Integrated Analysis Plan

Study Number:	MS202359_0002
Clinical Study Protocol Title:	A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high risk for relapse and are ineligible for high-dose cisplatin
Study Phase:	III
Merck Compound:	MSC2735845 (Debio 1143)
Protocol Version:	18 October 2023 /Version 6.0
Integrated Analysis Plan Author:	**Coordinating Author** Biostatistics, Merck

Function	Author(s) / Data Analyst(s)
PPD	PPD
PPD	PPD

Integrated Analysis Plan Date and Version:	25 September 2024/ Version Final 4.0

Function	Name
PPD	PPD

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Approval Page

Integrated Analysis Plan: MS202359_0002

A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high risk for relapse and are ineligible for high-dose cisplatin

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANC	Absolute Neutrophils Count
ANCOVA	Analysis of COVARIANCE
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BSA	Body Surface Area
CALCIO	Corrected Calcium and Ionized Calcium
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIF	Cumulative Incidence Function
CIPD	Clinically Important Protocol Deviation
CRP	C-reactive Protein
CRT	Chemoradiotherapy
CSR	Clinical Study Report
ctDNA	circulating tumor DNA
CV%	Coefficient of Variation
DMC	Data Monitoring Committee
DI	Dose intensity
DFS	Disease-Free Survival
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EDMS	Electronic Document Management System
EEA	European Economic Area

EORTC	European Organization for Research and Treatment of Cancer
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HB	Hemoglobin
H&N35	Head and neck cancer specific questionnaire
HPV	Human Papilloma Virus
HR	Hazard Ratio
HRQOL	Health Related Quality of Life
IA	Interim Analysis
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IMRT	Intensity Modulated Radiation Therapy
irAE	Immune-related adverse event
IPD	Important Protocol Deviation
IRC	Independent Review Committee
ITT	Intention To Treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LA SCCHN	Locally Advanced Squamous Cell Carcinoma of the Head and Neck
Max	Maximum
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
Min	Minimum
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
Nd	Not done
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OS	Overall Survival

PA	Primary Analysis
PD	Protocol Deviation
PLT	Platelet Count
PRO CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PT	Preferred Term
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity Scale
PK	Pharmacokinetics
PKAS	PK Analysis Set
PTV	Planning Target Volumes
QLQ-C30	Quality-of-life-Core 30 Questionnaire
RDI	Relative dose intensity
RT	Radiotherapy
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Screening analysis set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
VAS	Visual Analog Scale
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
Final 1.0	13Jan2023	PPD	N/A
Final 2.0	17Nov2023	PPD	External DM outputs update requested by External DMC members PK analysis updates Reference level for alcohol subgroup updated AESI ALT/AST wording updated Late Onset AESI definition updated AESI labels updated
Final 3.0	05Mar2024	PPD	Reviewers list updated AESI definition updated as per protocol External DMC planned analysis
Final 4.0	25Sep2024	PPD	Added section 6.4 6.4 Overview of Planned Analyses after discontinuation of Xevinapant trials Reason for being unfit for high-dose cisplatin updated according to protocol v6.0 Adverse events analysis updates Missing imputation updates Demographic and other baseline characteristics and previous or concomitant therapies analysis set updates Study treatment day definition added

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the interim and primary analysis of data collected for protocol MS202359_0002.

Results of the main analyses described in this IAP will be included in the Clinical Study Report (CSR), except when otherwise stated. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

CCI [redacted] Additional analyses of Health Related Quality of Life (HRQOL) to answer further HRQOL objectives e.g., psychometric characteristics will be described in a separate HRQOL analysis plan.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments.

Details of the External Data Monitoring Committee (DMC) analyses for review of the participants' safety without formal statistical analysis are provided in Appendix 1 – External DMC Analysis.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the Clinical Study Report (CSR) template, CDISC requirements and special requirements for table layouts. Therefore, the following approach is used:

Generally, the term 'participant' will be used instead of 'subject' or 'patient'. However, in tables and listings the term 'subject' will be used to match CDISC requirements, except for in-text tables where 'participant' will be used to match the CSR and protocol templates. Similarly, the term 'study intervention' will be used in this document instead of 'treatment' to match protocol and CSR templates, however, tables and listings will use 'treatment' for brevity reasons. Exceptions from this rule are commonly used terms like "on-treatment", "treatment-emergent", "treatment policy", "subject-years", "by-subject", or names of eCRF pages like "Treatment Termination" page.

5 Objectives and Estimands

Table 1 Study Objectives and Estimands

Objectives	Estimands	IAP section
Primary		

To demonstrate improvement in DFS with xevinapant compared to placebo when added to Radiotherapy (RT) irrespective of subsequent anticancer therapy.	Endpoint: DFS defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled DFS assessments after last evaluable assessment or randomization):
	• Death from any cause
	• Objective Disease Recurrence (earlier date of first imaging or biopsy collection confirming event at a DFS assessment):
	  • Local or regional relapse which is subsequently confirmed by histopathology unless medically contraindicated or medical risk of biopsy deemed too high
	  • Distant metastases. Confirmation of pathology is recommended in case of solitary metastasis (especially in the lung) after considering potential contraindication and/or medical risk associated with biopsy.
	Population: High-risk patients with Stage III, IVA or IVB resected locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) ineligible to receive high-dose cisplatin-based chemoradiotherapy (CRT) postoperatively
	Treatment: xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo
	Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy):
	• Discontinuation of treatment
	• Start of subsequent anticancer therapy
	Population-Level Summary: Hazard Ratio
		14.1

Objectives	Estimands	IAP section
Secondary		
To demonstrate improvement in OS with xevinapant compared to placebo when added to RT followed by subsequent anticancer therapy.	Endpoint: OS defined as the time from date of randomization to death Treatment: xevinapant and RT followed by xevinapant followed by subsequent cancer therapy vs. placebo and RT followed by placebo followed by subsequent cancer therapy Population / Population-level Summary / Intercurrent Event Strategy: same as primary estimand	14.2.1
To evaluate time to subsequent cancer treatments in participants treated with xevinapant compared to placebo when added to RT.	Endpoint: Time to subsequent cancer treatments, defined as time from randomization to start of first subsequent cancer treatment Population / Treatment / Population-level Summary: the same with primary estimand Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Occurrence of DFS event	14.3.1
To evaluate the safety and tolerability of xevinapant compared to placebo when added to RT.	Endpoints: Occurrence of adverse events (AEs) and treatment-related AEs	15
To evaluate xevinapant compared to placebo when added to RT followed by xevinapant monotherapy in terms of patient-reported head and neck pain, swallowing, and speech as measured by the EORTC H&N35 sub scales, patient-reported fatigue, physical function, and global health status as measured by the EORTC QLQ C-30 sub scales and EQ-5D-5L Visual Analog Scale (VAS).	Endpoints: Change from baseline at • end of combination therapy • completion of investigational therapy on • EORTC QLQ-HN35 subscale scores (head and neck pain, swallowing, and speech), • EORTC QLQ-C30 subscale scores (fatigue, physical function and global health status), and • EQ-5D-5L VAS Population/ Treatment: same as primary estimand Intercurrent Event Strategy: The endpoint will be analyzed up to the intercurrent event: • Permanent discontinuation of investigational therapy: while on treatment strategy • Death (while alive strategy) Population-Level Summary: Difference of least squared meanchange from baseline	14.4.1
Exploratory		
To assess the concentration-time profile of xevinapant.	Endpoints: Plasma concentrations of xevinapant during the treatment period Treatment: xevinapant and RT followed by xevinapant	16.1
CCI [redacted]	[redacted]	[redacted]

Objectives	Estimands	IAP section
CCI [redacted]	[redacted]	[redacted]
To describe patient-reported outcomes over time.	Endpoints: EORTC QLQ-C30 and HN35, PGIS (Patient Global Impression of Severity Scale) , PGIC (Patient Global Impression of Change), Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO CTCAE)	15.5

6 Overview of Planned Analyses

The planned efficacy and futility analyses timelines are shown in the table below.

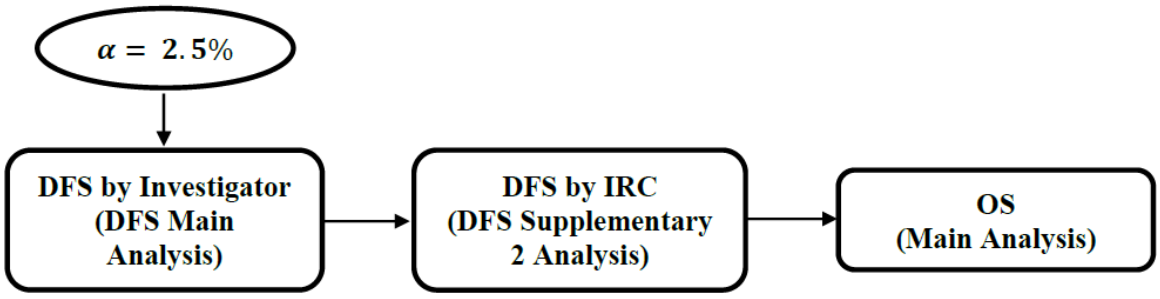
Table 2: Overview of cut-off definitions and timelines for primary and interim analyses

Analysis	Events (IF)	Expected Month[a] After FPI	Requirements for Confirmatory Test
DFS PA	409 (100%)	50	H_0^{DFS} tested in 'DFS supplementary 2' analysis only if it can be rejected in main analysis
OS IA1	344[b] (69%)	50	H_0^{OS} only tested, if H_0^{DFS} can be rejected in 'DFS supplementary 2' analysis at DFS PA
OS IA2	434 (88%)	66	H_0^{DFS} only tested, if H_0^{DFS} can be rejected in 'DFS supplementary 2' analysis, but not H_0^{OS} at OS IA1
OS PA	495[c] (100%)	88c	H_0^{DFS} only tested only if H_0^{DFS} can be rejected in 'DFS supplementary 2' analysis, but not H_0^{OS} at OS IA1 or OS IA2

DFS= Disease-Free Survival, IA= Interim Analysis, IF= Information Fraction, OS= Overall Survival, PA= Primary Analysis
a Projections based on assumptions as per Protocol Section 9.2.
b OS IA1 is conducted on same data set (and data cut-off date) as DFS PA.
c OS PA is conducted at the earlier of reaching the planned number of events or end of study (Protocol Section 4.4).

