.

In the expansion phase, approximately 56 participants will be enrolled.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration.

Study intervention(s)

Cohort B1: PD1/PD-L1-based regimen & platinum-based regimen treated R/M HNSCC after failure of no more than 2 regimens for R/M disease, SAR444245 + pembrolizumab

Dosing sequence: [redacted]

Investigational medicinal product(s)

Pembrolizumab

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

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

SAR444245

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: 24 µg/kg administered as an IV infusion over 30 mins every 3 weeks (Q3W) on Day 1 of each cycle (21 days per cycle) for **up to 35 cycles.**

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

Non-investigational medicinal products

Please refer to the master protocol.

Statistical considerations:

Please refer to the master protocol for description of common statistical considerations.

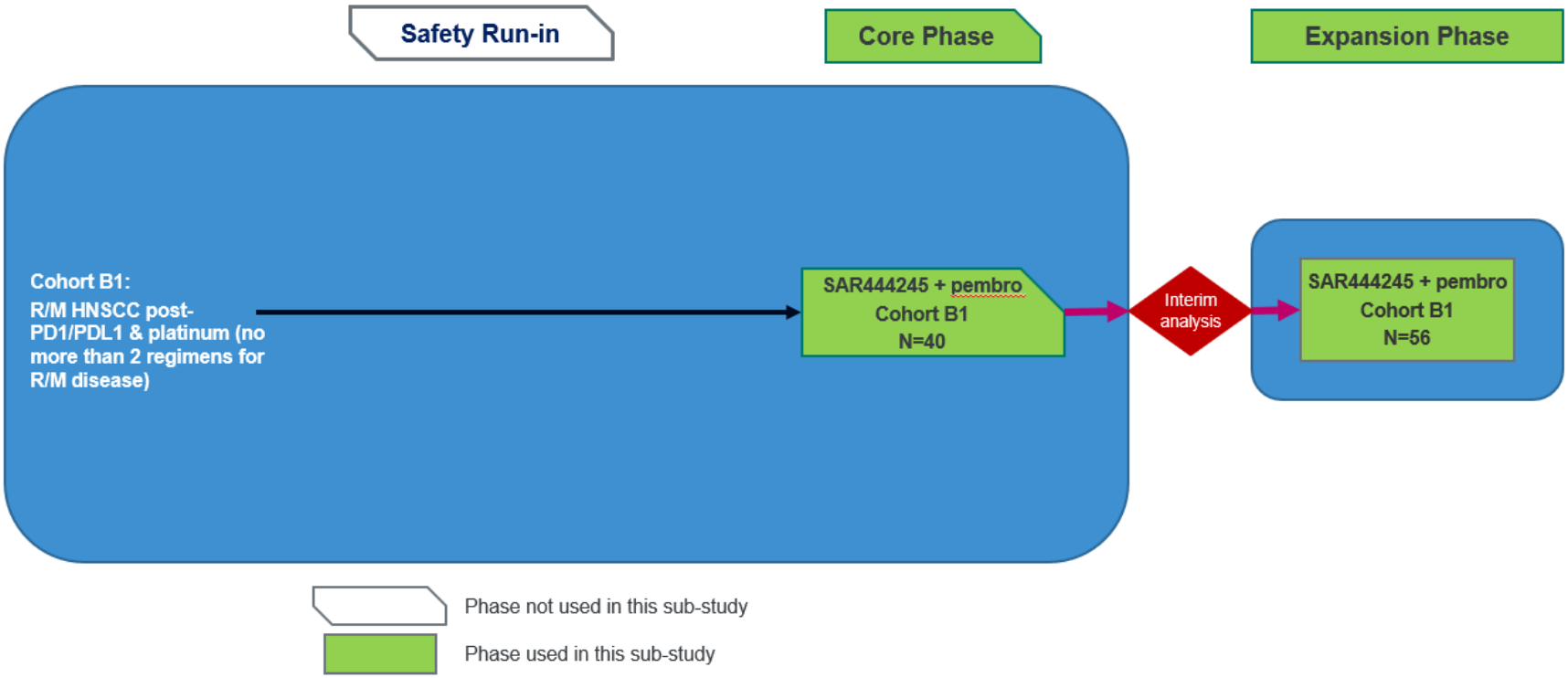
For Cohort B1, the cohort cut-offs for the analyses are as follows:

- Interim analysis cut-off: the date on which all participants in the core phase have at least 2 post-baseline tumor assessments or discontinue study treatment (whichever occurs first).
- The cohort cut-off for the primary objective response rate (ORR) endpoint analysis corresponds to approximately 9 months from last participant's first infusion in the expansion phase (to document that last participant response is maintained for 6 months in the expansion phase).

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Overall substudy schema



CPS: Combined Positive Score; HNSCC: head and neck squamous cell carcinoma; PD1: programmed death 1; PD-L1: programmed death ligand 1; pembro: pembrolizumab; Tx: treatment; R/M: recurrent/metastatic.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Elements of the schedule of activities (SoA) common to all cohorts are detailed in the master protocol. Cohort B1-specific evaluations are presented in this table.

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent Inclusion/Exclusion criteria	X											
IRT contact	X	X			X	X	X					
Demography, medical/surgical and disease history	X											See Section 8 of master protocol
Full physical examination	X						X					
Directed physical examination		X	X	X	X	X		X				See Section 8.2.1 of master protocol
Body weight/Height[e]	X	X			X	X	X	X				

Evaluation[a]	**Screening/ baseline**	**Treatment period[b]**					**End of treatment**	**Observation period[c]**			**Survival phone call follow-up period[d]**	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Vital signs	X	X	X	X	X	X	X	X				See Section 8.2.2 & Section 8.2.2 of master protocol
SpO_2	X	As clinically indicated										
Performance status (ECOG)	X	X	X	X	X	X	X	X				
12-lead ECG	X	X	As clinically indicated									See Section 8.2.3 of master protocol
LVEF	X	As clinically indicated										See Section 8.2.3 of master protocol

Evaluation[a]	**Screening/ baseline**	**Treatment period[b]**					**End of treatment**	**Observation period[c]**			**Survival phone call follow-up period[d]**	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Laboratory assessments												
Troponin	X	As clinically indicated				X (D1 Cycle 4)	As clinically indicated					See Section Section 8.2.3 & Section 10.2
Pregnancy test	X	X			X	X	X	X	X			See Section 8.2.5, Section 8.3.5 & Section 10.2 of master protocol
Blood chemistry/hematology	X	X	X	X	X	X	X	X				See Section 10.2 & Section 10.2 of master protocol
T3, FT4, TSH, and cortisol	X				X	X	X	X				See Section 10.2

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Coagulation	X	As clinically indicated										See Section 10.2 of master protocol
Urinalysis[k]	X	X				X	X	X				See Section 10.2 of master protocol
Hepatitis serology CD4 counts & Viral Load	X[f]	As clinically indicated										See Section 10.2 of master protocol
HPV p16 status for participants with oropharyngeal cancer	X											
PK	See PK Flow-Chart in Section 1.5											
ADA	See PK Flow-Chart in Section 1.5											

Evaluation[a]	Screening/ baseline	Treatment period[b]					End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2	Treatment Cycle 3 and beyond	EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Exploratory biomarkers												
PDy - Blood and tumor tissue collection[g]	See Biomarkers Flow-Chart in Section 1.4											
Disease assessment												
CT/MRI[h]	X					X	X	X	X	X		See Section 8.1 of master protocol
Brain imaging[i]	X											See Section 8.1 of master protocol
SAR444245 Administration		X			X	X						
Pembrolizumab		X			X	X						

Evaluation[a]	**Screening/ baseline**	**Treatment period**[b]					**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**	**Treatment Cycle 3 and beyond**	**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D1 (±3)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Administration												
AE/SAE assessment[i]	X	Continuously throughout treatment period						X				See Section 8.3 of master protocol
Prior medication	(within 28 days prior to first dose)											
Concomitant medication		Continuously throughout treatment period										See Section 6.8 of master protocol
First subsequent anticancer therapy							X	X	X	X	X	
Survival status											X	

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

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

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

d **Survival Phone Call Follow-Up Period**: Participant who moves into the Survival Follow-up Period should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

f For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8 of master protocol).

g If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

h **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP or more frequently if clinically indicated in the first 45 weeks. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the **head, neck, chest and abdomen (pelvis is optional)** and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment and during treatment period until PD. After the first documentation of response or the first documentation of progression (if the participant is clinically stable) per RECIST 1.1, confirmatory imaging should be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy.

i **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease as per protocol tumor assessment schedule. In all other cases, the lesions must be treated. Two additional scans obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive systemic therapy during these 4 weeks stabilization at the treating physician's discretion, this systemic therapy will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

j **AE/SAE assessment**: Severity will be graded according to NCI-CTCAE v 5.0, ICANS and cytokine release syndrome (CRS) will be graded using ASTCT criteria integrated with central laboratory cytokine results (1).

k Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; C: Cycle; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; FT4: free thyroxine; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; HPV: Human Papilloma virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; IMP: investigational medicinal product; IRT: Interactive Response Technology; LVEF; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common terminology criteria for adverse events; PDprogressive disease; PDy: pharmacodynamic; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SpO_2: oxygen saturation; T3: triiodothyronine; TSH: thyroid stimulating hormone.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHART

Cycle	Treatment Cycle 1				Treatment Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	**D1**		**D2**	**D8**	**D1**		
Time after start of SAR444245 dosing	**SOI**	**EOI**	**Any time**	**Any time**	**SOI**	**EOI**	
SAR444245 PK sample		P00[b]	P01			P00[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00

a Samples collected strictly before start of infusion (SOI).

b EOI samples must be taken at end of infusion (EOI) precisely ±5 minutes.

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

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort B1 (R/M HNSCC participants previously treated with PD1/PD-L1-based regimen & platinum-based regimen after failure of no more than 2 regimens for R/M disease), for the combination of SAR444245 with pembrolizumab.

Please refer to the master protocol for an introduction for ACT16903 study.

2.1 STUDY RATIONALE

Preclinical studies demonstrated that treatment with SAR444245 leads to polyclonal expansion of CD8+T cells in murine and NHP models while anti-PD-1 antibody prevents T cell suppression through the PD-1/PD-L1 pathway. The combination of anti-PD-1 treatment with SAR444245 was tested in a syngeneic mouse Ct-26 colon cancer model and demonstrated enhanced anti-tumor activity and prolonged survival compared to each monotherapy. These data support evaluation of SAR444245 in combination with pembrolizumab.

2.2 BACKGROUND

2.2.1 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications.

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

2.2.1.1 Pharmaceutical and therapeutic background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (2). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (3, 4).

The PD1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (5, 6).

The structure of murine PD1 has been resolved (7, 8). PD1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (3, 4, 5, 9). The mechanism by which PD1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (6, 10).

2.2.1.2 Pre-clinical trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (7, 11, 12, 13, 8, 14, 15). Anti-mouse PD1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (2, 8, 14, 15, 16). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo. Experiments have confirmed the in vivo efficacy of anti-mouse PD1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see pembrolizumab Investigator's brochure [IB]).

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

2.2.2 Rationale for HNSCC and selected participant population

Please refer to the master protocol.

2.2.3 Current standard of care in HNSCC

2.2.3.1 PD1/PD-L1 inhibitor monotherapy as second line therapy

Previously, R/M HNSCC patients in need of second-line treatment (eg, fit patients who progress on platinum-based first-line therapy in the R/M setting) primarily received either single-agent chemotherapy, targeted therapy with cetuximab, best supportive care, or entered into clinical trials (17, 18, 19).