As shown on Figure 1, a fixed-sequence strategy is used to test first the null hypothesis H_0^{DFS} at 1-sided alpha of 2.5% while planning for a total number of 409 DFS events as assessed by Investigator in the DFS main analysis, which uses Investigator assessment and the treatment-policy strategy for the intercurrent event 'Start of subsequent anticancer therapy'. If and only if H_0^{DFS} can be rejected in the main analysis, the full alpha is reallocated to test H_0^{DFS} according to 'DFS supplementary 2' on the same data set, which uses the IRC assessment and hypothetical strategy for the intercurrent event 'Start of subsequent anticancer therapy' (i.e. censoring on the date of the last adequate assessment prior to start of subsequent anticancer therapy). If and only if that second test rejects H_0^{DFS}, the null hypothesis H_0^{OS} is confirmatory tested in a group-sequential design with interim analyses as planned in Table 2, which uses alpha-spending according to Lan-DeMets with O'Brian-Fleming-like boundaries planning for a total number of 495 OS events at primary analysis. That procedure achieves a strong control of the FWER at 2.5% one-sided according to Glimm (2010). Actual event numbers will be used to recalculate boundaries at OS IAs and decisions will be made based on p-values.

Figure 1 Fixed-Sequence Strategy to Control FWER at 2.5% 1-Sided, where the Arrows Indicate the Alpha Reallocation Applied if the Originating Test Rejects its Null Hypothesis Otherwise Confirmatory Testing is Discontinued



DFS=disease-free survival, FWER=family-wise error rate, IRC=Independent Review Committee, OS=overall survival.

The external DMC will regularly meet to evaluate safety and tolerability data (subject disposition, important protocol deviations, demographic data, disease history, treatment delays and dose reductions, adverse events, and laboratory data). External DMC analysis will be performed by an independent unblinded analysis team (IDDI for clinical data and either independent clinical pharmacology analyst for PK data), during this period CRO and Sponsor teams will remain blinded until the time of the DFS Primary Analysis. Details of the External DMC analyses for review of the participants' safety without formal statistical analysis are provided in Appendix 1 – External DMC Analysis.

6.1 DFS Primary Analysis

This analysis will be the main analysis. All planned analyses identified in the Clinical Study Protocol and in this IAP will be performed when 409 DFS events as assessed by Investigator and the database is locked for the analysis. Unblinding will be performed at the time of the DFS primary analysis.

All data will be included up to a data cut-off date which is determined by the number of events for primary endpoint required for the analysis (see Table 2). The cutoff date will be determined prospectively based on an event projection as the date when approximately 409 events will be reached and a blinded data review meeting confirms the numbers of events for both Investigator read and IRC read are sufficient. The final number of events might deviate from the planned number, e.g., due to cleaning activities. The data cut-off date will not be adjusted retrospectively in this case.

6.2 OS Interim Analyses

The first OS interim analysis (OS IA1) will be combined by using data from the same data cut-off date as DFS primary analysis.

An extract of the primary analyses as specified in the TLF table of contents will be done in the second OS interim analysis (OS IA2). The cutoff date will be determined prospectively based on an event projection as the date when approximately434 OS events will be reached and a data

review meeting confirms the numbers of events. The final number of events might deviate from the planned number, e.g., due to cleaning activities. The data cut-off date will not be adjusted retrospectively in this case. The decision boundaries will be recalculated based on the actual event number for testing OS null hypothesis..

All data will be included up to the data cut-off date which is determined by the number of OS events required for the analysis (see Table 2). A futility analysis will be performed for OS due to OS is only part of the confirmatory strategy if DFS null hypothesis is rejected at DFS PA.

6.3 OS Primary Analysis

An extract of the primary analyses as specified in the TLF table of contents will be done in the second OS primary analysis when approximately 495 OS events will be reached and data review meeting confirms the numbers of events.. The final analysis will be conducted on all data collected until the end of study. The final number of events might deviate from the planned number, e.g., due to cleaning activities. The data cut-off date will not be adjusted retrospectively in this case. The decision boundaries will be recalculated based on the actual event number for testing OS null hypothesis.

6.4 Overview of Planned Analyses after discontinuation of Xevinapant trials

A review of the TrilynX study (MS202359_0006) data suggests that the experimental arms with Xevinapant demonstrated either lower efficacy compared to the control group or limited potential for added benefit over standard of care.

Consequently, the scope of analyses for this study (MS202359_0002) has been reduced. The analyses outlined in Table 2 will not be conducted as originally planned. However, a single analysis using the primary analysis cutoff of 26-Sep-2024, will be performed for an abbreviated CSR.

The analyses considered relevant for this purpose are listed below:

- Participant disposition
- Important protocol deviations
- Enrollment details
- Demographics, medical history and other baseline characteristics (disease history, nicotine usage, alcohol consumption, prior surgery for SCCHN, ECOG performance status and heigh, weight, body surface area and body mass index at baseline)
- Vaccines for COVID 19
- Previous and concomitant medications, procedures and subsequent anticancer therapies
- Treatment compliance and exposure
- Efficacy analyses:
    - Disease-Free survival

- DFS assessed by investigator
- Censoring/Event status of DFS assessed by investigator
- Kaplan Meier Curve of DFS assessed by investigator

- Overall survival
  - OS
  - Censoring/Event status of OS
  - Kaplan Meier Curve of OS
- Time to subsequent anticancer treatment listing
- Relapse assessment listing
- PRO
  - EQ-5D-5L: patient questionary responses listing
  - EORTC QLQ-HN35: patient questionary responses listing
  - EORTC QLQ-C30: patient questionary responses listing
  - PGIS: patient questionary responses listing
  - PGIC: patient questionary responses listing
  - PRO CTCAE: patient questionary responses listing
  - EORTC Item Library Q168: patient questionary responses listing
- Display of adverse events
  - Overview of treatment-emergent adverse events (TEAEs)
  - Overview of TEAEs leading to discontinuation of treatment
  - TEAEs
  - TEAEs by worst grade
  - Xevinapant/Placebo related TEAEs
  - IMRT related TEAEs
  - Serious TEAEs (SAE)
  - Non-serious TEAEs
  - Xevinapant/Placebo Related SAEs
  - IMRT related SAEs
  - TEAEs leading to temporary discontinuation of Xevinapant/Placebo
  - TEAEs leading to permanent discontinuation of Xevinapant/Placebo
  - TEAEs leading to permanent discontinuation of IMRT
  - AESI
  - Other safety topics
- Deaths
- Clinical laboratory
  - Hematology: summary statistics over the time, shift in toxicity grading from baseline to highest grade and listing
  - Biochemistry: summary statistics over the time, shift in toxicity grading from baseline to highest grade and listing
  - Coagulation listing

- Urinalysis listing
- Vital sings: descriptive statistics over the time and listing
- ECG: descriptive statistics over the time and listing

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses in the clinical study protocol.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

The Screening analysis set includes all participants who provided informed consent, regardless of the participant's randomization and study intervention status in the study.

Full Analysis Set (FAS)

The FAS will include all randomized participants. Participant will be analyzed according to the study intervention assigned at randomization as per the intent-to-treat principle. For participants who are randomized by mistake more than once with different participant identifier, the first randomization will be used in this analysis set.

Safety Analysis Set (SAF)

All participants, who were administered any dose of any study intervention. Participants will be classified according to the study intervention assigned at randomization unless the incorrect study intervention was received throughout the dosing period in which case participants will be classified according to the first study intervention received.

PK Analysis Set (PKAS)

The PKAS will consist of all participants who receive at least one dose of xevinapant and provide at least one measurable postdose concentration which is unaffected by relevant protocol deviations or important events affecting PK. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received.

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set		
Analyses	**FAS**	**SAF**	**PKAS**
Demographics and Other Baseline Characteristics		✓	
Previous or Concomitant Therapies		✓	
Study Intervention: Compliance and Exposure	✓*	✓	
Efficacy: Primary Estimand	✓		
Efficacy: Secondary Estimands	✓		
Safety and Tolerability (including safety-related HRQOL)		✓	
Pharmacokinetics			✓
[redacted]	[redacted]		

*only to be created if discordance between FAS and SAF is more than 5%

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on primary and secondary efficacy endpoints as defined below. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

For the definition of subgroup level, data as documented in the electronic Case Report Form (eCRF) will be taken. The category "missing" will not be included in any subgroup analysis.

In case of low number of participants within a category (< 35 participants, which is about 5% of the randomized population), categories will be pooled when meaningful.

The randomization stratification factors (based on IWRS data) are the following:

- Primary tumor site:
  - Oropharynx/ oral cavity (reference level)
  - Larynx
  - Hypopharynx

- HPV Status by p16 IHC:
  - Oropharynx HPV positive (reference level)
  - oropharynx HPV negative or larynx/hypopharynx/oral cavity
- Tumor stage:
  - III (reference level)
  - IV

The following baseline covariates are defined:

- Age
  - Age < 65 years (reference level)
  - Age 65 - < 75 years
  - Age ≥ 75 years
- Sex
  - Male (reference level)
  - Female
  - Undifferentiated
- Race
  - White (reference level)
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Native Hawaiian or Other Pacific Islander
  - Other
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino (reference level)
- Ethnicity 1:
  - Japanese
  - Non-Japanese (reference level)

- Ethnicity 2
  - Chinese
  - Non-Chinese (reference level)

Note: Race or Ethnicity category "Not permitted per local regulation" will be handled as "missing"

- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
  - ECOG PS 0 (reference level)
  - ECOG PS ≥1
- Renal impairment
  - eGFR<60 (reference level)
  - eGFR≥60
- Alcohol
  - Current use (reference level)
  - No current use
- Smoking
  - Current use (reference level)
  - History of use
  - No history of use

9 General Specifications for Data Analyses

The results of this study will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment arm and/or scheduled time point, as applicable.

Study intervention definition

In this study, xevinapant/placebo and IMRT are considered study interventions. The date of first study intervention will be defined as the earliest date of any treatments (xevinapant/placebo or IMRT). The date of last study intervention will be defined as the latest date of any treatments (xevinapant/placebo or IMRT).

Listings

In the individual participant data listing all individual data will be listed as measured. Repeated and unscheduled measurements will be included in the listings. All listings will be sorted by treatment arm, subject ID, intervention period, and/or nominal time point, as appropriate. Data which are measured before administration of the study intervention will be sorted by participant number and nominal time point (if appropriate).

Tables and Descriptive Statistics

All data will be summarized by treatment arm, and/or nominal time point, as appropriate. Repeated and unscheduled measurements included in the listings will not be used for statistical analyses or summaries.

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e., the number of participants with non-missing values (n), the number of participants with missing values (nmiss), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values the number of participants with missing values should be indicated by a 0.

Except for HRQOL, the number of participants with missing values are defined as:

> nmiss = N (number of participants in the treatment arm) – n (number of participants with available data at the time point)

For HRQOL, n+nmiss should be equal to the number of participants with the expected visit in each treatment arm. Expected visits are determined prior or at the data cut-off date and include conducted visits according to HRQOL assessment schedule following the study protocol (see Section 9.7 for further details).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include only data from scheduled visits. Unscheduled visits will be included in the derivation of baseline or worst on-treatment values.

The overall significance level is 2.5% one-sided. Confirmatory statistical tests will be described in Section 14 along with procedures for controlling the family wise error rate in the strong sense. All other statistical tests mentioned in this IAP are to be regarded as exploratory. Exploratory statistical tests comparing study intervention groups will be performed one-sided. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

In order to provide overall estimates of study intervention effects, data will be pooled across sites. The “site” factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of participants randomized at each site.

All analyses will be performed using SAS® Software version 9.4 or higher in the SAS Grid environment (Statistical Analysis System, SAS-Institute, Cary NC, USA) or R (www.r-project.org), Version 3.2.5 or higher. The computer program Phoenix® WinNonlin® Version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA) could be used for PK data.

9.1 Data Handling after Cut-off Date

By its nature, data after cut-off may be incomplete and subject to further change and will not be used for summary statistics, statistical analyses, listings or imputations.

Stop dates are not affected by this rule, e.g., a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

9.2 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to randomization will serve as the baseline measurement for efficacy as well as for safety analyses. Those values should be also used for subgroup classification. If no such value is available, the last measurement prior to the first study intervention will be used as the baseline measurement with the exception of pre-randomization assessments used for the derivation of efficacy endpoints.

If an assessment that is planned to be performed before randomization, or study intervention per protocol is performed on the same day as the randomization or start of study intervention, respectively, but the assessment time is not available, it will be assumed that it was performed prior and will be considered for derivation of baseline.

If a scheduled predose measurement actually occurred postdose, then the corresponding measurement will be analyzed similar to an unscheduled postdose measurement.

If both central and local labs are collected, the baseline will be derived based only on the central lab collected data.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.3 Study Day/ Study Treatment Day

Day 1 is the day of first dose of any study intervention, the day before is Day -1 (no Day 0 is defined). Study day is defined relative to Day 1.

9.4 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g., survival time (days) = date of death – date of randomization + 1) if not otherwise specified.

The time since an event (e.g., time since first diagnosis) will be calculated as reference date minus date of event.

9.5 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.6 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

Participants during survival follow-up:

- Last known to be alive date collected on the 'Survival Follow-up' eCRF

Participants on study intervention/during DFS follow-up:

- AE start dates
- Date of last study intervention
- Date of last relapse assessment (Adjusted RECIST 1.1 for adjuvant SCCHN [post-screening] form)

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

9.7 Time Window

The assignments of visit windows are described in the table below for the purpose of by-visit and modeling analyses on HRQoL data (compliance and summary statistics).

- Visit windowing will be applied during the study intervention phase until end of treatment.
- No visit windowing will be performed at end of treatment or follow-up visits.
- Visit windowing will be based on the actual date of assessment and not the intended date
- HRQoL scheduled assessments are included for visit windowing, while unscheduled assessments are excluded.
- If there are multiple assessments for any specified visit and some of them are from scheduled visits, the assessment from the scheduled visit which is the closest to the planned study assessment day will be used for analysis.
- If there are multiple assessments for any specified visit and none of them are from scheduled visits, the closest assessment to each visit will be used for analysis.
- If there are two or more scheduled assessments with the same distance to the planned study day such as (-1/+1 day), the assessment prior to the planned study day will be used.

Table 3 Visit Window Definition for EQ-5D questionnaires for end of combination therapy endpoint

From	To	Planned Study Day	Analysis Visit
~	1	1	Baseline*
12	32	22	Cycle 2 Day 1
33	53	43	Cycle 3 Day 1
NA	74	64	End of combination therapy**

* Last value prior randomization
** Last measurement available prior to day 74 will be considered as end of combination therapy

For subjects who prematurely discontinued treatment End of Treatment Visit should be included on the time window calculation

Table 4 Visit Window Definition for EQ-5D questionnaires for completion of investigational therapy endpoint

From	To	Planned Study Day	Analysis Visit
~	1	1	Baseline*
12	32	22	Cycle 2 Day 1
33	53	43	Cycle 3 Day 1
54	74	64	Cycle 4 Day 1
75	95	85	Cycle 5 Day 1
96	116	106	Cycle 6 Day 1
NA	NA	134	End of Treatment

* Last value prior randomization

Table 5 Visit Window Definition for EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires for end of combination therapy endpoint

From	To	Planned Study Day	Analysis Visit
~	1	1	Baseline*
12	22	22	Cycle 2 Day 1
NA	74	64	End of combination therapy**

* Last value prior randomization
** Last measurement available prior to day 74 will be considered as end of combination therapy
For subjects who prematurely discontinued treatment End of Treatment Visit should be included on the time window calculation

Table 6 Visit Window Definition for EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires for completion of investigational therapy endpoint

From	To	Planned Study Day	Analysis Visit
~	1	1	Baseline*
12	43	22	Cycle 2 Day 1
44	85	64	Cycle 4 Day 1
86	120	106	Cycle 6 Day 1
NA	NA	134	End of Treatment

* Last value prior randomization

For ECG analysis, post-baseline values will be averaged based on their observed visits/time points according to time windows defined below. Values collected outside of Cycle Day 1 and Cycle Day 8 will not be taken into consideration in summary statistics but displayed in the related listing.

Table 7 Visit Window Definition for ECG

Time window	Analysis Visit
Values collected on Day 1 before the dose is taken	Cycle 1 Day 1 pre-dose
Values collected on Day 1 after the dose is taken	Cycle 1 Day 1 post-dose
Values collected on Day 8 before the dose is taken	Cycle 1 Day 8 pre-dose
Values collected on Day 8 after the dose is taken	Cycle 1 Day 8 post-dose

9.8 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study intervention day to the last administration day of study intervention + 30 days, or the cut-off date or death or the start day of subsequent anticancer drug therapy - 1 day, whichever occurs first.

For participants with treatment ongoing at cut-off date, all data from the first study intervention up to the cut-off date will be considered under the on-treatment period.

Any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy as documented in the "Anticancer treatment after discontinuation details", "Radiotherapy after discontinuation details" and "Surgery after discontinuation details" eCRF pages will be considered as subsequent anticancer therapy.

9.9 Exposure time

Radiotherapy exposure (weeks) = (end date – date of first dose of study intervention +3)/7

Xevinapant / Placebo exposure (weeks)= (end date – date of first dose of study intervention +8)/7

Overall treatment exposure is defined as the maximum of xevinapant / placebo treatment duration, and RT treatment duration

9.10 Follow-up time

Not applicable.

9.11 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

Partial dates, which are not to be imputed according to the IAP, will be presented in the format like "_____YYYY". If values are imputed according to the IAP, imputed values will be presented in participant data listings and imputed information will be flagged.

Missing statistics, e.g., when they cannot be calculated, should be presented as "ne". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "ne".

Disease history	Incomplete dates for disease history (e.g., initial diagnosis date, date of documented, locally advanced disease diagnosis) will be imputed as follows: • If the day is missing, it will be imputed to the 15th day of the month. • If both day and month are missing and the year is prior to the year of the first study intervention, the month and day will be imputed as July 1st. • If both day and month are missing and the year is same as the year of the first study intervention, the month and day will be imputed as January 1st. • If the date is completely missing, no imputation will be performed.
Adverse events	Incomplete AE-related dates will be imputed as follows: • In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing). • In all other cases, the missing onset day or missing onset month will be imputed by 1.

	• Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date. • In all other cases, the incomplete stop date will not be imputed. Note: The imputation rules could be adapted in case they are contradictory to any sequence of dates (e.g., change of severity or grading for the same AE).
Previous and concomitant medication and procedures	Incomplete prior/concomitant medication start and stop dates will be imputed as presented in Table 8. For the derivation of previous and concomitant medications following rules will be applied: Previous Medication: • Start date ≤ Start of study med OR • Start date = Missing Concomitant Medication: • End date ≥ Start of study med. AND (Start date ≤ End of study med OR Start date=Missing) OR • End date = Missing AND (Start date ≤ End of study med. OR Start date = Missing) The derivation is based on the following principles • Imputation leads to max. reasonable duration • Worst case: If medication is administered the same day as start of study medication, medication is classified as concomitant and previous

Table 8 Imputation rules for missing/incomplete start/end dates of medication and nicotine usage

	Start Date	End Date
Day missing only	Day = 1	Day = Last day of month
Month missing	Day = 1 Month = Jan	Day = 31 Month = Dec
Year missing	Date = Missing No imputation	

All	if imputed date > date of death: imputation by date of death

Nicotine usage	Incomplete nicotine usage start and end dates will be imputed as presented in Table 8.
Dates of study intervention	Start date of study interventions: In case the start date is missing, it is assumed that the first dose of study intervention is given at the randomization date. The randomization date will replace incomplete dates of the first dose of study intervention.
Death date	For the purpose of survival analyses partially missing death dates will be imputed as follows: If only the day is missing, the death date will be imputed to the maximum of the (non-imputed) day after the date of last contact and the 15th day of the month. Otherwise, it will not be imputed. Note: For participants who died and for whom no complete death date is available usually the death date is not imputed. For survival analyses imputation rules are applied, but in death listings non-imputed data will be presented.
Relapse assessments	All investigation dates (e.g., CT scan, biopsy) must be completed with day, month and year. If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (e.g., X-ray, CT-scan). If all measurement dates for an evaluation have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.
Dates of subsequent anticancer therapy	Incomplete dates for start date of subsequent anticancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period.

	• If only day is missing, it will be imputed as the last day of the month unless the end date of subsequent anticancer therapy is before that date. In that case, the incomplete anticancer therapy start date will be imputed as the end date of the anticancer therapy. • If both day and month are missing, no imputation will be performed. • Incomplete subsequent anticancer therapy stop dates will not be imputed.

9.12 Scoring of HRQOL Data

Unless otherwise specified, HRQOL items will be scored using their published administration and most current scoring manual. For items with missing responses, the response will be managed as per the scoring manual. See Appendix 1 for details.