KEYNOTE-040 was a randomized, Phase 3 study evaluating the efficacy of 2nd line pembrolizumab. This multicenter, open-label study compared OS post-treatment with pembrolizumab to investigator's choice (IC) of standard systemic therapy (weekly methotrexate, weekly cetuximab or, Q3W docetaxel). In the intention-to-treat (ITT) population, irrespective of PD-L1 status, median OS was 8.4 months (95% CI 6.4-9.4) with pembrolizumab versus 6.9 months (5.9-8.0) with standard of care (SOC) (hazard ratio 0.80, 0.65-0.98; p = 0.0161) (20). Among patients with a CPS; the number of PD-L1 positive cells (including tumor, lymphocytes and macrophages, in relation to total tumor cells) for tumor and immune cell PD-L1-expression of at least 1, median OS was 8.7 months (95% CI 6.9-11.4) with pembrolizumab versus 7.1 months (5.7-8.3) with standard treatments (HR 0.74; 95% CI: 0.58-0.93, p = 0.0049). Among patients with a Combined Positive Score (CPS) score of less than 1, median OS was 6.3 months (3.9-8.9) with pembrolizumab compared to 7.0 months (5.1-9.0) with SOC (HR 1.28; 95% CI: 0.8-2.07, p = 0.8476).

Additionally, incidence of Grade 3-5 treatment-related adverse events (TRAEs) was significantly lower in the pembrolizumab cohort (13.0%) compared to the SOC cohort (36.0%), with 2 and 1%, respectively, reporting deaths due to TRAEs (20). Thus, while pembrolizumab increased median OS compared with standard chemotherapy irrespective of PD-L1 status, the benefit of pembrolizumab was greater in patients with PD-L1 CPS ≥1 and TPS ≥50% (20).

CheckMate 141 was a randomized, Phase 3 study of a PD-1 inhibitor in HNSCC and enrolled 361 patients regardless of tumor PD-L1 status. In this trial, patients received either 3 mg/kg nivolumab every 2 weeks (Q2W)or investigator's choice of weekly systemic standard therapy (methotrexate, weekly docetaxel, or cetuximab). Patients who received nivolumab demonstrated increased median OS (7.5 months versus 5.1 months, respectively) and an increased overall response rate (ORR; 13.3% versus 5.8%, respectively) compared to patients who received chemotherapy. At the first interim analysis, estimated one-year OS was 36% with nivolumab compared to 16.6% with standard therapy (9). Furthermore, only 13.1% of patients treated with nivolumab experienced grade 3-4 TRAEs compared to 35.1% of patients treated with standard therapy.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

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

2.3.1.1 Pembrolizumab

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

The use of pembrolizumab may cause infusion-related reactions (IRR) (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome [CRS]); Pembrolizumab use may be associated with infections (pneumonia), bone marrow suppression (anemia, thrombocytopenia, leukopenia), increase in the level of hepatic enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), kidney damage (nephritis, acute kidney injury), as well as adverse effects on the functioning of nervous system (dizziness, headache, peripheral neuropathy, dysgeusia (very common) and lethargy (common). In combination therapy with other chemotherapeutic drugs, pembrolizumab administration is commonly associated with hypertension and cardiac arrhythmia (including atrial fibrillation).

Immune-mediated adverse events are designated as important identified risk for pembrolizumab (21).

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

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

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

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

2.3.1.2 SAR444245 combined with pembrolizumab

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

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

2.3.2 Benefit assessment

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

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

2.3.3 Overall benefit: risk conclusion

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

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

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

In addition, the impact of PD-1 blockade therapy on Coronavirus disease 2019 (COVID-19) severity was explored by 2 groups who did not find a clinically meaningful signal (22, 23).

3 OBJECTIVES AND ENDPOINTS

Please refer to the master protocol for description of objectives and endpoints.

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include participants with R/M HNSCC previously treated with PD1/PD-L1-based regimen & platinum-based regimen, after failure of no more than 2 regimens for R/M disease and will assess SAR444245 combined with pembrolizumab.

Overall, approximately 40 participants will be enrolled and treated in the core phase of Cohort B1.

In the expansion phase, approximately 56 participants will be enrolled.

The maximum number of cycles allowed in this Cohort B1 substudy is 35 cycles.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with the anti-PD1 antibody pembrolizumab, will result in a significant increase in the percentage of trial participants with HNSCC experiencing an objective response.

After the core phase to gather more safety data with the confirmed dose, the substudy may be expanded to enroll more participants and accumulate evidence of clinical activity.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Pembrolizumab dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB).
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications.
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD1 saturation over a wide range of tumor penetration and PD1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD1 saturation in both blood and tumor.

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

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort B1-specific criteria.

5.1 INCLUSION CRITERIA

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

Type of participant and disease characteristics

I 01. Provision of tumor tissue:

- **Optional** baseline biopsy for participants **in Core Phase**.
- **Mandatory baseline biopsy for all participant in Expansion Phase** (minimum **10 slides with 4-5 micron thickness**). Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - Location of the tumor not amenable to biopsy due to significant risk, OR
  - Less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment.

I 02. Prior anticancer therapy

Have failed no more than 2 systemic anti-cancer regimens (a platinum-containing regimen, AND an anti-PD-1/PD-L1 based regimen, administered either sequentially or concurrently, unless these regimens are already given in locally advanced disease) in R/M disease:

- One previous anti-PD-1/PDL1 based regimen (may include chemotherapy agents as part of the regimen) failure defined as **disease progressed (when participants are still receiving) but after documented benefit, on an anti-PD1/PDL-1 based regimen** per RECIST 1.1. **Documentation of benefit** defined as stable disease [SD] at ≥1 radiographic imaging scan, CR, or PR from anti-PD1/PDL-1 based regimen. An anti PD-1/PD-L1 containing regimen is defined as either an anti PD-1/PD-L1 monotherapy, or an anti-PD-1/PD-L1 agent administered in the same cycle as another systemic anti-cancer therapy. If an anti-PD-1/PDL-1 agent was used beyond initial radiological progression (without change the anti-PD-1/PDL-1 agent used before progressive disease), it's still considered as the same regimen. The site's study team must have reviewed previous tumor assessments (including screening tumor imaging) to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the anti PD-1/PD-L1 containing regimen.

AND

- One previous platinum-containing regimen failure defined as either disease progression on or after treatment with a platinum-containing regimen.

5.2 EXCLUSION CRITERIA

Please refer to master protocol.

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING (ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION)

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

The maximum number of cycles allowed in this Cohort B1 substudy is 35 cycles.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245, and pembrolizumab administered as described in Section 4.1. Details of each IMP component to be administered are shown in Table 1.

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

Table 1 - Overview of IMP administered

Intervention name	SAR444245	Pembrolizumab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	25 mg/mL
Dosage level(s)[a]	24 µg/kg Q3W	200 mg Q3W
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	IMP	IMP
Packaging and labeling	See master protocol	Supplied in single-dose vials containing 100 mg/4 mL pembrolizumab labelled with a multilingual booklet. 1 vial per treatment box.
Current/Former name(s) or alias(es)	NA	Keytruda

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

6.1.2 Non-investigational medicinal product

Please refer to the master protocol.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

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

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

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

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

If a toxicity leads to SAR444245 discontinuation, pembrolizumab must be discontinued unless the TEAE leading to permanent IMP discontinuation is clearly attributable only to SAR444245, and patients have clinical benefit as determined by the treating physician.

Participants who continue pembrolizumab in this scenario are informed as part of the initial consent process that pembrolizumab monotherapy is not a standard of care. In this case it is partial permanent discontinuation and the end of treatment (EOT) assessment will be 30 days after the date of the last administration of the remaining IMP. When all IMP components are permanently discontinued it is full permanent discontinuation.

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

6.5.2 Cycle delay

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

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

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

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

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

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

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

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

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

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

6.5.4 Guidelines for the management of specific adverse events

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

6.5.4.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2.1 of the master protocol prior to SAR444245 administration, to prevent or reduce the incidence or severity of infusion-related reactions (IRR).

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

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

infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 2.

After an infusion-related reaction due to pembrolizumab infusion, the SAR444245 infusion will be delayed and can be administered after resolution of symptoms. The Investigator should discuss with the Sponsor's Medical Monitor if the SAR444245 infusion needs to be delayed more than 1 day.

Guidelines for the management of SAR444245 IRR events are provided in Table 3. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 2 - Pembrolizumab infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids, • Antihistamines, • NSAIDs, • Acetaminophen, • Narcotics. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; urgent intervention indicated	Stop Infusion Additional appropriate medical therapy may include but is not limited to: • Epinephrine*, • IV fluids, • Antihistamines, • NSAIDs, • Acetaminophen, • Narcotics, • Oxygen, • Pressors, • Corticosteroids. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.

Table 3 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

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

NCI CTCAE Grade	Treatment
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; urgent intervention indicated	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

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

6.5.4.2 Anaphylaxis

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

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines) (24, 25, 26).

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

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

Monitoring of vital signs is detailed in Section 8.2.2.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 4. If any grade of CRS is suspected, sites should make every effort to draw an additional blood sample for cytokines levels (by central laboratory) prior to the administration of tocilizumab or alternative therapies per site practice in CRS management, as well as C-reactive protein (CRP) and ferritin (by local laboratory).

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

Guidelines for management of CRS according to severity grading are provided in Table 4. ASTCT CRS consensus grading scale is provided in Section 10.13 of the master protocol.

Table 4 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 if event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Increase monitoring of vital signs, cardiac and other organ functions closely as medically indicated until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask	If CRS grade 3, temporarily cycle delay SAR444245 and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 4, permanently discontinue SAR444245. If CRS Grade 3 or Grade 4, initiate IV corticosteroids (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines
	CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS.
	If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, initiate management for persistent or worsening CRS. Re-evaluation for other contributing conditions will be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants weighing ≥30 kg) or alternative therapies per site practice in CRS management should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension, fever and other manifestations, is observed after the first dose of tocilizumab, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab or alternative therapies per site practice in CRS management and steroids, alternative options will be discussed with clinical site specialists

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

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

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

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

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

6.5.4.4 Immune-related adverse events

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

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs because the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. For suspected irAEs, adequate evaluation should be performed to confirm etiology or exclude neoplastic, infectious, metabolic, toxin, or other etiologic causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SAR444245 and administer corticosteroids.

SAR444245 may increase the incidence and severity of these events.

Dose modification and toxicity management guidelines for irAEs are provided in Table 5. Of note, if the AE is considered immune-related, both drugs in the combination should be held according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

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

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

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 5, the combination of SAR444245 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to SAR444245 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with the Sponsor.

Table 5 - Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and SAR444245

General instructions:

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

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

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

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

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

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

6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.13 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab or alternative therapies per site practice in CRS management should only be used in the context of CRS, as outlined in Table 6. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 6 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	Delay SAR444245[a]. Initiate treatment with IV corticosteroids as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to [redacted] µg/kg as per Investigator with Sponsor consultation.
Severe or Life-threatening Grade 3 ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention.	If Grade 3 ICANS, delay SAR444245. When symptoms have resolved or improved to Grade 1 after corticosteroid taper, SAR444245 can be either restarted at [redacted]µg/kg or permanently discontinued, as clinically indicated, and upon discussions between the Investigator and Sponsor. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Section 6.5.4.3 Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days.
Grade 4 ICE score: 0 (participant is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging;	If Grade 4 ICANS, permanently discontinue SAR444245. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab or alternative therapies per site practice in CRS management and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS If there is no clinical improvement within 24 to 72 hours, then re-evaluation for other contributing conditions should be done. Administration of IV Tocilizumab at 8 mg/kg (for participants weighing ≥30 kg, total dose should not exceed 800 mg) or alternative therapies per site practice in CRS

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	management should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant clinical specialists should be involved whenever indicated.

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

6.5.4.6 Vascular Leak Syndrome (VLS)

Vascular leak syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic, shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 7. These guidelines are not comprehensive and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (27).

Table 7 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	Delay SAR444245. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg. The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, permanently discontinue SAR444245. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery.
	During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

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

Definition of pembrolizumab overdose is provided in Section 8.3.8.

There is no specific antidote for overdose with pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical examinations

Please refer to the master protocol.

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively;
  - Vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose.
  - At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring (to be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting).
- **For the core phase participants**: from Cycle 2 to Cycle 4 study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.

8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)

Please refer to the master protocol.

8.2.4 Clinical safety laboratory assessments

Please refer to the master protocol.