9.13 Age at Time of an Event

Not applicable.

9.14 Other Derivations

Rescreened participants	Rescreened participants will be only counted once in the screening analysis set, considering the latest screening (screening with latest informed consent).
Unscheduled assessments	As per database definition, the safety unscheduled assessments are always linked to a scheduled timepoint (each unscheduled assessment is linked to the previous scheduled timepoint). Safety data retrieved from an unscheduled timepoint (vital signs, electrocardiogram [ECG] and laboratory data) will be analyzed according to the following scenario: • For shift table, they will be taken into account in the definition of the worst assessment during study • For description at baseline, the last available result before first study intervention will be taken into account in the analysis in case of multiple values For PK analysis, unscheduled samples will not be linked to a scheduled timepoint and will be excluded from summaries.
Reason for being unfit for high-dose cisplatin	Reason for being unfit for high-dose cisplatin will be derived as: • Screening eGFR < 60 mL/min /1.73 m^2

	• History of hearing impairment, defined as Grade ≥ 2 audiometric hearing loss or tinnitus Grade ≥ 2 as collected in the Audiometry eCRF page. • Peripheral neuropathy Peripheral neuropathy (SMQ) ≥ Grade 2 as collected in the Medical History eCRF page (note neuropathy is expected to be ongoing at baseline) • Age ≥ 70 years and unfit according to G8 questionnaire (Score ≤ 14) as collected in the Disease History eCRF page or ineligible for cisplatin treatment due to age limit according to national guidelines (subjects with age ≥ 70 with informed consent date after 10-OCT-2023 in Spain, 27-OCT-2023 in China and 24-OCT-2023 in the UK) • Unknow: for the participants that not fit on the categories listed above More than one condition could be met

10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented by treatment arm and total, where applicable. Percentages will be presented with respect to the number of randomized participants.

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of participants who discontinued from the study prior to randomization overall and grouped by the main reason (e.g., Protocol non-compliance, withdrawal of consent)
- Number and percentage of randomized participants.

The end of study intervention status will be summarized by:

- Number and percentage of randomized participants who did not receive any dose of study intervention
- Number and percentage of randomized participants with ongoing xevinapant/placebo (for EDMC only)
- Number and percentage of randomized participants with ongoing IMRT (for EDMC only)

- Number and percentage of randomized participants who completed xevinapant/placebo
- Number and percentage of randomized participants who completed IMRT
- Number and percentage of randomized participants who discontinued xevinapant/placebo (overall and by primary reason)
- Number and percentage of randomized participants who discontinued IMRT (overall and by primary reason)

The end of study status will be summarized by:

- Number and percentage of participants with ongoing study intervention (for EDMC only)
- Number and percentage of randomized participants off-treatment and in DFS follow-up
- Number and percentage of randomized participants off-treatment and in OS follow-up
- Number and percentage of randomized participants who completed or prematurely discontinued the study after randomization, grouped by main reason

Disposition of participants by allocated study intervention group will be presented in a CONSORT Flow Diagram.

Additionally, the number of participants screened, and randomized in each analysis set will be provided overall, by region (Europe, EEA, South America, Asia and Australia), by country within region and by site.

The results of the randomization algorithm (according to IWRS) will be summarized as follows:

- Number and percentage of randomized participants by randomization strata (IWRS)
- Cross tabulation: stratum by IWRS (primary tumor site, HPV p16 status and tumor stage) vs. stratum by CRF (site of primary tumor, local HPV testing and pathological stage at study entry)
- Cross tabulation: participants randomized (xevinapant/placebo) vs. treated (xevinapant/placebo)

Participants' information on informed consent date, start and end of combination therapy date, start and end of monotherapy, study discontinuation date and reason for withdrawal (from study intervention or study) will be listed.

The results of the EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L in terms of completion and compliance rates will be summarized as follows:

- Number and percentage of randomized participants who completed EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L by visit as expected (compliance rate using all expected QoL questionnaires in the denominator)

- Number and percentage of randomized participants who completed EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L by visit as expected (compliance rate using FAS analysis set in the denominator)

- Number and percentage of randomized participants with at least one evaluable EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L subscale by visit as expected (completion rate using all expected HRQOL questionnaires in the denominator)
- Number and percentage of randomized participants with at least one evaluable EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L subscale by visit as expected (completion rate using FAS analysis set in the denominator)

A questionnaire is considered returned when it has been received with a completion date. A questionnaire is considered evaluable if HRQOL scores can be derived according to scoring manual at least for one subscale.

Population-level summary (per instrument):

$$\%\ \text{Compliance(exp)} = 100 \times \frac{\text{number of participants who returned QoL questionnaire}}{\text{number of participants for whom a QoL questionnaire is expected}}$$

$$\%\ \text{Compliance(FAS)} = 100 \times \frac{\text{number of participants who returned QoL questionnaire}}{\text{number of participants on FAS}}$$

$$\%\ \text{Completion(exp)} = 100 \times \frac{\text{number of participants with at least one evaluable QoL subscale}}{\text{number of participants for whom a QoL questionnaire is expected}}$$

$$\%\ \text{Completion(FAS)} = 100 \times \frac{\text{number of participants with at least one evaluable QoL subscale}}{\text{number of participants on FAS}}$$

Compliance and completion rates will be displayed for each instrument by study intervention group and by baseline assessment and subsequent scheduled visits.

Reasons for non-completion will also be described as follows:

- Number and percentage of randomized participants with non-expected EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L by reasons for non-compliance (data-cut, death, lost-to follow-up, withdrawal of consent, other)
- Number and percentage of randomized participants with missing EORTC QLQ-HN35, EORTC QLQ-C30 and EQ-5D-5L by reasons for non-completion (administrative reasons, subjective reasons, medical reasons and other)
    - Administrative reasons will include the following eCRF categories:
        - Administrative failure to distribute the questionnaire to the subject
        - Site was closed
    - Subjective reasons will include the following eCRF categories:
        - Subject felt too ill
        - Subject felt it was inconvenient

- Subject felt it takes too much time
- Subject felt it was not relevant
- Subject felt it was a violation of privacy
- Subject did not understand the actual language
- Subject unable to come to site
- Subject did not come for unknown reasons

- Medical reasons will include the following eCRF categories:
  - Clinician or nurse felt the subject was too ill
  - Investigator decision

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations include:

- Participants enrolled and dosed on the study who did not satisfy enrolment criteria
- Participants that develop withdrawal criteria whilst on the study but are not withdrawn
- Participants that receive the wrong study intervention
- Participants that receive an excluded concomitant medication
- Failure to collect data necessary to interpret primary endpoints
- Failure to collect necessary key safety data
- Deviation from Good Clinical Practice (GCP)
- Any other protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

Important protocol deviations will be identified for all participants by either site monitoring, medical review processes or programming and confirmed prior to or at the Data Review Meeting at the latest.

Any important protocol deviation is documented in SDTM datasets whether identified through site monitoring, medical review or programming. The management of protocol deviations is outside of this IAP document.

Important protocol deviations or important events that might have an effect on PK include, but may not be limited to the following:

- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g., dose administration delayed, dose change or missed doses), when dosing information is available
- Pre-dose or trough sample collected after the actual dosing
- Concomitant medications and dietary or herbal supplements that are known potent inhibitors or inducers of P-glycoprotein (Table 12 of protocol).

Should one or more of these events be available at the Data Review Meeting, its implication for PK evaluation will be discussed and agreed amongst relevant study team members (e.g., Sponsor Clinical Pharmacology/Biostatistics/Clinical Pharmacokinetics & Pharmacodynamics team representative). Appropriate action will be taken such as flagging individual values to be excluded from analysis.

A frequency table as well as a listing of important protocol deviations, will be provided based on the FAS.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

All criteria/reasons leading to the exclusion of a participant from an Analysis Set should be summarized and listed (see Section 10.1).

If participants are excluded from the PK Analysis Set, the reasons for exclusion will be listed.

10.3 COVID-19 Impact

An overview table and listing of the impact by COVID-19 will be prepared. The following aspects will be summarized:

- Any potential impact by COVID-19
- COVID-19 associated adverse events (MedDRA SMQ “COVID-19”)
- COVID-19 vaccinations
- Protocol deviations (important and non-important)
- Missed visits (including number of missed visits)
- Missed efficacy evaluations (including number of missed efficacy evaluations)
- Missed HRQOL evaluation
- Xevinapant/placebo - missed doses

- IMRT - missed doses
- Xevinapant/placebo discontinuation
- IMRT discontinuation
- Study discontinuation

A listing will be generated using the MedDRA SMQ for COVID related terms. The following information will be provided:

- Study, study intervention dose, participant ID, country
- Age, gender, race
- Date of first, last study intervention
- COVID-19 associated AE start date (day), COVID-19 associated AE stop date (day)
- AE-PT, verbatim,
- Toxicity grade
- Seriousness
- Relationship to study intervention (investigator assessment)
- Action taken
- Outcome

Additionally, a summary of COVID-19 vaccination according to the SDGs subgroup "Vaccines for COVID-19" and corresponding SDG subcategories of the current WHO Drug Dictionary will be provided.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the safety analysis set, by treatment arm and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline Visit eCRF pages.

The following demographic characteristics will be included:

- Sex: male, female, undifferentiated
- Race: American Indian or Alaska Native, Asian (Chinese, Japanese, Korean, other Asian), Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not permitted per local regulation
- Ethnicity: Hispanic or Latino/Not Hispanic or Latino, Not permitted per local regulation

- Age (years)
- Age categories:
  - < 65 years,
  - ≥ 65 years
    - 65-74,
    - 75-84,
    - ≥85 years
- Pooled Region:
  - North America
  - Europe
  - Asia
  - Rest of the World
- Geographic Region:
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australia
  - Asia
- BSA (m^2) at Baseline
- Weight (kg)
- Height (cm)
- BMI (kg/m^2) at Baseline
- Eastern Cooperative Oncology Group (ECOG) Performance status (0,1,2,3,4)

Specifications for computation:

- BSA $[m^2] = \sqrt{\frac{height[cm] \times weight[kg]}{3600}}$
- BMI $[kg/m^2] = \frac{weight\ [kg]}{height[cm]^2} \times 10000$
- Site codes will be used for the determination of the participant's geographic region.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order. All medical history data will be listed.