8.2.5 Pregnancy testing

Please refer to the master protocol.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information

Please refer to the master protocol for AEs and serious adverse events (SAEs) collection. For participants in Cohort B1 irAEs will be collected until 90 days following last administration of study treatment regardless of whether or not another anticancer therapy is initiated.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

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

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Not applicable.

8.3.8 Adverse event of special interest

Please refer to the master protocol.

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

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

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

Sample size:

The plan is to treat a total of 40 participants in core phase of Cohort B1. In the expansion phase, approximately 56 participants will be enrolled and treated.

Core Phase

Please refer to the master protocol.

Expansion Phase

At the end of the core phase of Cohort B1, the overall antitumor activity and safety will be assessed. The sponsor may decide to open a 56-participant expansion part based on the totality of data if the posterior probability that the true ORR is greater than 9%, which is considered minimal efficacious signal of interest, is greater than 80% with durable response. Based on a conjugate non-informative prior of beta (0.5, 0.5) at the time of the design of the study, at least 6 responders out of 40 exposed participants at the confirmed dose (confirmed ORR=15%) need to be observed in the core phase. However, emerging data generated from outside of the study may warrant a different prior to be considered before the formal IA. Analyses based on the total 96 participants by combining core phase and expansion phase will be performed. Table 8 lists estimated ORR and the corresponding 95% exact CIs by number of responders from a sample size of 96 participants evaluable for activity in each cohort.

Table 8 - Estimated objective response rate (ORR) and 95% CI for Cohort B1 (combining core and expansion phases)

Number of responders (N=96)	ORR	95% CI for ORR (Clopper-Pearson)
10	10.4%	(5.1%, 18.3%)
12	12.5%	(6%, 20.8.5%)
14	14.6%	(8.2%, 23.3%)
15	15.6%	(9%, 24.3%)

With a sample size of 40 study participants in the core phase, the probability of observing 1 or more instances of an AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. With a sample size of 96 study participants in total, the probability of observing 1 or more instances of an AE with a true incidence rate of 1%, 2%, or 5% is 61.9%, 85.6%, or >99%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this study.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Periodic Data Monitoring Committees (DMCs) are planned (details are in the master protocol).

At the end of the core phase, Cohorts B1 will have one formal interim analysis when all participants in the core phase have at least 2 post-baseline tumor assessments or discontinued study treatment (whichever occurs first). The sponsor will decide if the expansion will be initiated based on totality of the data observed.

The cohort cut-off for the primary ORR endpoint analysis corresponds to approximately 9 months from the date of the last participant's first infusion in the expansion phase (to document that last participant response is maintained for 6 months).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort B1-specific evaluations are presented in Table 9.

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Endocrine function tests[a]	Thyroid-stimulating hormone (TSH)
	Tri-iodothyronine (T3)
	Free thyroxine (FT4)
	Cortisol (preferably in the morning)

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

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

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Please refer to the master protocol.

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

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

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

Table 10 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion-related reactions	Pembrolizumab Common, but infusion-related reactions in labeling include drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome.	Pembrolizumab Dose modification and treatment guidelines for pembrolizumab infusion-related reactions are provided in Section 6.5.4.1.
Hypersensitivity, including anaphylaxis	Pembrolizumab Not specifically reported, but included among infusion-related reactions in label.	Exclusion of participants with known hypersensitivity to any components of pembrolizumab.
Infections	Pembrolizumab Common: pneumonia.	See routine mitigation in the master protocol.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hepatotoxicity	Pembrolizumab Pembrolizumab can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving pembrolizumab, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of pembrolizumab in 0.3% (9) of patients. All patients who were withheld reinitiated pembrolizumab after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.	Dose modification and treatment guidelines for liver enzyme increase are provided under immune-related reactions in Section 6.5.4.4.
Nephrotoxicity	Pembrolizumab Common: nephritis, acute kidney injury.	Dose modification and treatment guidelines for nephrotoxicity are provided under immune-related reactions in Section 6.5.4.4.
Neurological AEs	Pembrolizumab Dizziness, headache, neuropathy peripheral, dysgeusia (very common) and lethargy (common) for pembrolizumab in combination with chemotherapy. Uncommon: epilepsy.	Dose modification and treatment guidelines for neurological AEs are provided under immune-related reactions in Section 6.5.4.4.
Immune-mediated Adverse Events	Pembrolizumab Immune-mediated adverse events are designated as important identified risk for pembrolizumab.	Dose modification and treatment guidelines for immune-related reactions are provided in Section 6.5.4.4.
Risks related to special populations		
Pregnancy and lactation exposure and outcomes	Pembrolizumab Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.	See master protocol for exclusion of participants, guidance on highly effective contraceptive methods, and pregnancy tests to be performed regularly.
Drug-drug interactions	No data available.	
Overdose and its treatment	No specific information is available on the treatment of overdose of pembrolizumab.	See Section 6.7

10.11 APPENDIX 11: ABBREVIATIONS

AEs:	adverse events
AESIs:	adverse events of special interest
ASTCT:	American Society for Transplantation and Cellular Therapy
COVID-19:	Coronavirus disease 2019
CPS:	Combined Positive Score
CR:	complete response
CRS:	cytokine release syndrome
CTLA-4:	cytotoxic T-lymphocyte-associated protein 4
e-CRF:	electronic case report form
EOT:	end of treatment
FDA:	Food and Drug Administration
HNSCC:	head and neck squamous cell carcinoma
IB:	Investigator's brochure
ICANS:	Immune cell-associated neurotoxicity syndrome
ICU:	intensive care unit
Ig:	immunoglobulin
IMP:	investigational medicinal product
irAEs:	immune-related AEs
IRR:	infusion-related reactions
IV:	intravenous
LVEF:	left ventricular ejection fraction
NCI-CTCAE:	National Cancer Institute- Common Terminology Criteria for Adverse Event
NSCLC:	non-small cell lung cancer
ORR:	objective response rate
PBPK:	physiologically-based PK
PD1:	programmed cell death-1
PD-L1:	programmed cell death-ligand 1
PD-L2:	programmed cell death ligand 2
PK:	pharmacokinetic
Q2W:	every 2 weeks
Q3W:	every 3 weeks
R/M:	recurrent and/or metastatic
SAEs:	serious adverse events
SoA:	schedule of activities
SOC:	standard of care
TEAE:	treatment-emergent adverse event
TIL:	tumor infiltrating lymphocytes
TRAEs:	treatment-related adverse events
VLS:	vascular leak syndrome

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (26 July 2021)

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 overall rationale for the amendment is to respond to the Health Authorities (Food and Drug Administration, [FDA]) requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4 Guidelines for the management of specific adverse events	For clarity and brevity, command language has been used in the toxicity management sections.	Regulatory Authority (FDA) request
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 3 the following text has been revised: Under Grade 3 and Grade 4: - “prematurely” deleted from “prematurely permanently discontinued”. - “clearly attributable” deleted from “If IRR is clearly attributable to SAR444245”as the table title already indicates treatment with regards to SAR444245 IRRs. Under Grade 2, Grade 3 and Grade 4: “if applicable” deleted in the sentence that reads “SAR444245 infusion should be interrupted if applicable”.	Regulatory Authority (FDA) request
	In Table 2 and Table 3, the following text “requires therapy or infusion interruption” has changed to “Therapy or infusion interruption indicated', and “pressor or ventilator support indicated” has been changed to “urgent intervention indicated".	For consistency with Common terminology criteria for adverse events (CTCAE) guidelines (version 5)
Section 6.5.4.1 Infusion-related reactions (IRR) and Section 10.10 Risk assessment (Table10)	The text “SAR444245 infusion-associated reaction” was changed to “SAR444245 infusion-related reaction”.	For consistency

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 4 the following text "If subsequent administration is tolerated, increasing the SAR444245 dose to ■ µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor" has been removed for Grade 3.	Regulatory Authority (FDA) request
	For Grade 3, the following sentence has been changed from "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1 at ■µg/kg or permanently discontinued, as clinically indicated" to "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at ■ µg/kg or permanently discontinued, as clinically indicated".	For consistency and clarity
	For Grade 4 "as clinically indicated" has been removed from the subtitle.	
	The following sentence has been added: "Monitoring of vital signs is detailed in Section 8.2.2" for clarity.	
Section 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 6 the following text has been added under Grade 3 ICANS: "Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days."	Regulatory Authority (FDA) request
	The following text "diffuse cerebral edema" has been revised to "signs of diffuse cerebral edema".	For consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus
Sections 8.2.1 Physical examinations, Section 8.2.2 Vital signs, Section 8.2.3 Electrocardiograms, Section 8.2.4 Clinical safety laboratory assessments, and Section 8.2.5 Pregnancy testing	Sections newly inserted.	For clarity
Section 8.2.2 Vital signs	Details regarding monitoring of vital signs provided in the Master protocol have been added.	Regulatory Authority (FDA) request
Section 10.10: Appendix 10: Risk assessment	In Table 10 assessment under hepatoxicity for pembrolizumab was revised to be aligned with the last version of USPI warnings and precautions for pembrolizumab.	Regulatory Authority (FDA) request
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

Amended protocol 02 (19 August 2021)

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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to add a new study cohort (Cohort A2, substudy protocol 02) and clarify the priority of recruitment of participants between Cohorts A1 and A2 (see Master protocol). Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Columns indicating D8 (±1) and D15 (±1) for treatment Cycle 2 and treatment Cycle 3 and beyond were removed.	Change made for correction
	"IMP Administration (SAR444245 Administration)" has been changed to "SAR444245 Administration" with a reference to the master protocol.	Change made for clarification
Section 5.1 Inclusion criteria	In I06 "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment"	Harmonization per program level approach
Section 6.5.2 Cycle delay, and Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following text regarding the treatment resumption after Cycle delay has been deleted: "or is stable and manageable through supportive/medical therapy".	Change made for correction
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The name "Study Committee" has been changed to "Study Board".	Change made to ensure clarity and avoid confusion with any Independent Committee
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 3 under Grade 3 and Grade 4, the following text "Interrupt SAR444245 infusion" has been removed.	Change made for clarification
Section 8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	The following text: "and left ventricular ejection fraction (LVEF)" has been added to the naming of the section.	Change made for clarification
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

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act16903-16-1-1-amended-protocol03-substudy04

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 03 (SUBSTUDY 05)

Protocol title:	**A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with cetuximab for the treatment of cetuximab-naïve participants in 2nd/3rd line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)**
Protocol number:	**ACT16903-S05**
Amendment number:	**03**
Compound number (INN/Trademark):	**SAR444245 (Not applicable)**
Brief title:	**A study of SAR444245 combined with cetuximab for the treatment of cetuximab-naïve participants in 2nd/3rd line R/M HNSCC**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette, 91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	IND156423
EudraCT:	2021-002105-99
NCT:	NCT05061420
WHO:	U1111-1251-5073

Date: 22-Dec-2021 Total number of pages: 59

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03 (Substudy 05)	All	22 December 2021, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02 (Substudy 05)	All	19 August 2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Substudy 05)	All	26 July 2021, version 1 (electronic 2.0)
Clinical Trial Protocol (Substudy 05)	All	11 June 2021, version 1 (electronic 1.0)

Amended protocol 03 (22 December 2021)

This amended protocol (Amendment 03) 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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to address requests from the French (National Agency for the Safety of Medicines and Health Products [ANSM]), Spanish (Agency for Medicine and Health Products [AEMPS]), Italian (Medicines Agency [AIFA]) and German (Federal Institute for Drugs and Medical Devices [BfArM]) Health Authorities after initial review. Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities (SoA)	A complete Table of SoA is provided for this substudy with procedures taken from the master protocol.	For clarity and consistency
	For electrolytes, “weekly under treatment and then at the EOT, at FU visit 1” has been removed, and a cross has been presented for appropriate times instead.	For clarification
	Troponin test has been added at screening, at C4D1, and as clinically indicated during treatment period until Follow-up visit 1.	To allow assessments of any potential cardiotoxicity
1.4 Biomarker flow-chart and 1.5 Pharmacokinetic flow-chart	Complete biomarker and pharmacokinetic flow-charts applicable for this substudy have been provided with procedures taken from the master protocol.	For clarity and consistency

Section # and Name	Description of Change	Brief Rationale
1.5.1 B2 Cohort	The cetuximab PK sample labelling has been changed from "P00" to "SC00" at start of infusion (SOI) and from "P01" to "SC01" at end of infusion (EOI).	For correction and clarity
6.5.3 General guidelines for the management of treatment-related adverse events	As the Study Board does not intervene for this substudy, any reference to it has been removed.	For consistency
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	Information on cytokine-release syndrome (CRS) reported with cetuximab and recommended guidelines for management have been added. A column mentioning "Recommended Cetuximab dose modifications and supportive care guidelines" has been added to Table 7.	To add recommended guidelines for management of CRS reported with cetuximab
6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS) and 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	The following statement "or alternative therapies per site practice in CRS management" has been added to "tocilizumab".	For flexibility following an issue with tocilizumab availability
6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 8 under Grade 4, "signs of" has been removed before "diffuse cerebral edema on neuroimaging".	Change made for consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus and correction
10.1 Appendix 1: Regulatory, ethical, and study oversight considerations	A new subsection 10.1.6 entitled "Dissemination of clinical study data" has been added with the following text: "Study participants results summaries will be provided in any one of the clinical trial portals after completion of the substudy, until the end of study".	Per CTFG guidance 2019: Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials
10.10 Appendix 10: Risk assessment	The following wording has been added: "The information below is per currently available USPI and EU SmPC. Please always refer to the latest version of the SAR444245 IB and cetuximab local label for the most up-to-date safety data".	To refer to the latest version of IB or local label for the safety data
10.11 Appendix 11: Abbreviations	List of abbreviations has been revised.	For consistency
11 References	List of references has been updated.	For consistency
Throughout the document	Minor editorial corrections were made.	For consistency

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1 PROTOCOL SUMMARY

Please refer to the Master Protocol for description of common protocol elements. Substudy B2-specific protocol elements are described below.

1.1 SYNOPSIS

Protocol title:

A Phase 2 non-randomized, open-label, multi-cohort, multi-center study assessing the clinical benefit of SAR444245 (THOR-707) combined with cetuximab for the treatment of cetuximab-naïve participants in 2nd/3rd line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC)

Brief title: A study of SAR444245 combined with cetuximab for the treatment of cetuximab-naïve participants in 2nd/3rd line R/M HNSCC

Rationale:

Clinical data from the on-going monotherapy dose escalation of SAR444245 has indicated a peripheral increase in the number of NK cells. NK cells are important effector cells which mediate antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab. Furthermore, in vitro data have shown that NK-cell–mediated lysis of head and neck tumor cells is significantly enhanced by the combination of cetuximab therapy with immune stimulatory cytokines, including IL-2. This was demonstrated in SAR444245 in vitro studies, where NK cells pretreated with SAR444245 and then co-cultured with the epidermal growth factor receptor (EGFR)-expressing CAL27 cancer cells improved the ADCC function of cetuximab in a dose-dependent fashion. Cetuximab can prime the immune system for anti-PD-1 therapy by recruiting cytotoxic cell effectors of both the innate and adaptive immune systems to the intra tumoral space.

The proposed study aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with cetuximab will result in a significant increase in the percentage of participants with HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease experiencing an objective response.

Objectives and endpoints

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

Table 1 - Objectives and endpoints

Objectives	Endpoints
Secondary	
To assess the concentrations of cetuximab	Concentrations of cetuximab

Overall design:

Please refer to the master protocol.

Brief summary:

Cohort B2: This substudy will include participants with R/M HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease and will assess SAR444245 combined with cetuximab.

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

Number of participants:

Overall, approximately 40 participants will be enrolled and treated in the core phase of Cohort B2.

In the expansion phase, approximately 56 participants will be enrolled.

Intervention groups and duration:

Please refer to the master protocol for common description of the study duration.

Study intervention(s)

Cohort B2: cetuximab-naïve & platinum-based regimen treated R/M HNSCC after failure of no more than 2 regimens for R/M disease, SAR444245 + cetuximab

Dosing sequence: [redacted]

Investigational medicinal product(s)

Cetuximab

- **Formulation:**
  - a clear, colorless solution for injection provided as 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL in a single-dose vial

  or

  - 100 mg/20 mL or 500 mg/100 mL

  or

  - any other cetuximab formulation approved locally.
- **Route of administration:** IV infusion.
- **Dose regimen**: cetuximab will be given on Cycle 1 Day 1 as an initial loading dose of 400 mg/m^2 infused over 120 minutes (maximum infusion rate 10 mg/min or as per local practice and labels) followed by weekly 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) for all subsequent doses starting with the Cycle 1 Day 8 administration **until progressive disease (PD)**.

SAR444245

- **Formulation**: SAR444245 is provided as a 2 mg/mL concentrate for solution for infusion in a single-dose vial with an extractable volume of 1 mL.
- **Route of administration**: intravenous (IV) infusion.
- **Dose regimen**: 24 μg/kg administered as an IV infusion over 30 mins every 3 weeks (Q3W) on Day 1 of each cycle (21 days per cycle) **until PD.**

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

Non-investigational medicinal products

Please refer to the master protocol for SAR444245 premedication.

Premedication for cetuximab

All participants who will receive cetuximab should be pre-medicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab, or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions (IR).

When SAR444245 and cetuximab are given on the same day, participants who have received diphenhydramine as cetuximab premedication may skip the diphenhydramine as SAR444245 premedication.

Statistical considerations:

Please refer to the master protocol for description of common statistical considerations.
Cohort B2-specific analysis:

- **Analysis of other secondary endpoints:**

Plasma concentrations of cetuximab will be summarized with descriptive statistics.

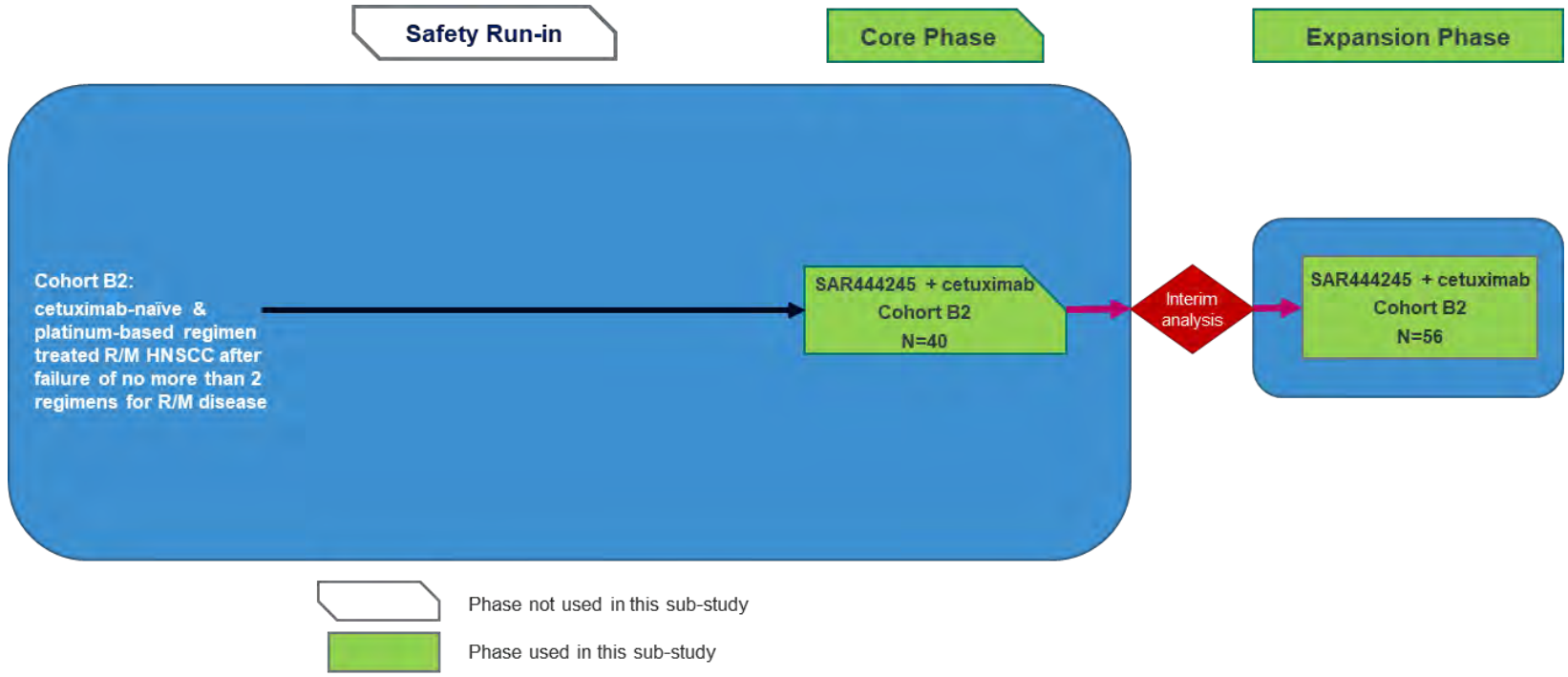
For Cohort B2, the cohort cut-offs for the analyses are as follows:

- Interim analysis cut-off: the date on which all participants in the core phase have at least 2 post-baseline tumor assessments or discontinue study treatment (whichever occurs first).
- Primary analysis cut-off: the date on which the last participants response is maintained for 6 months in the expansion phase (approximately 9 months from last participant's first infusion in the expansion phase).

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Overall substudy schema



HNSCC: head and neck squamous cell carcinoma; R/M: recurrent/metastatic.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Elements of the schedule of activities (SoA) common to all cohorts are detailed in the master protocol. Cohort B2-specific evaluations are presented in this table.

Evaluation[a]	**Screening /baseline**	**Treatment period**[b]									**End of treatment**	**Observation period**[c]			**Survival phone call follow-up period**[d]	**Notes**
		Treatment Cycle 1			**Treatment Cycle 2**			**Treatment Cycle 3 and beyond**			**EOT Visit**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and beyond**	**Phone call follow-up**	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Informed consent Inclusion/Exclusion criteria	X															
IRT contact	X	X			X			X			X					
Demography, medical/surgical and disease history	X															See Section 8 of master protocol
Full physical examination	X										X					
Directed physical examination		X	X	X	X			X				X				See Section 8.2.1 of master protocol
Body weight/Height[e]	X	X			X			X			X	X				

Evaluation[a]	Screening /baseline	Treatment period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X				See Section 8.2.2 of master protocol & Section 8.2.2
SpO_2	X	As clinically indicated														
Performance status (ECOG)	X	X	X	X	X			X			X	X				
12-lead ECG	X	X	As clinically indicated													See Section 8.2.3 of master protocol
LVEF	X	As clinically indicated														See Section 8.2.3 of master protocol
Laboratory assessments																
Troponin	X	As clinically indicated						X (D1 Cycle 4)			As clinically indicated					See Section 8.2.3 & Section 10.2 of master protocol
Pregnancy test	X	X			X			X			X	X	X			See Sections 8.2.5, 8.3.5 & 10.2 of master protocol
Blood chemistry/ hematology	X	X	X	X	X	X	X	X	X	X	X	X				See Section 10.2 & Section 10.2 of master protocol
Electrolytes	X	X	X	X	X	X	X	X	X	X	X	X	as clinically indicated			

Evaluation[a]	Screening /baseline	Treatment period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	D-28 to D-1	D1	D8 (±1)	D15 (±1)	D1 (±3)	D8 (±1)	D15 (±1)	D1 (±3)	D8 (±1)	D15 (±1)	30 (±7) days after last IMP or prior to initiation of further therapy	3 months from last IMP admin ±7 days	6 months from last IMP admin ±7 days	Every 3 months ±7 days	Every 3 months ±14 days	
Coagulation	X	As clinically indicated														See Section 10.2 of master protocol
Urinalysis[k]	X	X						X			X	X				See Section 10.2 of master protocol
Hepatitis serology CD4 counts & Viral Load	X[f]	As clinically indicated														See Section 10.2 of master protocol
HPV p16 status for participants with oropharyngeal cancer	X															
PK	See PK Flow-Chart in Section 1.5															
ADA	See PK Flow-Chart in Section 1.5															
Exploratory biomarkers																
PDy - Blood and tumor tissue collection[g]	See Biomarkers Flow-Chart in Section 1.4															
Disease assessment																
CT/MRI[h]	X							X			X	X	X	X		See Section 8.1 of master protocol
Brain imaging[i]	X															See Section 8.1 of master protocol