11.3 Other Baseline Characteristics

Information on disease characteristics collected at baseline will be summarized. Summary statistics will be presented for

- Site of primary tumor
- Time since initial cancer diagnosis (months)
- Histopathological grade
- Pathological stage and TNM classification at study entry
- Nodal involvement
    - Were there any malignant Level V or Level VI nodes at initial diagnosis? (Yes/ No)
    - How many nodes (at any level) have been removed by surgery?
    - How many of the removed nodes were positive for malignancy?
- G8 total score
- Reason for being unfit for high-dose cisplatin
- Nicotine usage
    - Nicotine usage (never smoker, current smoker, former smoker)
    - Nicotine usage type (cigarettes, cigars, pipes, chewing tobacco, nicotine gum, e-cigarettes or vapor)
    - Nicotine exposure (pack-years)
    - Nicotine exposure time (years)
    - Years since quitting
- Alcohol consumption
    - Alcohol consumption (Yes/No)
    - Alcohol consumption (units per week)

- Prior surgery for SCCHN
- ECOG performance status
- Height, Weight, Body Surface Area, and Body Mass Index
- HPV status ay screening

Nicotine usage will be derived using information about the use of nicotine products that can be smoked: cigarettes, cigars, pipes.
The information collected about products that are smoked will be used to derive the smoking status for each participant:

- Current Smoker: a participant is a current smoker if at least one smoked product was answered "Current" (missing information about one or more smoked products is allowed);
- Former Smoker: a participant is a former smoker if he/she is not a current smoker and at least one smoked product was answered "Former" (missing information about one or more smoking options is allowed);
- Never Smoker: a participant is considered to have never smoked if all the smoking options were answered "Never".
- Missing: in case the information is missing for one or more of these smoking options and the participant cannot be classified as current or former smoker, the smoking status should be "Missing", even though all the remaining options were answered "Never".

Nicotine history computation:

- Chewing tobacco, nicotine gum and e-cigarette are not taken into account for nicotine exposure calculation
- Cigarette equivalents are calculated as follow: 1 cigar is regarded equivalent to 5 cigarettes and 1 pipe is regarded equivalent to 3 cigarettes
- Duration of smoking (years):
    - (end date of smoking – start date of smoking +1)/ 365.25
- Pack-year:
    - Calculate cigarette equivalents per day using the conversion factors given above
    - Convert to packs per day where 20 cigarettes are regarded as 1 pack
    - Pack-year=packs per day*duration of smoking (years)

Alcohol consumption computation:

- Units per day are calculated as follow: 360ml or 12oz of beer is regarded equivalent to 1 unit, 150ml or 5oz of wine is regarded equivalent to 1 unit and 45ml or 1.5oz of spirits is regarded equivalent to 1 unit

- units per week:

    - Calculate units per day equivalents using the conversion factors given below

    - Convert to units per week *7

Baseline characteristics with respect to vital signs, ECG and hematology/biochemistry will be part of Section 15 (Safety Evaluation).

In addition, listings will be created to report the following information collected at Screening only: audiometry, central HBV, HCV, HIV tests, local HIV test, local SARS-CoV-2 test and pregnancy test.

12 Previous or Concomitant Therapies/Procedures

If not stated otherwise, the following analyses will be performed based on the safety analysis set, by treatment arm and overall.

Concomitant medications are medications, other than study intervention, which are taken by participants any time during the on-treatment period, see Section 9.8.

Previous medications are medications, other than study intervention for study interventions, which started before first administration of study interventions.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date.

Concomitant and previous medication each will be summarized by number and percentage of participants from the "Previous and Concomitant medication and/or Therapies" eCRF. Preferred term within ATC Classification code level 2 will be tabulated as given from the WHO-DD dictionary most current version.

If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.

The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of preferred term in a given drug class. In case of equal frequency regarding ATC classification level 2 or preferred term, alphabetical order will be used.

In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Each participant will only be counted once, even if he/she received the same medication at different times.

All **concomitant procedures**, which were undertaken during the on-treatment period will be summarized according to the CRF page "Concomitant Procedures Details". Concomitant

procedures will be presented according to MedDRA SOC and PT. Number and percentage of participants with concurrent procedures (Prior, on or after the first day of study intervention or within 30 days after last dose of study intervention) overall and by type of procedure will be presented.

Subsequent anticancer therapy

Anticancer therapy after end of study intervention will be summarized according to the respective CRF page. Treatments will be categorized using the same approach as for concomitant medications will be applied based on ATC level 2 and preferred term.

Number and percentage of participants with any anticancer post study treatment and by type (anticancer treatment, radiotherapy, surgery) will be presented.

Summary statistics will be created for best response across all post study treatments (as indicated on "AntiCancer Treatment After Discontinuation Details" page). For participants who received more than one anticancer drug therapy after discontinuation of study intervention, the best overall response among all anticancer drug therapies will be summarized.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the safety analysis set by treatment arm.

All dosing calculations and summaries will be based on "Xevinapant / Placebo Administration Details" and "IMRT Administration Details" CRFs pages.

If the total dose is missing, the dose level as entered in the CRF will be used.

In case the start date is missing, it is assumed that the first dose of study treatment is given at the randomization date. The randomization date will replace incomplete dates of the first dose of study intervention.

In case the last date of study intervention is incomplete the date of last study intervention administration will be taken from the End of Treatment page.

For Cycle X, actual cycle start date for each participant is:

- the earliest start date of dosing in the Cycle X taken from eCRF exposure page, if the participant received study intervention on that visit (i.e., any study intervention with dose>0 at that visit). Cycle 1 will take into account all administration start dates ≤ 3 weeks from treatment start, cycle 2 all administration start dates > 3 – ≤6 weeks, cycle 3 all administration start dates > 6 – ≤9 weeks, cycle 4 all administration start dates > 9 - ≤12 weeks, cycle 5 all administration start dates > 12 – ≤15 weeks and cycle 6 all administration start dates > 15 - ≤18 weeks.
- the first day of assessments in the Cycle X Day 1 visit, if the participant did not receive study intervention on that visit (i.e., all study interventions had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs (assuming vital signs are the first assessment of the cycle on Cycle X Day 1 visit).

Actual cycle end date for each participant is:

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day;
- for the last cycle, actual cycle end date = actual cycle start date + intended cycle duration (in days) – 1 day

Treatment duration planned per protocol is 18 weeks, consisting of six 3-week cycles.

Duration of treatment cycle (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study intervention, only cycles with non-zero dose of study intervention of at least one of the study interventions should be included.

A dose is regarded to be administered, if the actual dose per day is > 0, or the start date or end date is not missing.

Xevinapant/Placebo Cumulative dose (mg) overall is the sum of the actual doses of study intervention received overall. Actual dose per day is collected using mL on eCRF. This dose will be converted to mg as:

Actual dose (mg) = Actual dose (mL)*20 (mg/mL)

IMRT Cumulative dose (Gy) overall is the sum of the actual doses of study intervention received overall. If a IMRT dose modification will occur PTV1 new reported value will be used for the calculation.

The **dose intensity** of treatment (DI) (mg/day) of Xevinapant/Placebo during the study is defined as the total dose of xevinapant /matched placebo taken during a cycle, divided by the cycle duration in days as:

$$\text{DI of treatment (mg/day)} = \frac{Total\ dose\ of\ treatment\ \ taken\ during\ the\ cycle\ (mg)}{Duration\ of\ treatment\ cycle\ (days)}$$

DI during combination therapy, monotherapy and overall period is calculated as the mean of the DIs of the individual cycles.

The **relative dose intensity** (RDI) is defined as the actual dose intensity divided by the planned dose intensity during the study and expressed in percentage:

$$\text{Xevinapant/Placebo RDI of treatment (\%)} = 100\times\left(\frac{\text{DI of treatment (mg/day)}}{planned\ dose\ \text{(mg/day)}}\right)$$

Where the planned dose is 200 mg/day.

Actual dose per day is collected using mL on eCRF. This dose will be converted to mg as follow:

$$\text{Actual dose (mg)} = \text{Actual dose (mL)}*20\text{mg/mL}$$

$$\text{IMRT RDI of treatment (\%)} = 100\times\left(\frac{\text{Cumulative (Gy)}}{\textit{planned dose}\ \text{(Gy)}}\right)$$

Where the planned dose is 66 Gy.

In addition, the number and percentage of participants who had missed, reduced, or discontinued doses, together with the reason(s) will be summarized for each treatment component (xevinapant/placebo, and RT) in the following time period: ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 – 15 weeks, > 15 – 18 weeks.

The summary of study intervention exposure will include the following information:

- Total duration of xevinapant/placebo and IMRT (weeks) and by categories of ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 – 15 weeks, > 15 – 18 weeks
- Number of IMRT Fractions
- Total number of cycles received
- Xevinapant/Placebo Cumulative dose (mg)
- IMRT Cumulative dose (Gy)
- Dose intensity (mg/kg/cycle)
- Xevinapant/Placebo Relative dose intensity (%)
- IMRT Relative dose intensity (%)
- Xevinapant/Placebo dose reduction per time period
    - Number of participants with dose reduction (including the number of reduction)
    - Number of participants with dose reduction related to COVID-19 (display only if cases available)
- Xevinapant/Placebo missed doses per time period
    - Number of participants with missed doses
    - Number of participants with missed doses related to COVID-19 (display only if cases available)
    - Number of missed doses per participant
- Xevinapant/Placebo discontinuation per time period
    - Number of participants with permanent treatment discontinuation
    - Primary reason for permanent treatment discontinuation
- IMRT dose reduction per time period

  - Number of participants with dose reduction (including the number of reduction)
  - Number of participants with dose reduction related to COVID-19 (display only if cases available)

- IMRT missed doses per time period
  - Number of participants with missed doses
  - Number of participants with missed doses related to COVID-19 (display only if cases available)
  - Number of missed doses per participant

- IMRT discontinuation per time period
  - Number of participants with IMRT discontinuation
  - Primary reason for IMRT discontinuation

The following by-participant data listings will be provided:

- Listing of xevinapant/placebo and IMRT start/end dates for each treatment day together with the reason for change in dose and no dose.
- Listing of xevinapant/placebo and IMRT exposure time, cumulative dose, dose intensity, relative dose intensity, and compliance.

14 Efficacy Analyses

The following analyses will be performed based on the FAS by treatment arm except when otherwise stated. Participants will be analyzed according to the treatment assigned at randomization as per the ITT principle.

For estimands analyzed using a model adjusting for randomization stratification factors, the following randomization strata will be added to the model:

Stage III/ oropharynx/ p16 positive, Stage III/ oral cavity or oropharynx/ p16 negative, Stage III/ larynx, Stage III/ hypopharynx, Stage IV/ oral cavity or oropharynx/ p16 negative, Stage IV/ larynx, Stage IV/ hypopharynx

14.1 Primary Estimand: DFS

This section provides detailed information related to the analysis of the primary efficacy estimand, including sensitivity and subgroup analyses.

Attributes of the estimand are described in the table below.

Endpoint	DFS defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled DFS assessments after last evaluable assessment or randomization): • Death from any cause • Objective Disease Recurrence (earlier date of first imaging or biopsy collection confirming event at a DFS assessment): o Local or regional relapse which is subsequently confirmed by histopathology unless medically contraindicated or medical risk of biopsy deemed too high o Distant metastases. Confirmation of pathology is recommended in case of solitary metastasis (especially in the lung) after considering potential contraindication and/or medical risk associated with biopsy.
Population(s)	High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively
Treatment	Xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo
ICE handling strategy	The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy
Population-level summary measure	Hazard ratio

If there are multiple scan dates associated with an evaluation, i.e., radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of relapse evaluation. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If there is a biopsy collection and also a scan/ multipe scans associated with an evaluation the earlier date of first imaging or biopsy collection will be used as the date of assessment.

For equivocal findings of relapse (e.g. very small and uncertain new lesions), treatment or observation may continue until the next scheduled assessment or until biopsy confirmation. If at the next scheduled assessment relapse is confirmed, the earlier date of first imaging or biopsy collection were the lesion is identified for the first time (using lesion number) will be used as the date of assessment.

Censoring rules for the primary and sensitivity analyses of DFS are summarized in

Table 9 below. If a participant is meeting a multiple censoring situation, the earliest censoring criterion will be applied.

Table 9: Censoring rules for DFS

Situation	Primary, Sensitivity 1 - 3, Supplementary 3 - 7	Sensitivity 4	Supplementary 1, 2
No event (objective disease recurrence or death)	Right censored on the date of the last relapse assessment	Right censored on the date of the last relapse assessment	Right censored on the date of the last relapse assessment
No evaluable baseline relapse assessment or postbaseline relapse assessments	Right censored on the randomization date	Right censored on the randomization date	Right censored on the randomization date
An event after a long time-gap between two relapse assessments	Right censored on the date of the last relapse assessment before the long time-gap or at the randomization date, whichever comes later	Not censored	Right censored on the date of the last relapse assessment before the long time-gap or at the randomization date, whichever comes later
An event after initiation of new anticancer treatment prior to any event	Not censored	Not censored	Right censored on the date of the last evaluable relapse assessment before anticancer therapy is given

* long time-gap between two relapse assessments is defined as follows:

Last evaluable assessment prior to event at	Censor if time since last evaluable tumor assessment or randomization is larger than
Day 1 to Day 365	182 days
Day 366 to Day 1095	244 days
after Day 1095	365 days

14.1.1 Main Analysis: DFS assessed by investigator

DFS assessed by investigator between the 2 study intervention groups will be compared using a one-sided stratified log rank test controlling for a one-sided type I error of 2.5%.

The date of objective disease recurrence is defined as the earliest date of first imaging or biopsy collection confirming event at a DFS assessment when the objective disease recurrence is first documented. The objective disease recurrence is documented by item #5.7 of TU3DT (Adjusted RECIST 1.1 for adjuvant SCCHN [post-screening] - lesion) eCRF form, i.e. “Was this lesion a relapse?” = “Yes”, whatever the confirmation by a biopsy. The assessment of the disease recurrence is scheduled at least 3 months (± 2 weeks) after IMRT termination, and every 3 months the first year (FU9 and FU12 visits), every 4 months from the second year until end of third year (FU16, FU20, FU24, FU28, FU32 and FU36) and every 6 months from forth year until end of the fifth year (FU42, FU 48, FU54 and FU60 visits).

DFS dates will be imaging dates (so also for censoring date), but in case of a Biopsy-driven detected/confirmed relapse, the earlier of scan date or biopsy collection date is used (that should cover both situations: a) imaging provokes biopsy, b) biopsy assessment without imaging [for whatever reason]).

The study intervention effect on DFS time assessed by investigator will be estimated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS. The hazard ratio (HR) together with its 95% CI will be provided.

Each stratum will define a separate baseline hazard function, i.e., for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the study intervention group and β is the unknown regression parameter. Ties will be handled by replacing the proportional hazards model by the discrete logistic model (the discrete logistic model for regression as computed by the SAS PHREG procedure using TIES=DISCRETE on the model option).

Kaplan-Meier estimates (product-limit estimates) for the time to DFS assessed by investigator will also be provided by study intervention group together with a summary of associated statistics (median, Q1 and Q3, minimum and maximum) including the corresponding two-sided 95% CI of the median (calculated according to Brookmeyer and Crowley). Rates of participants with DFS assessed by investigator together with their 95% CI (using the log-log transformation according to Kalbfleisch and Prentice) will be provided at month 12, 18, 24, 36 and 60. The estimate of the standard error will be computed using Greenwood's formula. In addition, frequency (number and percentage) of participants with each event type (relapse or death) and intercurrent events will be tabulated by study intervention group.

A plot of Kaplan-Meier curve per study intervention group will be provided for DFS by study intervention group.

A Kaplan-Meier plot for DFS follow-up duration will be generated to assess the follow-up duration in the study intervention groups reversing the DFS censoring and event indicators.

Kaplan-Meier estimates will be presented by study intervention group together with the median time of follow-up for DFS. In particular, the follow-up rate at 12, 18, 24, 36 and 60 months will be estimated with corresponding two-sided 95% CIs.

14.1.2 Sensitivity Analysis 1 of DFS evaluating robustness of treatment effect towards IWRS strata and corresponding eCRF variables

The study intervention effect on DFS time assessed by investigator will be estimated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata. Randomization strata will be taken using eCRF data. The hazard ratio (HR) together with its 95% CI will be provided.

One-sided p-value from the stratified log rank test will be reported.

14.1.3 Sensitivity Analysis 2 of DFS evaluating proportionality of hazards

The proportionality of hazards for DFS will be evaluated using Cox model with piecewise treatment effect (the piecewise proportional hazard model as computed by the SAS PHREG procedure using piecewise=hazard [interval=numeric timepoint intervals list] on the bayes option). The hazard ratio (HR) together with its 95% CI will be provided.

In a piecewise proportional hazard model, the overall hazard is the multiple of the overall baseline hazard (inestimable in semi-parametric case) and the sum of all the relative hazards over the event time. The hazard function value comes between defined pieces or interval time of all patients. The defined interval times for this model will be month 12 after randomization and month 24.

In addition, frequency (number and percentage) of participants with each event type (relapse or death) and intercurrent events will be tabulated by study intervention group.

A Schoenfeld residual plot will be included for check the validity of the proportional hazard assumption for each covariate in the fitted Cox model for the primary estimand. The plot will be produced by a two steps code:

```
PROC PHREG ;
    CLASS treatment (REF=placebo);
    MODEL DFS time*censor(1) = treatment;
    STRATA stratification_factors;
    OUTPUT OUT= PHCHECK RESSCH = SCHRES;
RUN;
PROC SGPLOT DATA=PHCHECK;
    LOESS X = DFS time Y = SCHRES / CLM;
RUN;
```

14.1.4 Sensitivity Analysis 3 of DFS evaluating the robustness of treatment effect regarding assessor of DFS

The study intervention effect on DFS time assessed by IRC will be estimated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS. The hazard ratio (HR) together with its 95% CI will be provided. In addition, frequency (number and percentage) of participants with each event type (relapse or death) and intercurrent events will be tabulated by study intervention group.

One-sided p-value from the stratified log rank test will be reported.

14.1.5 Sensitivity Analysis 4 of DFS evaluating the scientific question whether the drug improves DFS irrespective of subsequent anticancer therapy or long time-gap between DFS assessments

The study intervention effect on DFS time assessed by investigator including all DFS events regardless of the time since last evaluable assessment or randomization, or whether the participant had a subsequent anticancer therapy, will be estimated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS. The hazard ratio (HR) together with its 95% CI will be provided. In addition, frequency (number and percentage) of participants with each event type (relapse or death) and intercurrent events will be tabulated by study intervention group.

One-sided p-value from the stratified log rank test will be reported.

14.1.6 Supplementary Analysis 1 of DFS evaluating the isolated effect with the study intervention

The inferential analysis of the primary estimand (Section 14.1.1) will be reproduced using a similar methodology to the one for the primary analysis including the following censoring rule:

- Participants who start new anticancer treatment prior to an event will be censored on the date of the last evaluable relapse assessment before anticancer therapy is given.

  Note: any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy will be considered as new/subsequent anticancer therapy and in absence of an event prior to start new anticancer treatment may lead to censoring.

14.1.7 Supplementary Analysis 2 of DFS evaluating the isolated effect with the study intervention while relying on DFS as assessed by IRC

DFS evaluating the isolated effect with the study intervention while relying on DFS as assessed by IRC will be reproduced using a similar methodology to the sensitivity analysis 3 including the following censoring rule:

- Participants who start new anticancer treatment prior to an event will be censored on the date of the last evaluable tumor assessment before anticancer therapy is given.

  Note: any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy will be considered as new/subsequent anticancer therapy and in absence of an event prior to start new anticancer treatment may lead to censoring.

DFS assessed by IRC between the 2 study intervention groups will be compared using a one-sided stratified log rank test controlling for a one-sided type I error of 2.5%, if and only if log rank test of the main analysis (see section 14.1.1) rejected the null hypothesis.

14.1.8 Supplementary Analysis 3 DFS evaluating the time to local relapse and time to distant metastases as subtypes events for of DFS endpoint while considering the competing risk of death

DFS evaluating the time to local relapse and time to distant metastases as subtypes events for of DFS endpoint while considering the competing risk of death will be estimated using a Cox's proportional hazard model of both local relapse and distant metastasis separately over time between the two study intervention groups and will be compared in terms of the cause-specific hazard taking the competing risk of death prior relapse into account, including confidence interval, estimated by means of a cause-specific proportional hazards model (multistage approach). Stacked cumulative incidence functions by arm and cause based on a proportional hazards model on the cause-specific hazards will be plotted at month 12, 18, 24, 36 and 60.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

Cox proportional hazard models will be fit, one for local relapse and another for distant metastasis and will otherwise be consistent with what had been done in Section 14.1.1.