Evaluation[a]	Screening /baseline	Treatment period[b]									End of treatment	Observation period[c]			Survival phone call follow-up period[d]	Notes
		Treatment Cycle 1			Treatment Cycle 2			Treatment Cycle 3 and beyond			EOT Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Phone call follow-up	
Cycle day (Visit window in Days)	**D-28 to D-1**	**D1**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**D1 (±3)**	**D8 (±1)**	**D15 (±1)**	**30 (±7) days after last IMP or prior to initiation of further therapy**	**3 months from last IMP admin ±7 days**	**6 months from last IMP admin ±7 days**	**Every 3 months ±7 days**	**Every 3 months ±14 days**	
SAR444245 administration		X			X			X								
Cetuximab administration		X	X[l]	X[l]	X	X[l]	X[l]	X	X[l]	X[l]						
AE/SAE assessment[j]	X	Continuously throughout treatment period										X				See Section 8.3 of master protocol
Prior medication	X (within 28 days prior to first dose)															
Concomitant medication		Continuously throughout treatment period														See Section 6.8 of master protocol
First subsequent anticancer therapy											X	X	X	X	X	
Survival status															X	

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

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

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

d **Survival Phone Call Follow-Up Period**: Participant who moves into the Survival Follow-up Period should be contacted by telephone approximately every 3 months ±14 days to assess for survival status. Information on the first subsequent anticancer treatment, best reported response, and date of progression will also be collected. Updated survival status may be requested by the Sponsor at any time during the study.

e **Weight/Height**: Height is required at baseline only. Weight is required at Screening and prior to starting each infusion. The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle.

f For participants with known HIV, hepatitis B and hepatitis C infection under antiviral treatment to confirm controlled infection, and for all participants in Germany and Italy (see details and specific instructions in Section 10.2 and Section 10.8 of master protocol).

g If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

h **CT/MRI**: The initial tumor imaging will be performed within 28 days prior to the C1D1. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of enrollment. On study imaging will be performed every 9 weeks (63 ±7 days) after the date of first IMP or more frequently if clinically indicated in the first 45 weeks. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a participant throughout the trial. After Week 45 tumor imaging should be performed every 12 weeks (84 ±7 days). CT scan of the **head, neck, chest and abdomen (pelvis is optional)** and any other locations with suspicion or evidence of disease involvement is required for the baseline assessment and during treatment period until PD. After the first documentation of response or the first documentation of progression (if the participant is clinically stable) per RECIST 1.1, confirmatory imaging should be performed no fewer than 28 days later. Alternately, the scan performed at the next scheduled time point (eg, every 63 ±7 days) may be used as confirmation. Tumor assessment is not needed for participants who start another anti-cancer therapy.

i **Brain imaging**: For participants with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. Patients with asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease as per protocol tumor assessment schedule. In all other cases, the lesions must be treated. Two additional scans obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. If participants receive systemic therapy during these 4 weeks stabilization at the treating physician's discretion, this systemic therapy will be considered as part of prior anti-cancer therapy. Participants with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least 4 weeks apart. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved, and the participant is not using steroids for at least 14 days prior to study treatment. The screening brain scan may be collected up to 42 days prior to enrollment.

j **AE/SAE assessment**: Severity will be graded according to NCI-CTCAE v 5.0, ICANS and cytokine release syndrome (CRS) will be graded using ASTCT criteria integrated with central laboratory cytokine results (1).

k Urinalysis using dipstick for glucose, blood, pH, protein, ketones, leukocytes and microscopic examination (if blood or protein is abnormal) will be performed every 4 cycles during the Treatment period and as clinically indicated.

l Cetuximab dosing only.

Abbreviations: ADA: anti-drug antibodies; AE: adverse event; ASTCT: American Society for Transplantation and Cellular Therapy; C: Cycle; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; FU: follow-up; HPV: Human Papilloma virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; ICF: informed consent form; IMP: investigational medicinal product; IRT: Interactive Response Technology; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NCI-CTCAE: National Cancer Institute-Common terminology criteria for adverse events; PD: progressive disease; PDy: pharmacodynamic; PK: pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; SAE: serious adverse event; SpO_2: oxygen saturation.

1.4 BIOMARKER FLOWCHART

1.5 PHARMACOKINETIC FLOWCHART

1.5.1 B2 Cohort

Cycle	Treatment Cycle 1				Treatment Cycles 2, 3, 4, 6, 8, 10 + every 4th cycle thereafter		EOT visit 30 (±7) days after last IMP admin
Day	**D1**		**D2**	**D8**	**D1**		
Time after start of SAR444245 dosing	**SOI**	**EOI**	**Any time**	**Any time**	**SOI**	**EOI**	
SAR444245 PK sample		P00[b]	P01			P00[b]	
SAR444245 ADA sample	AB00[a]			AB01	AB00[a]		ABF00
Time after start of dosing cetuximab	**SOI**	**EOI**	**D2**	**D8**	**SOI**	**EOI**	
Cetuximab PK sample	SC00[a]	SC01[b]			SC00[a]	SC01[b]	

a Samples collected strictly before start of infusion (SOI).

b EOI samples must be taken at end of infusion (EOI) precisely ±5 minutes.

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

2 INTRODUCTION

This study is developed as a master protocol in order to accelerate the investigation of SAR444245 in combination with various anticancer therapies by identifying early signals. The information that is common to all cohorts is included in the master protocol, and this substudy provides details specific to Cohort B2 (participants with HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease), for the combination of SAR444245 with cetuximab.

Please refer to the master protocol for an introduction for ACT16903 study.

2.1 STUDY RATIONALE

2.1.1 Cohort B2: SAR444245 combined with cetuximab

Clinical data from the on-going monotherapy dose escalation of SAR444245 (HAMMER study) has indicated a peripheral increase in the number of NK cells. NK cells are important effector cells which mediate ADCC for IgG1 antibodies such as cetuximab. In vitro data where NK cells pretreated with SAR444245 and then co-cultured with the EGFR-expressing A431 cancer cells improved the ADCC function of cetuximab in a dose dependent fashion. These data support the evaluation of SAR444245 in combination with cetuximab.

2.2 BACKGROUND

2.2.1 Cetuximab

Cetuximab is an immunoglobulin G1 (IgG1) monoclonal antibody against the ligand binding domain of EGFR, which is abnormally activated in many epithelial cancers including HNSCC (2). The mechanism of action of cetuximab appears to include antibody dependent cell mediated cytotoxicity (3) in addition to EGFR blockade, which may contribute to its efficacy and may be further exploited. Erbitux (Cetuximab) is indicated for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy; recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil. It is also indicated for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck.

2.2.2 Rationale for HNSCC and selected participant population

Please refer to the master protocol.

2.2.3 Current standard of care in HNSCC

2.2.3.1 Cetuximab monotherapy as second line therapy

Patients with platinum-refractory disease may also achieve a treatment benefit with cetuximab. In an open-label multicenter Phase II study, cetuximab demonstrated activity as monotherapy in patients with R/M HNSCC who had failed platinum-based chemotherapy with a 13% response rate, DCR of 46%, and median response duration of 126 days (4). This study provided the main support for the regulatory approval of single agent cetuximab for this population in the US.

2.3 BENEFIT/RISK ASSESSMENT

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

2.3.1 Risk assessment

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

Risk assessment of SAR444245 combined with cetuximab results from anticipated risks for SAR444245 and from the label information for Erbitux® (cetuximab), taking into account potential overlapping risks. The available safety data for cetuximab, along with proposed mitigation strategies are summarized below and also provided in Table 13.

2.3.1.1 Cetuximab

The important identified risks for cetuximab include but are not limited to: IRs (including anaphylaxis on the first dose); interstitial lung disease severe adverse skin reactions (with increased risk of secondary bacterial infection), electrolyte disturbances (hypomagnesemia, hypokalemia, hypocalcemia) cardiac AEs (including cardiopulmonary arrest/sudden death), and eye disorders (including ulcerative keratitis).

The most common adverse reactions (incidence ≥25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

The following precautions and warnings are to be acknowledged:

Cetuximab can cause serious and fatal IRs. Infusion reactions of any grade occurred in 8.4% of patients who received cetuximab across clinical trials. Grades 3 and 4 IRs occurred in 2.2% of patients. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose

(alpha-gal). Approximately 90% of severe IRs occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion. Premedication with a histamine-1 (H1) receptor antagonist is recommended together with monitoring of patients for at least 1 hour following each infusion.

Cardiopulmonary arrest or sudden death have occurred in 2%-3% patients with squamous cell carcinoma of the head and neck receiving cetuximab with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil cetuximab. A history of coronary artery disease, congestive heart failure, or arrhythmias and abnormal serum electrolytes may be predisposing factors.

Interstitial lung disease (ILD), that may be fatal, has occurred in <0.5% of patients receiving cetuximab in clinical trials.

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of patients across clinical trials. Grades 3 or 4 acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping treatment in most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis).

Cetuximab can cause hypomagnesemia, which occurred in 55% of patients in various clinical trials, including Grades 3 and 4 in 6% to 17% of cases. Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating treatment. It is recommended to monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of treatment, and to replete electrolytes as necessary.

Based on animal data and its mechanism of action, cetuximab may potentially cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys resulted in an increased incidence of embryo-lethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development.

Please refer to the country-approved cetuximab labeling (eg, United States product insert [USPI], Summary of Product Characteristics [SmPC]) for more detailed prescribing information.

2.3.1.2 SAR444245 combined with cetuximab

Combining SAR444245 with cetuximab may lead to an increased frequency and/or severity of AEs related to immune activation or may lead to additional AEs related to immune system activation for each substance individually or may cause occurrences of qualitatively different AEs. SAR444245 could also increase the incidence of cetuximab-induced cutaneous toxicities.

As these two substances are biologic agents, they may have the propensity to induce infusion-related reactions (IRR) that may have higher rate of occurrence and severity when SAR444245 with cetuximab are used in combination.

The MTD of SAR444245 combined with the approved dosing of cetuximab is under assessment in the HAMMER study using a Q3W schedule. Safety data generated from the combination of SAR444245 and cetuximab have informed the selection of the combination dose in this study.

2.3.2 Benefit assessment

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

Head and neck squamous cell carcinoma (HNSCC) is a tumor type that benefits from cetuximab treatment. Preclinical and preliminary clinical data indicates that SAR444245 expands NK cells which are important effector cells mediating antibody-dependent cellular cytotoxicity (ADCC) for IgG1 antibodies such as cetuximab. In vitro experiments show that SAR444245 improved the ADCC function of cetuximab in a dose-dependent fashion.

The combination regimen proposed to be evaluated in this study is anticipated to bring benefit to the cetuximab-naïve HNSCC cohort.

2.3.3 Overall benefit: risk conclusion

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

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

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

There are no data regarding safety of cetuximab in metastatic HNSCC patients during the COVID-19 pandemic. Nevertheless, as cetuximab does not cause significant immune suppression, there is no direct evidence to support changing or withholding cetuximab.

3 OBJECTIVES AND ENDPOINTS

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

Table 2 - Objectives and endpoints

Objectives	Endpoints
Secondary	
To assess the concentrations of cetuximab	Concentrations of cetuximab

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to the master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This substudy will include participants with R/M HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease and will assess SAR444245 combined with cetuximab.

Overall, approximately 40 participants will be enrolled and treated in the core phase of Cohort B2. In the expansion phase, approximately 56 participants will be enrolled.

Enrolled participants in this Cohort B2 will receive treatment with both SAR444245 and cetuximab until PD.

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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The proposed substudy aims to establish proof-of-concept that non-alpha IL-2 SAR444245 combined with cetuximab, will result in a significant increase in the percentage of participants with HNSCC previously treated with platinum-based regimen & cetuximab-naïve after failure of no more than 2 regimens for R/M disease experiencing an objective response.