Additionally, a cumulative incidence function (CIF) plot will be created separately for local relapse and distant metastasis by the SAS PHREG procedure PLOT=CIF on the PHREG statement. Also, a CIF plot will be created with two sets of lines, one set for local relapse and another set for distant metastasis.

14.1.9 Supplementary Analysis 4 of DFS adjusting for selected baseline covariates

The study intervention effect on DFS time adjusting for selected baseline covariates will be evaluated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata including the covariates listed on Section 8.2 without interactions.

The hazard ratios of all selected explanatory variables from the clinical database and of the treatment effect will be reported including 2-sided 95% confidence intervals.

14.1.10 Supplementary Analysis 5 of DFS interaction effect for each selected baseline covariates

The study intervention effect on DFS time interaction effect for each selected baseline covariates will be evaluated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata including separately for each covariate. The Cox model will include the treatment effect, baseline covariate, and their interaction will be tested by Wald-Test.

Analysis described on section 14.1.9 and 14.1.10 will be displayed together.

14.1.11 Supplementary Analysis 6 of DFS exploring homogeneity of treatment effect across subgroups

The study intervention effect on DFS exploring homogeneity of treatment effect across subgroups will be evaluated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata performed within each subgroup levels listed as covariates on Section 8.2 . As specified in Section 8.2, subgroup levels may be pooled in case of insufficient number of participants. The Cox model will include treatment group as only covariate. A Forest plot displaying the HR for each model as well as the CI will be provided.

14.1.12 Supplementary Analysis 7 of DFS evaluating the DFS considering only relapse or disease-specific deaths

DFS evaluating the DFS considering only relapse or disease-specific deaths will be evaluated using a Cox's proportional hazard model with study intervention group as main effect and stratified by the randomization strata considering DFS defined as the time from randomization to earlier of relapse or the disease-specific death (progressive disease and/or disease related condition reported as primary reason for death).

14.1.13 Supplementary Analysis 8 of DFS Concordance between IRC and investigator assessment for DFS

A summary of the investigator assessment versus IRC assessment will be provided including numbers of concordant and discordant assessments as well as the number of cases where disease recurrence was assessed at different timepoints by IRC and investigator. Table 5 outlines the possible outcomes by investigator and IRC (Amit et al. 2011).

Table 10: Possible Outcomes for Investigator vs IRC

		IRC	
		Disease recurrence	*No dissease recurrence*
Investigator	*Dissease recurrence*	*a* [= a1 + a2 + a3]	*b*
	No dissease recurrence	*c*	*d*

[a1: number of agreements on timing and occurrence of relapse;
a2: number of times agreement on relapse but INV declares relapse later than IRC;
a3: number of times agreement on relapse but INV declares relapse earlier than IRC;]
N= a+b+c+d.
[The timing agreement of disease recurrence has to be defined as a window of [Z] days] Note: ± 7 days could be used or it could be based on acceptable delay per protocol for the relapse assessment [every 6 ±1 weeks]

The following measure of agreement and discordance will be calculated for each study intervention arm:

- Total Event Discrepancy Rate: (b+c) / N
- Total Event Agreement rate: (a+d) / N
- Rate of Unconfirmed Investigator PDs: b / (a+b)
- Early Discrepancy Rate (EDR): (a3+b) / (a+b)
- Late Discrepancy Rate (LDR): (a2+c) / (a2+a3+b+c)
- Overall Discrepancy Rate: (a2+a3+b+c) / N

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares relapse earlier than IRC within each study intervention group as a proportion of the total number of investigator assessed relapses.

The LDR quantifies the frequency with which the investigator declares relapse later than IRC as a proportion of the total number of discrepancies within the study intervention group.

Discordance metrics are calculated for each study intervention group and, for each metric, the difference in discordance between the study intervention groups is used to evaluate potential bias.

If the discordance is similar across the study intervention groups then this suggests the absence of evaluation bias favoring a particular study intervention group. A negative differential discordance for EDR and/or a positive differential discordance for LDR may be indicative of investigator evaluation bias in favor of the study intervention group (Amit et al, 2011 [1]).

14.2 Secondary Estimand: OS

This section provides detailed information related to the analysis of the OS secondary efficacy estimand, including primary, sensitivity, and subgroup analyses.

14.2.1 Secondary Estimand: Derivation and analysis of the secondary estimand OS

Attributes of the estimand are described in the table below.

Endpoint	OS defined as the time from date of randomization to death
Population(s)	High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively
Treatment	Xevinapant and RT followed by xevinapant followed by subsequent cancer therapy vs. placebo and RT followed by placebo followed by subsequent cancer therapy
ICE handling strategy	The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy

Population-level summary measure	Hazard ratio

OS between the two study intervention groups will be compared using a one-sided stratified logrank test controlling for a one-sided type I error of 2.5% in a group-sequential design (see also Section 0) for the second OS interim analysis and the primary OS analysis. For the first OS, in case DFS null hypothesis is rejected at DFS PA and alpha can be reallocated to test H_0^{OS} without stopping at OS IA1.

The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval (both adjusted and unadjusted), estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

Kaplan-Meier estimates (product-limit estimates) for the OS time will also be provided by study intervention group together with a summary of associated statistics (median, Q1 and Q3, minimum and maximum) including the corresponding two-sided 95% CI of the median (calculated according to Brookmeyer and Crowley). Rates of participants with OS together with their 95% CI (using the log-log transformation according to Kalbfleisch and Prentice) will be provided at month 4 after randomization and every 6 months after study intervention period until the end of the study. The estimate of the standard error will be computed using Greenwood's formula. In addition, the number of participants with at least one event (overall and by treatment arm) will be presented.

A Kaplan-Meier plot for OS follow-up duration will be generated to assess the follow-up duration in the study intervention groups reversing the OS censoring and event indicators.

Kaplan-Meier estimates will be presented by study intervention group together with the median time of follow-up for OS. In particular, the follow-up rate at month 4 after randomization and every 6 months after study intervention period until the end of the study will be estimated with corresponding two-sided 95% CIs.

14.2.2 Sensitivity Analysis 1 of the OS evaluating robustness of treatment effect towards IWRS strata and corresponding eCRF variables

The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval (both adjusted and unadjusted), estimated by means of a Cox proportional hazards model, stratified by the eCRF strata. Randomization strata will be taken as specified and documented in the eCRF and each stratum will define a separate baseline hazard function.

14.2.3 Supplementary Analysis 1 of the OS exploring the interaction of treatment effect and selected baseline covariates

The OS exploring the interaction of treatment effect and selected baseline covariates will be reproduced using a similar methodology to the one for the Section 14.2.1. The Cox model will include the treatment effect, baseline covariate, and their interaction will be tested by Wald-Test for the covariates listed on Section 8.2.

14.2.4 Supplementary Analysis 2 of the OS exploring homogeneity of treatment effect across subgroups

The OS estimand exploring homogeneity of treatment effect across subgroups will be reproduced using a similar methodology to the Section 14.2.3 but performed within each subgroup levels listed as covariates on Section 8.2. As specified in Section 8.2, subgroup levels may be pooled in case of insufficient number of participants. Cox model will include treatment group as only covariate.

14.2.5 Supplementary Analysis 3 of the OS evaluating the OS considering only disease-specific deaths

The inferential analysis of the secondary estimand (Section 14.2.1) will be reproduced using a similar methodology to the one for the primary analysis considering OS defined as the time from randomization to the disease-specific death.

Attributes of the supplementary analysis are described in the table below.

Endpoint	OS defined as the time from date of randomization to disease-specific death (Primary reason for death = Progressive disease and/or disease related condition)
ICE handling strategy	The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Discontinuation of treatment • Start of subsequent anticancer therapy • Death due to any other cause different to disease-specific (will be censored at the last know alive date)

14.3 Secondary Estimand: Time to subsequent anticancer treatments

This section provides detailed information related to the analysis of the time to subsequent anticancer treatments secondary efficacy estimand, including supplementary analyses.

14.3.1 Secondary Objective: Derivation and analysis of the secondary estimand Time to subsequent anticancer treatments

Attributes of the estimand are described in the table below.

Endpoint	To evaluate time to subsequent cancer treatments in participants treated with xevinapant compared to placebo when added to RT
Population(s)	High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively
Treatment	Xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo
ICE handling strategy	The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Occurrence of DFS event
Population-level summary measure	Hazard ratio

Time to subsequent cancer treatments is defined as the time from randomization to the start for the first new anticancer treatment (any systemic anticancer therapy, any anticancer surgery and any anticancer radiotherapy will be considered as new/subsequent anticancer therapy).

The following censoring rules will also be applied for the participants that did not receive any subsequent cancer treatment:

- Participants will be censored at the last alive date available.

The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

Kaplan-Meier estimates (product-limit estimates) for the time to subsequent cancer treatments will also be provided by study intervention group together with a summary of associated statistics (median, Q1 and Q3, minimum and maximum) including the corresponding two-sided 95% CI of the median (calculated according to Brookmeyer and Crowley). Rates of participants with new subsequent cancer treatments together with their 95% CI (using the log-log transformation according to Kalbfleisch and Prentice) will be provided at month 4 after randomization period and every 6 months after study intervention period until the end of the study. The estimate of the standard error will be computed using Greenwood's formula. In addition, the number of participants with at least one event (by treatment arm) will be presented.

Cumulative distribution function estimated using Kaplan-Meier method will be displayed by treatment arm.

14.3.2 Supplementary Analysis 1 of the Time to subsequent anticancer treatments adjusting for each selected baseline covariates

The inferential analysis of the primary estimand (Section14.3.1) will be reproduced using a similar methodology to the Section 14.3.1 but performed within each subgroup levels listed as covariates on Section 8.2 . As specified in Section 8.2, subgroup levels may be pooled in case of insufficient number of participants. Cox model will include treatment group as only covariate.

14.4 Secondary Estimand: HRQOL

This section provides detailed information related to the analysis of the HRQOL secondary efficacy estimand, including supplementary analyses.

14.4.1 Secondary Objective: Derivation and analysis of the secondary estimand HRQOL

Attributes of the estimand are described in the table below.