Please refer to the master protocol for more information.

4.2.1 Participant input into design

There was no participant input into design of the trial.

4.3 JUSTIFICATION FOR DOSE

4.3.1 SAR444245 dose

Please refer to the master protocol.

4.3.2 Cetuximab dose

This study proposes to evaluate the clinical benefit of 24 µg/kg SAR444245 Q3W combined with the approved dose of 400 mg/m² cetuximab as an IV infusion on day 1 of the study followed by subsequent doses of 250 mg/m² cetuximab IV QW.

4.4 END OF STUDY DEFINITION

Please refer to the master protocol.

5 STUDY POPULATION

See the master protocol for a full list of common inclusion and exclusion criteria and the subsections below for Cohort B2-specific criteria.

5.1 INCLUSION CRITERIA

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

Type of participant and disease characteristics

I 01. Provision of tumor tissue:

- **Optional** baseline biopsy for participants **in Core Phase**
- **Mandatory baseline biopsy for all participant in Expansion Phase** (minimum **10 slides with 4-5 micron thickness**). Archival tumor tissue samples should be obtained from biopsies done within 6 months, and there should be no systemic anti-cancer therapy between collection of biopsy and enrollment. Slides specifications are detailed in Lab Manual.
- The Sponsor may approve the written request to enroll, on a case-by-case basis, participants with:
  - location of the tumor not amenable to biopsy due to significant risk, OR
  - less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment.

I 02. Prior anticancer therapy

- Participants should have failed no more than 2 systemic anti-cancer regimens (at least one should be a platinum-containing regimen, unless it's already given in **locally advanced** disease) in **R/M disease**. Previous anti-programmed cell death-1 (PD1)/ programmed cell death ligand 1 (PDL-1) based regimen is allowed.

5.2 EXCLUSION CRITERIA

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

E 01. Electrolytes (magnesium, calcium and potassium) outside the normal ranges.

Prior/concomitant therapy

E 02. Prior treatment with cetuximab (prior cetuximab allowed if used for the treatment of locally advanced disease, with no PD for at least 4 months from completion of prior cetuximab therapy).

5.3 LIFESTYLE CONSIDERATIONS

Please refer to the master protocol.

5.4 SCREEN FAILURES

Please refer to the master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING [ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION]

Please refer to the master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 STUDY INTERVENTION(S) ADMINISTERED

Please refer to the master protocol.

Enrolled participants in this Cohort B2 will receive treatment with both SAR444245 and cetuximab until PD.

Dosing sequence: [redacted]

6.1.1 Investigational medicinal product

Investigational medicinal product (IMP) is defined as SAR444245 and cetuximab administered as described in Section 4.1. Details of each IMP component to be administered are shown in Table 3.

Preparation and administration of IMP are detailed in the pharmacy manual.

Hydration is required for SAR444245 infusions. Details are provided in Section 6.1.3 of the master protocol.

Table 3 - Overview of IMP administered

Intervention name	SAR444245	Cetuximab
Type	See master protocol	Biologic
Dose formulation	See master protocol	Solution for infusion
Unit dose strength(s)	See master protocol	100 mg/ 50 mL (2 mg/mL)
Dosage level(s)[a]	24 µg/kg Q3W	400 mg/m^2 C1D1 and QW 250 mg/m^2 at C1D8 and subsequent administrations
Route of administration	See master protocol	IV infusion
Use	See master protocol	Treatment of cancer (combination)
IMP or NIMP	IMP	IMP
Packaging and labeling	See master protocol	Supplied as 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL in a single-dose vial or 100 mg/20 mL or 500 mg/100 mL or any other formulation approved locally.
Current/Former name(s) or alias(es)	NA	Erbitux

a The total dose will be calculated based on the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. Study sites should make every effort to measure body weight as close to the infusion day as possible considering the variability of local process from site to site. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, the participant must still be weighed on D1 of each cycle, and the weight recorded in the electronic case report form (e-CRF). For SAR44245, study sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of 5 minutes and +10 minutes is permitted.

6.1.2 Non-investigational medicinal product

Please refer to the master protocol for SAR444245 premedication.

Premedication for cetuximab

All participants who will receive cetuximab should be pre-medicated with diphenhydramine 25 to 50 mg IV (or equivalent) prior to the first dose of cetuximab, or any other recommended premedication as per local requirements. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior IRs.

When SAR444245 and cetuximab are given on the same day, participants who have received diphenhydramine as cetuximab premedication may skip the diphenhydramine as SAR444245 premedication.

6.1.3 Hydration guidelines for SAR444245 administration

Please refer to the master protocol.

6.1.4 Readiness for treatment of severe cytokine release syndrome

Please refer to the master protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Please refer to the master protocol.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Please refer to the master protocol.

6.5 DOSE MODIFICATION

6.5.1 General rules

Dose modifications for SAR444245 and cetuximab are permitted according to the guidelines described in this section. Modification of dose levels in case of dose reduction for cetuximab is described in Table 4.

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

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

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

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

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

6.5.2 Cycle delay and dose omission

The treatment window is ±3 days for each of the Q3W IMP administrations. The treatment window is ±1 day for cetuximab administration on Day 8 and Day 15 of each cycle.

A cycle is deemed to have been delayed if the treatment is administered ≥4 days beyond the theoretical day of Q3W IMP administration. The participant may receive the next dose after recovery from the toxicity as described in Section 6.5.3. After cycle delayed, such participants may be considered for treatment resumption once the toxicity resolves or improves to Grade 1 or baseline.

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

- For Q3W IMP administration: If toxicity occurs and the participant does not recover on the day of planned administration; restart of study IMPs could occur only on the initiation of the subsequent cycle.
- For cetuximab Day 8 and Day 15 administration in each cycle: if toxicity occurs and the patient does not recover on the day of planned infusion or within the following 3 days, infusion may be omitted.
- In case of cycle delay or dose omissions for the recovery of toxicity, the following rules should be followed for restart or discontinuation of the treatment:
  - In case of a cycle delay up to 14 days or a dose omission, it is per Investigator's decision to restart the study treatment.

- After a cycle delay of >14 days and ≤84 days, or 2 to 4 consecutive dose omissions, it is per Investigator's decision to restart the study treatment or the IMP that is omitted, if a clear benefit from treatment is observed and after consultation with the Sponsor.
- The study treatment must be permanently discontinued if the cycle delay is longer than 84 days, or if the participant has more than 4 consecutive dose omissions.
- For any delayed cetuximab treatment, do not repeat the initial dose of 400 mg/m². At the restart of cetuximab treatment, all subsequent infusions will be at the appropriate dose level according to Table 4.

- Cycle delay or dose omission may be considered for situations other than TEAEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 21 days of the scheduled delay or dose omission, unless otherwise discussed with the Sponsor (for example for national or regional emergencies). The reason for this delay or dose omission should be documented in the participant's study record.

Modification of dose levels in case of dose reduction

Dose reduction steps for cetuximab are shown in Table 4. One or several doses of cetuximab can be omitted.

Table 4 - Dose levels for cetuximab dose reduction

Starting dose	Dose level 1	Dose level 2
400 mg/m² then 250 mg/m²	200 mg/m² (20% decrease)	150 mg/m² (20% decrease)

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

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

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

No delay/omission or dose modification is required for Grade 1 events.

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

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

Recommended guidelines for the management of specific AEs including immune-related AEs (irAEs), cytokine release syndrome (CRS), vascular leak syndrome (VLS) and IRRs are presented in Section 6.5.4.

6.5.4 Guidelines for the management of specific adverse events

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

6.5.4.1 Infusion-related reactions (IRR)

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

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

Guidelines for the management of SAR444245 IRR events are provided in Table 5. Participants who develop Grade 2 IRR should have the next SAR444245 infusion given at half the infusion rate. For instructions on premedication at subsequent dosing, please see Section 6.1.2.1 of the master protocol.

Table 5 - SAR444245 Infusion-related reaction dose modification and treatment guidelines

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

NCI CTCAE Grade	Treatment
	Give the next infusion at half the infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.
Grade 4 Life-threatening; urgent intervention indicated	Permanently discontinue SAR444245. The participant can continue treatment with the other anti-cancer therapy in combination During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids. Increase monitoring of vital signs as medically indicated until the participant recovers.

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

Participants who experience cetuximab-related IRs should have cetuximab reduced according to Table 6 and continue to receive antihistamine premedication prior to administration. Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it should remain decreased for all subsequent infusions. If the participant experiences a second infusion reaction at the decreased rate, cetuximab should be permanently discontinued. If any Grade 3-4 infusion reaction occurs, cetuximab treatment should be discontinued immediately and permanently.

Severe IRRs, including anaphylactic reactions, may commonly occur, in some cases with fatal outcome. Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Some of these reactions may be anaphylactic or anaphylactoid in nature or represent a CRS. Symptoms may occur during the first infusion and for up to several hours afterwards or with subsequent infusions.

Table 6 - Cetuximab Infusion-related reaction dose modification and treatment guidelines

NCI CTCAE Grade	Dose modification
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Stop cetuximab infusion and administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; urgent intervention indicated	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Permanently discontinue Cetuximab. The participant can continue treatment with SAR444245.

Abbreviations: CTCAE = Common terminology criteria for adverse events; IRR = Infusion related reaction; NCI = National Cancer Institute.

6.5.4.2 Anaphylaxis

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

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines in [5, 6, 7]).

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

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

Monitoring of vital signs is detailed in Safety Assessments (Section 8.2.2).

Cetuximab may be associated with CRS. Cytokine-release syndrome typically occurs within one hour after infusion and is less commonly associated with bronchospasm and urticaria. Cytokine-release syndrome is normally most severe in relation to the first infusion of cetuximab. Cetuximab related IRRs, including CRS, are discussed in Section 6.5.4.1 of the protocol. Please refer to Table 6 for Cetuximab IRR dose modifications and treatment guidelines.

Cytokine-release syndrome should be graded as per American Society for Transplantation and Cellular Therapy (ASTCT) criteria integrated with central laboratory cytokine results, and managed per guidelines in Table 7. If any grade of CRS is suspected, sites should make every

effort to draw an additional blood sample for cytokines levels (by central laboratory) prior to the administration of tocilizumab or alternative therapies per site practice in CRS management, as well as CRP and ferritin (by local laboratory).

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

Guidelines for management of CRS according to severity grading are provided in Table 7. ASTCT CRS consensus grading scale is provided in Section 10.13 of the master protocol.

Table 7 - Guidelines for the management of suspected cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b] • No hypotension • No hypoxia	No dose modification of SAR444245[a] Appropriate symptomatic treatment may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves.	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening.
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	Temporarily interrupt SAR444245 event occurs during infusion Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NSAIDs and acetaminophen. Increase monitoring of vital signs, cardiac and other organ functions closely as medically indicated until the participant recovers. Transfer to ICU may be required. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours treatment with corticosteroids and/or tocilizumab or alternative therapies per site practice in CRS management should be considered, as per guidance for Grade 3 events. IMP may be resumed when clinical symptoms have resolved or improved to Grade 1 and corticosteroid taper. No dose modification is required but decreasing to half the infusion rate can be considered.	Stop cetuximab infusion and administer intravenous fluids, bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once the event has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask	If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at [redacted] µg/kg or permanently discontinued, as clinically indicated.	Stop the cetuximab infusion immediately, administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Cetuximab should be permanently discontinued. The participant can continue treatment with SAR444245.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	If CRS Grade 4, permanently discontinue SAR444245. If CRS Grade 3 or Grade 4, initiate IV corticosteroids (outside of the context of CAR-T cells, corticosteroids alone maybe initiated in first intention) and tocilizumab or alternative therapies per site practice in CRS management considered, and/or epinephrine and/or other vasopressors should be administered as needed. Participants with severe CRS may require management in intensive care setting, with monitoring of clinical status and laboratory tests performed at least daily. As the participant improves, the intensity of the monitoring and setting can be decreased, but the participant should not be discharged from the hospital until clinically stable. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. In general, tapering of steroids can start when vasopressors and high-flow oxygen are no longer needed. CRS is considered resolved when there is sustained resolution of fever and there is no longer a need for oxygen supplementation to relieve hypoxia nor vasopressors to maintain blood pressure; however, normalization of temperature alone does not define resolution of CRS.	

Event severity (ASTCT CRS Consensus Grading)	Recommended SAR444245 dose modification and supportive care guidelines	Recommended Cetuximab dose modifications and supportive care guidelines
	If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, initiate management for persistent or worsening CRS. Re-evaluation for other contributing conditions will be done, such as infection, cardiac, thromboembolic and other complications. Intravenous **Tocilizumab** at 8 mg/kg (for participants weighing ≥30 kg) or alternative therapies per site practice in CRS management should be administered, and steroids should be administered concurrently. If still no improvement in oxygenation, hypotension fever and other manifestations is observed after the first dose of tocilizumab, it may be repeated after an interval of at least 8 hours and should not exceed 4 doses in total. For participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab or alternative therapies per site practice in CRS management and steroids, alternative options will be discussed with clinical site specialists	

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

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

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

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

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

6.5.4.4 Immune-related adverse events

Of note, if the AE is considered immune-related, both drugs in the combination should be delayed according to recommended dose modifications. If a participant experiences several irAEs, the most conservative recommendation should be followed.

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

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

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study drugs.
- If the toxicities do resolve, the combination of SAR444245 and cetuximab may be restarted at the discretion of the investigator.

6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome (ICANS) is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.13 of the master protocol). Recommendations for ICANS management mainly include the use of steroids, whereas tocilizumab or alternative therapies per site practice in CRS management should only be used in the context of CRS, as outlined in Table 8. The proposed management should be considered only as recommendations and in light of recommendations from site specialist.

Table 8 - Guidelines for the management of immune Cell-Associated Neurotoxicity Syndrome (ICANS)

Event severity (ASTCT Consensus Grading criteria)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Moderate Grade 2 ICE score 3-6. Awakens to voice.	Delay SAR444245[a]. Initiate treatment with IV corticosteroids should be initiated as needed. SAR444245 may be resumed only after participant recovery or improvement to Grade 1 after corticosteroid taper. Consideration for reduction of SAR444245 dose to[redacted] µg/kg as per Investigator with Sponsor consultation.

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

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

6.5.4.6 Vascular Leak Syndrome (VLS)

Vascular leak syndrome is a disorder characterized by leakage of intravascular fluids into the extravascular space and can lead to generalized edema and multiple organ failure. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. In various human diseases, an increase in capillary permeability to proteins leads to the loss of protein-rich fluid from the intravascular to the interstitial space manifested by any of the following **clinical presentations: diffuse pitting edema, exudative serous cavity effusions, noncardiogenic pulmonary edema, hypotension, and, in some cases, hypovolemic, shock with multiple-organ failure.** Fluid management is the cornerstone of VLS management; it is a balance between maintaining the intravascular volume to ensure organ perfusion to prevent organ failure, while avoiding volume overload. The management of VLS according to severity grading is described in Table 9. These guidelines are not comprehensive, and the Investigator should exercise clinical judgment based on the symptoms and condition of the individual participant and refer to current guidelines to the topic (8).

Table 9 - Guidelines for the management of Vascular Leak Syndrome (VLS)

Event severity (NCI-CTCAE V5.0)	Recommended SAR444245 dose modification and supportive care guidelines
Mild Grade 1 Asymptomatic	No intervention required other than clinical monitoring.
Moderate Grade 2 Symptomatic; medical intervention indicated	Delay SAR444245. Upon resolution of VLS or improvement to Grade 1, SAR444245[a] can be resumed at the reduced dose of [redacted] µg/kg The initial strategy is to administer boluses of crystalloids with a goal of providing the minimum effective volume that optimizes blood pressure together with a fluid-restrictive strategy is advocated to limit interstitial fluid volume expansion.
Severe or Life-threatening Grade 3: Severe symptoms; intervention indicated Grade 4: Life-threatening consequences; urgent intervention indicated	If Grade 3 or Grade 4 VLS, permanently discontinue SAR444245. In participants with severe shock, blood pressure may be only partially responsive or refractory to IV crystalloid fluids. Severe or persistent hypotension is to be managed by the administration of vasopressors. A trial of 25% albumin IV is an additional option, although its efficacy is limited to those with a severe capillary leak. In those who remain with refractory shock in the setting of low filling pressures, high molecular weight starches such as hetastarch (MW 450 kDa) and pentastarch (MW 264 kDa) may be effective in expanding the intravascular volume. Supportive care with invasive and noninvasive ventilation as well as renal replacement may be necessary in severe cases. When available, disease-specific therapy should be initiated as soon as possible to facilitate recovery. During the recovery phase from severe capillary leak, the endothelial injury resolves and the capillary leak becomes less important, resulting in stabilization of blood pressure, at which time fluid overload symptoms and signs may predominate (eg, pulmonary edema, pleural effusions, acute respiratory distress syndrome, systemic edema, ascites). Volume removal with loop diuretics is the first-line therapy in these patients. In those with marginal blood pressure and fluid overload, the combination of loop diuretics and 25% albumin IV may facilitate volume removal. Patients with AKI refractory to diuretics will require renal replacement.

a Information for preparation and storage of SAR444245 is provided in the pharmacy manual.
Abbreviations: AE = Adverse event; CTCAE = Common terminology criteria for adverse events; IV = Intravenous; NCI = National Cancer Institute.

6.5.4.7 Dermatologic Toxicity

Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis.

The dosing of cetuximab will be omitted 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. If acneiform rash improves during this time, then the dose of cetuximab should be reduced as indicated in Table 10. The dose modification guidelines in Table 4 should be followed for dermatologic toxicities other than acneiform rash.

If acneiform rash does not improve during this time, cetuximab will be permanently discontinued.

Participants who have omitted cetuximab therapy for more than 2 consecutive infusions due to acneiform rash, and upon resolution of the toxicity are still felt to be benefiting from cetuximab treatment may resume cetuximab with Sponsor approval.

The management of dermatologic toxicities according to severity grading is described in Table 10.

Table 10 - Cetuximab dose Modification for dermatologic toxicities

Dermatologic toxicities and infectious sequelae (eg, acneiform rash, mucocutaneous disease)	Recommended IMP dose modification
1st occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, continue at the same dose of 250 mg/m2. If no improvement, discontinue cetuximab.
2nd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at Dose level 1. If no improvement, discontinue cetuximab.
3rd occurrence; Grade 3 or 4	Day 1 of cycle: delay cycle until condition improves Within cycle: Omit infusion 1 to 2 weeks; if condition improves, permanently reduce at Dose level 2. If no improvement, discontinue cetuximab.
4th occurrence; Grade 3 or 4	Permanently discontinue cetuximab.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF STUDY

Please refer to the master protocol.

6.7 TREATMENT OF OVERDOSE

Please refer to the master protocol for SAR444245.

No specific information is available on the treatment of overdose of cetuximab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

6.8 CONCOMITANT THERAPY

Please refer to the master protocol.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to the master protocol.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to the master protocol.

7.3 LOST TO FOLLOW UP

Please refer to the master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

Please refer to the master protocol.

8.1 EFFICACY ASSESSMENTS

Please refer to the master protocol.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical examinations

Please refer to the master protocol.

8.2.2 Vital signs

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be measured after 5 minutes rest.
- At Cycle 1 Day 1, vital signs after infusion initiation will be collected more intensively;
  - Vital signs will be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5) hours after start of SAR444245 dose.
  - At Investigator's discretion, participants (not in the safety run-in) may have intensive vital sign monitoring (to be measured at Pre-dose, 0.5 (±0.25), 1 (±0.25), 2 (±0.5), 4 (±0.5), 8 (±0.5), 12 (±1), 16 (±1), 20 (±1), 24 (±1) hours after start of SAR444245 dose in an in-patient setting).
- **For the core phase participants**: from Cycle 2 to Cycle 4 study therapy will be administered for all patients in out-patient clinic with vital signs taken at baseline, at least 4 to 6 hours after the start of SAR444245 dosing, or for longer periods of time if clinically indicated.

8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)

Please refer to the master protocol.

8.2.4 Clinical safety laboratory assessments

Please refer to the master protocol.

8.2.5 Pregnancy testing

Please refer to the master protocol.

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

Please refer to the master protocol.

8.3.1 Time period and frequency for collecting AE and SAE information

Please refer to the master protocol.

8.3.2 Method of detecting AEs and SAEs

Please refer to the master protocol.

8.3.3 Follow-up of AEs and SAEs

Please refer to the master protocol.

8.3.4 Regulatory reporting requirements for SAEs

Please refer to the master protocol.

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

8.3.5 Pregnancy

Please refer to the master protocol.

8.3.6 Cardiovascular and death events

Please refer to the master protocol.

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

Not applicable.

8.3.8 Adverse event of special interest

Please refer to the master protocol.

8.3.9 Guidelines for reporting product complaints

Please refer to the master protocol.

8.4 PHARMACOKINETICS

Please refer to the master protocol for description of common pharmacokinetic (PK) evaluations, substudy specific evaluations are summarized below.

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

8.5 GENETICS AND/OR PHARMACOGENOMICS

Please refer to the master protocol.

8.6 BIOMARKERS

Please refer to the master protocol.

8.7 IMMUNOGENICITY ASSESSMENTS

Please refer to the master protocol.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Please refer to the master protocol.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Please refer to the master protocol.

9.2 SAMPLE SIZE DETERMINATION

Sample size:

The plan is to treat a total of 40 participants in the core phase of Cohort B2. In the expansion phase, approximately 56 participants will be treated.

Core Phase

Please refer to the master protocol.

Expansion Phase

At the end of the core phase of Cohort B2, the overall antitumor activity and safety will be assessed. The sponsor may decide to open a 56-participant expansion part based on the totality of data if the posterior probability that the true ORR is greater than 9%, which is considered minimal efficacious signal of interest, is greater than 80% with durable response. Based on a conjugate non-informative prior of beta (0.5, 0.5) at the time of the design of the study, at least 6 responders out of 40 exposed participants at the confirmed dose (confirmed ORR=15%) need to be observed in the core phase. However, emerging data generated from outside of the study may warrant a different prior to be considered before the formal IA. Analyses based on the total 96 participants by combining core phase and expansion phase will be performed. Table 11 lists estimated ORR and the corresponding 95% exact CIs by number of responders from a sample size of 96 participants evaluable for activity.

Table 11 - Estimated objective response rate (ORR) and 95% CI for Cohort B2 (combining core and expansion phases)

Number of responders (N=96)	ORR	95% CI for ORR (Clopper-Pearson)
10	10.4%	(5.1%, 18.3%)
12	12.5%	(6%, 20.8.5%)
14	14.6%	(8.2%, 23.3%)
15	15.6%	(9%, 24.3%)

With a sample size of 40 study participants in the core phase, the probability of observing 1 or more instances of an AE with a true incidence rate of 1%, 2%, or 5% is 33.1%, 55.4%, or 87.1%, respectively. With a sample size of 96 study participants in total, the probability of observing 1 or more instances of an AE with a true incidence rate of 1%, 2%, or 5% is 61.9%, 85.6%, or >99%, respectively. This provides reasonable assurance that events occurring at ≥5% frequency can be identified in this substudy.

9.3 POPULATIONS FOR ANALYSES

Please refer to the master protocol.

9.4 STATISTICAL ANALYSES

Please refer to the master protocol.

9.4.1 General considerations

Please refer to the master protocol.

9.4.2 Primary endpoint(s)

Please refer to the master protocol.

9.4.3 Secondary endpoint(s)

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

9.4.3.1 Other secondary endpoints

Plasma concentrations of cetuximab will be summarized with descriptive statistics.

9.4.4 Tertiary/exploratory endpoint(s)

Please refer to the master protocol.

9.5 INTERIM ANALYSES

Periodic Data Monitoring Committes are planned (details are in the master protocol).

At the end of the core phase, Cohort B2 will have one formal interim analysis when all participants in the core phase have at least 2 post-baseline tumor assessments or discontinued study treatment (whichever occurs first). The sponsor will decide if the expansion will be initiated based on totality of the data observed.

Primary analysis cut-off will occur when the last participant response is maintained for 6 months in the expansion phase (approximately 9 months from the last participant's first infusion in the expansion phase).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

Please refer to the master protocol.

10.1.6 Dissemination of clinical study data

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Clinical laboratory tests that are common to all cohorts are detailed in the master protocol. Cohort B2-specific evaluations are presented in Table 12.

Table 12 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Clinical chemistry[a]	See master protocol

a For participants in Cohorts B2 electrolytes to be done weekly under treatment and then at the end of treatment, at FU visit 1 and as clinically indicated. Additional electrolytes monitoring for Cohort B2, outside the visits, maybe done according the local standard institutional care.

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

Please refer to the master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

Please refer to the master protocol.

10.5 APPENDIX 5: GENETICS

Please refer to the master protocol.

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

Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Please refer to the master protocol.

10.8 APPENDIX 8: CRITERIA FOR RESPONSE ASSESSMENT

Please refer to the master protocol.

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

Please refer to the master protocol.

10.10 APPENDIX 10: RISK ASSESSMENT

Please refer to the master protocol for detailed information about SAR444245. Available information about cetuximab is shown in Table 13. The information below is per currently available USPI and EU SmPC.

Please always refer to the latest version of the SAR444245 IB and cetuximab local label for the most up-to-date safety data.

Table 13 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Infusion reactions	Cetuximab	Cetuximab Premedicate with a histamine-1(H1) receptor antagonist as recommended. Monitor patients for at least 1 hour following each cetuximab infusion, in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue cetuximab based on severity. Immediately interrupt cetuximab and permanently discontinue cetuximab for serious IRRs.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	Cetuximab can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal). Consider testing patients for alpha-gal IgE antibodies using FDA-cleared methods prior to initiating cetuximab. Negative results for alpha-gal antibodies do not rule out the risk of severe infusion reactions. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion.	Advise patients that the risk of serious infusion reactions may be increased in patients who have had a tick bite or red meat allergy. Advise patients to contact their healthcare provider and to report signs and symptoms of infusion reactions, including late onset infusion reactions, such as fever, chills, or breathing problems.
Cardiopulmonary arrest	Cetuximab Cetuximab can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients treated with radiation therapy and cetuximab in BONNER. BONNER (NCT00004227) was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced HNSCC being treated with cetuximab in combination with radiation therapy. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. In EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of 219 patients treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.	Carefully consider use of cetuximab with radiation therapy or platinum-based therapy with fluorouracil in patients with SCCHN with a history of coronary artery disease, congestive heart failure, or arrhythmias. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab administration (see Hypomagnesemia and Accompanying Electrolyte Abnormalities). Advise patients of the risk of cardiopulmonary arrest or sudden death and to report any history of coronary artery disease, congestive heart failure, or arrhythmias.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Pulmonary effects	Cetuximab can cause ILD. Interstitial lung disease (ILD), including 1 fatality, occurred in less than 0.5% of 1570 patients receiving cetuximab in clinical trials.	Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue cetuximab for confirmed ILD. Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
Electrolyte abnormalities (including Hypomagnesemia)	Cetuximab can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving cetuximab in Study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%. In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No Electrolyte abnormalities (including Hypomagnesemia) and accompanying electrolyte abnormalities can occur days to months after initiating cetuximab.	Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of cetuximab. Replete electrolytes as necessary.
Dermatological effects	Cetuximab: Cetuximab can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis. Acneiform rash occurred in 82% of the 1373 patients who received cetuximab across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients. Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping cetuximab in most patients. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed in patients who received cetuximab. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis). Cutaneous adverse reactions (including rash, pruritus and nail changes) are the most common adverse reaction (incidence greater than 25%).	Monitor patients receiving cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during cetuximab therapy. Withhold, reduce dose or permanently discontinue cetuximab based on severity of acneiform rash or mucocutaneous disease. Advise patients to limit sun exposure during cetuximab treatment and for 2 months after the last dose of cetuximab. Advise patients to notify their healthcare provider of any sign of acne-like rash, (which can include itchy, dry, scaly, or cracking skin and inflammation, infection or swelling at the base of the nails or loss of the nails), conjunctivitis, blepharitis, or decreased vision.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Risks related to special populations		
Reproductive toxicity	Cetuximab Based on animal data and its mechanism of action, cetuximab can cause fetal harm when administered to a pregnant woman. There are no available data for cetuximab exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Human IgG is known to cross the placental barrier; therefore, cetuximab may be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15-20% respectively. Pregnant cynomolgus monkeys were administered cetuximab intravenously once weekly during the period of organogenesis (gestation day [GD] 20-48) at dose levels 0.4 to 4 times the recommended dose of cetuximab based on body surface area (BSA). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams on GD 49. While no fetal malformations occurred in offspring, there was an increased incidence of embryolethality and abortions at doses approximately 1 to 4 times the recommended dose of cetuximab based on BSA. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development), and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling.	Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with cetuximab and for 2 months after the last dose of cetuximab. Verify pregnancy status in females of reproductive potential prior to initiating cetuximab.

10.11 APPENDIX 11: ABBREVIATIONS

ADCC:	antibody-dependent cellular cytotoxicity
AEs:	adverse events
AESIs:	adverse events of special interest
ASTCT:	American Society for Transplantation and Cellular Therapy
CRS:	cytokine release syndrome
e-CRF:	electronic case report form
EGFR:	epidermal growth factor receptor
EOT:	end of treatment
FDA:	Food and Drug Administration
HNSCC:	head and neck squamous cell carcinoma
ICANS:	immune Cell-Associated Neurotoxicity Syndrome
ICU:	intensive care unit
IgG1:	immunoglobulin G1
IMP:	investigational medicinal product
IR:	infusion reaction
irAEs:	immune-related AEs
IRR:	infusion-related reactions
IV:	intravenous
LVEF:	left ventricular ejection fraction
NCI-CTCAE:	National Cancer Institute- Common Terminology Criteria for Adverse Event
ORR:	objective response rate
PD:	progressive disease
PK:	pharmacokinetic
Q3W:	every 3 weeks
R/M:	recurrent and/or metastatic
SAEs:	serious adverse events
SmPC:	Summary of Product Characteristics
SoA:	schedule of activities
TEAE:	treatment-emergent adverse event
TRAEs:	treatment-related adverse events
USPI:	United States product insert
VLS:	vascular leak syndrome

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (26 July 2021)

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 overall rationale for the amendment is to respond to the Health Authorities (Food and Drug Administration, [FDA]) requests.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.5.1 B2 Cohort	The frequency of sampling for ADA has been increased to obtain data every cycle for the first 3 cycles, every other cycle for 4 samples, then every 4th cycle.	Regulatory Authority (FDA) request
Section 6.5.4 Guidelines for the management of specific adverse events	For clarity and brevity, command language has been used in the toxicity management sections.	Regulatory Authority (FDA) request
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 5 the following text has been revised: Under Grade 3 and Grade 4: - “prematurely” deleted from “prematurely permanently discontinued”. - “clearly attributable” deleted from “If IRR is clearly attributable to SAR444245” as the table title already indicates treatment with regards to SAR444245 IRRs. Under Grade 2, Grade 3 and Grade 4: “if applicable” deleted in the sentence that reads “SAR444245 infusion should be interrupted if applicable”.	Regulatory Authority (FDA) request
	In Table 5 and Table 6, the following text “requires therapy or infusion interruption” has changed to “Therapy or infusion interruption indicated', and “pressor or ventilator support indicated” has been changed to “urgent intervention indicated".	For consistency with Common terminology criteria for adverse events (CTCAE) guidelines (version 5)
Section 6.5.4.1 Infusion-related reactions (IRR) and Section 10.10 Risk assessment (Table 9)	The text “SAR444245 infusion-associated reaction” was changed to “SAR444245 infusion-related reaction”.	For consistency

Section # and Name	Description of Change	Brief Rationale
Section 6.5.4.3 Fever, flu-like symptoms and cytokine-release syndrome (CRS)	In Table 7 the following text "If subsequent administration is tolerated, increasing the SAR444245 dose to ■ µg/kg at subsequent administration can be considered based on the clinical judgement of the Investigator with the Sponsor" has been removed for Grade 3.	Regulatory Authority (FDA) request
	For Grade 3, the following sentence has been changed from "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1 at ■ µg/kg or permanently discontinued, as clinically indicated" to "If CRS grade 3, temporarily cycle delay SAR444245, and resume subsequent treatment only when symptoms have resolved or improved to Grade 1. SAR444245 can be either restarted at ■ µg/kg or permanently discontinued, as clinically indicated". The following sentence has been added: "Monitoring of vital signs is detailed in Safety Assessments (Section 8.2.2)" for clarity.	For consistency and clarity
Section 6.5.4.5 Immune Cell-Associated Neurotoxicity Syndrome (ICANS)	In Table 8 the following text has been added under Grade 3 ICANS: "Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Section 6.5.4.3. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days."	Regulatory Authority (FDA) request
	The following text "diffuse cerebral edema" has been revised to "signs of diffuse cerebral edema".	For consistency with the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus
Sections 8.2.1 Physical examinations, Section 8.2.2 Vital signs, Section 8.2.3 Electrocardiograms, Section 8.2.4 Clinical safety laboratory assessments, and Section 8.2.5 Pregnancy testing	Sections newly inserted.	For clarity
Section 8.2.2 Vital signs	Details regarding monitoring of vital signs provided in the Master protocol have been added.	Regulatory Authority (FDA) request
Section 10.10: Appendix 10: Risk assessment	In Table 13, risk assessment for cetuximab was revised to be aligned with the most recent version of USPI for cetuximab.	Regulatory Authority (FDA) request
	Reference to "pembrolizumab" has been deleted from Section 10.10.	For correction
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

Amended protocol 02 (19 August 2021)

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 (see Master protocol).

OVERALL RATIONALE FOR THE AMENDMENT

The main rationale for this amendment is to add a new study cohort (Cohort A2, substudy protocol 02) and clarify the priority of recruitment of participants between Cohorts A1 and A2 (see Master protocol). Other changes have been made for clarification, accuracy, and correction.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis: Intervention groups and duration and Section 6.1.1 Investigational medicinal product	"Weekly" or "QW" has been added before "250 mg/m²" for administration of cetuximab dose regimen.	Change made for clarification
Section 1.3 Schedule of Activities (SoA)	"IMP Administration" has been changed to "Cetuximab Administration", and a row indicating "SAR444245 Administration" has been added with a refence to the master protocol.	Change made for clarification
Section 5.1 Inclusion criteria	In I06 "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to screening" has been revised to "participants with less than required number of slides or archival tumor tissue sample collected more than 6 months prior to enrollment"	Harmonization per program level approach
Section 6.5.2 Cycle delay and dose omission, and Section 6.5.3 General guidelines for the management of treatment-related adverse events	The following text regarding the treatment resumption after cycle delay (or dose omission) has been deleted: "or is stable and manageable through supportive/medical therapy".	Change made for correction
Section 6.5.3 General guidelines for the management of treatment-related adverse events	The name "Study Committee" has been changed to "Study Board".	Change made to ensure clarity and avoid confusion with any Independent Committee
Section 6.5.4.1 Infusion-related reactions (IRR)	In Table 5, under Grade 3 and Grade 4, the following text "Interrupt SAR444245 infusion" has been removed.	Change made for clarification
Section 6.5.4.1 Infusion-related reactions (IRR), and Section 6.5.4.7 Dermatologic Toxicity	The following text "and permanently" has been added after "If any Grade 3-4 infusion reaction occurs, cetuximab treatment should be discontinued immediately". In Table 6 and Table 10, "prematurely" has been deleted from "prematurely, permanently discontinued".	Change made for clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.2.3 Electrocardiograms and left ventricular ejection fraction (LVEF)	The following text: “and left ventricular ejection fraction (LVEF)” has been added to the naming of the section.	Change made for clarification
Throughout the document	Minor editorial corrections were made.	Changes made for consistency

11 REFERENCES

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