Endpoint	Change from baseline at • end of combination therapy • completion of investigational therapy (EoT visit) or last scheduled HRQOL score prior to death (whatever comes earlier) on • EORTC QLQ-HN35 subscale scores (head and neck pain, swallowing, and speech), • EORTC QLQ-C30 subscale scores (fatigue, physical function and global health status), and • EQ-5D-5L VAS
Population(s)	High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively
Treatment	Xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo
ICE handling strategy	The endpoint will be analyzed up to the intercurrent event: • Permanent discontinuation of investigational therapy: while on treatment strategy (including EOT visit) • Death (while alive strategy). ~~the last observation prior to death will be used.~~
Population-level summary measure	Difference of least squared mean change from baseline

As described in Section 9.7, HRQOL assessments will be assigned to calculated time windows (using study day) and mapped to baseline, combination therapy, monotherapy and disease-free survival episodes (FU visits). Observed EORTC QLQ-HN35 subscale scores (head and neck pain, swallowing, and speech), EORTC QLQ-C30 subscale scores (fatigue, physical function and global health status), and EQ-5D-5L VAS (absolute value and change from Baseline) will be summarized

by treatment group at baseline, end of combination therapy and completion of investigational therapy (EoT visit). Mixed model for repeated measurements (MMRM) will be employed for the comparative assessment of treatment groups and also for a descriptive presentation of estimates including a boxplot of percent changes from baseline in HRQOL scores by previous specified timepoints.

Two models, one until end of combination therapy and one until EoT visit, will be run with the only difference being the visits included. In case of death prior to the key time points the last planned HRQOL observation will be carried forward following a while-alive intercurrent event strategy. In case of premature treatment discontinuation, assessments as obtained at the EOT visit will be considered for analysis purposes using the time windows accordingly, i.e. time window for week 9 (day 64) for the end of combination therapy.

Per time window, the value the closest to the planned study assessment day as described on Section 9.7 will be included in the model.

The effect of study interventions from randomization until either end of combination therapy (MMRM1) or death and end of study intervention (MMRM2) or death, whichever comes earlier, will be compared between treatment groups using the difference in least-squares means, based on mixed model for repeated measurements (MMRM) for CFB of specific HRQOL endpoints:

- For EORTC QLQ-HN35 head and neck pain, swallowing, and speech subscale scores
- For EORTC QLQ-C30 fatigue, physical function and global health status subscale scores
- For EQ-5D-5L VAS

1-sided p-values, 95% 2-sided CI will be reported. Unless otherwise specified p-values are considered descriptive measures without adjustment for multiplicity.

The MMRM model will include as fixed effect terms: intervention group, visit as categorical, variable, intervention group by visit interaction, baseline score, baseline score by visit interaction, randomization strata (from IVRS), and participant as random effect. Restricted maximum likelihood (REML) estimation will be used. The average effect over visits will be estimated giving each visit equal weight. The unstructured covariance matrix will be used to model the within-subject error. If the model fails to converge, a simple covariance structure will be used. If model still won´t converge, visits with sparse data (<5) will be combined. Denominator degrees of freedom will be computed using Kenward and Roger's method (Kenward 1997).

Sample code using generic visits as continuous variable:

```
PROC MIXED data=dataset method=reml;
        CLASS subj_id trt visit strata
        MODEL pro_cfb = trt visit trt*visit pro_base
pro_base*visit strata /s ddfm=kr;
        REPEATED visit / TYPE=un SUBJECT=subj_id
        LSMEANS trt / at means diff alpha=0.05 cl;
```

*LSMEANS trt*visit / SLICE=visit diff alpha=0.05 cl; * estimates treatment by visit interaction using all visits*
run;
trt = interventional treatment
visit = generic visit according to time windowing approach
pro_cfb = change from baseline PRO score
pro_base = baseline PRO score

Subscales and items scores for EORTC QLQ-C30, EORTC QLQ-HN35, EQ-5D-5L VAS, PGIS and PGIC will be displayed in a listing at each time point.

14.4.2 Supplementary Analysis 1 of the HRQOL Secondary Estimand exploring the proportion of disease-free who at least maintain or regain their baseline level for each treatment group at assessments after completion of investigational therapy

The proportion of participants who improved / maintained / deteriorated compared to baseline score will be described at each planned FU visit between End of treatment visit and End of study visit and presented by treatment group considering a while-alive intercurrent event strategy for deaths. Only assessments prior to investigator disease recurrence or death will be taken into account for the calculations, i.e. participants with disease recurrence or death will not be considered in the denominator. For the End of treatment visit, the assessment will not be considered if participants are prematurely discontinued from treatment. The threshold for maintenance should correspond to the anchor based minimal important difference (MID) for either improvement or deterioration of within treatment group differences as published by Musoro et al. If not available a distribution-based threshold of 0.3 SD will be considered, unless anchor based evidence on MID can be provided.

15 Safety Analyses

This section includes specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

Safety analyses will be done on the safety analysis set and according to the as-treated principle.

15.1 Adverse Events

Treatment-emergent AEs (TEAEs) are those events with onset dates on or after the first administration of study intervention. Any AE occurring before the administration of study intervention on Day 1 and resolved before administration of study intervention or not worsening after administration of study intervention will be included in the AE listings but will not be included in the summary tables (unless otherwise stated). These will be referred to as “pre-treatment” AEs.

In case AE-related dates are partial, the available information will be used in a conservative approach to determine whether the AE is treatment-emergent.

All analyses described in this section will be based on TEAEs if not otherwise specified.

Treatment-emergent adverse events (TEAE) are those events with onset or worsening (seriousness or severity) dates occurring within the on-treatment periods as defined in Section 9.8 and up to 30 days for general AE analyses. AEs will be considered as late onset AEs from 30 days after last treatment administration until the end of the study.

This includes also AEs ongoing at baseline, which first improve under study intervention and then worsen irrespective of baseline. Adverse events with changes in toxicity grade/severity, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF v8.4 by 'AECHGID' in SUPPAE). Records of the same AE will be considered as one event in the analysis. If the severity of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition. If the worse record starts outside of the on-treatment period, it will not appear on the summaries of TEAEs, unless otherwise specified. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The overall outcome of the adverse event is the outcome of the last event in the sequence. When such AEs are listed, start, end date and outcome should be provided together with change date, toxicity grade/severity and seriousness per episode.

Adverse events related to study intervention are those events with relationship missing or related.

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest by treatment arm primary SOC and PT in alphabetical order.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

The 3-tier approach to AE reporting will be applied.

15.1.1 All Adverse Events

Description of the Three-tier Analysis Approach

The 3-tier approach for summarizing and analyzing AEs in clinical studies will be followed. AEs in different tiers are analyzed using different types of statistical analysis.

The pre-specified AEs listed on Section 18.3 will be analyzed as part of Tier 1 if they fulfill the rule-of-4 (at least 4 participants in any of the study intervention groups). Otherwise, such AEs will be included in Tier 3 (see section 15.2.3 and Section 18.3 for further details).

Statistical Outputs

Analysis (Analysis Set)	Safety Tier	Endpoint Derivation	Statistical Analysis Methods
Secondary endpoint: occurrence of AEs and treatment-related AEs			
SAF	Tier 1	The TEAEs prespecified for Tier 1 reporting in this study are Hyperlipasemia, Increased transaminases, QTc prolongation, Nephrotoxicity, Myelodysplastic syndrome, acute myeloid leukemia, or any second malignancy	The Tier 1 (if reported by ≥ 4 participants) TEAEs will be assessed with a 95% CI for between-group comparisons. For the difference in incidence proportions, the CIs will be based on Miettinen & Nurminen (MN) method (Miettinen & Nurminen, 1985). All Tier 1 TEAEs will be presented in the body of CSR. No multiplicity adjustment will be applied.
	Tier 2	TEAEs will be further classified into Tier 2 using the rule-of-4	The Tier 2 TEAEs will be assessed with a 95% CI for between-group comparisons. For the difference in incidence proportions, the CIs will be based on Miettinen & Nurminen (MN) method (Miettinen & Nurminen, 1985). While analyses will be done for all Tier 2 TEAEs, only TEAEs with incidence proportion [≥5% in at least one group] will be presented in the body of CSR. No multiplicity adjustment will be applied.
	Tier 3	TEAEs will be further classified into Tier 3 (including TEAEs in Tier 1 being too rare)	The Tier 3 TEAEs will be assessed via summary statistics.

Unless otherwise stated, AEs will be displayed with SOC terms and PTs within each SOC term sorted alphabetically.

For determining incidence counts, within each level of TEAE term, if a participant experiences more than one occurrence, the participant will only be counted once for that TEAE.

Adverse events related to any study intervention are those events with relationship unknown or related.

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 5.0) per participant, using the latest version of MedDRA PT as event category and MedDRA primary SOC body term as Body System category.

In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in Section 9.9.

Treatment-emergent AEs and participants experiencing TEAEs will be summarized by frequencies (number and percentage) by treatment arm and overall in tables with:

- Overview of TEAEs including:
    - TEAEs
    - TEAEs, grade ≥ 2, grade ≥ 3, grade ≥ 4
    - Study intervention related TEAEs
    - Xevinapant/placebo related TEAEs
    - IMRT related TEAEs
    - Study intervention related TEAEs, grade ≥ 2, grade ≥ 3, grade ≥ 4
    - Xevinapant/placebo related TEAEs, grade ≥ 2, grade ≥ 3, grade ≥ 4
    - IMRT related TEAEs, grade ≥ 2, grade ≥ 3, grade ≥ 4
    - Serious TEAEs
    - Non-serious TEAEs
    - Study intervention related serious TEAEs
    - Xevinapant/placebo related serious TEAEs
    - IMRT related serious TEAEs
    - TEAEs leading to death
    - Study intervention related TEAEs leading to death
    - Xevinapant/placebo related TEAEs leading to death
    - IMRT related TEAEs leading to death
    - Late onset AEs
    - Late onset AEs, grade ≥ 2, grade ≥ 3, grade ≥ 4
    - Late onset AEs with fatal outcome
- Tier 1, Tier 2 and Tier 3 TEAEs (displayed by PT including incidences, risk differences and respective confidence limits for the difference in treatment group incidence

proportions, as applicable according to Rule-of-4) as described above in the 3-tier analysis approach (see description of the 3-tier approach above)

- TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4)
- Xevinapant/placebo Related TEAEs by SOC and PT
- IMRT Related TEAEs by SOC and PT
- Xevinapant/placebo Related TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4)
- IMRT Related TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4)
- TEAEs excluding SAEs, with frequency ≥ 5% in any study intervention group by SOC and PT. "Number of subjects with at least one event" represents the number of participants with at least one AE among AEs where frequency is ≥ 5% in at least one study intervention group.

For Tier 1 and Tier 2 events a forest plot displaying incidence rates, differences in incidence rates as well as the CI for the difference will be provided.

A listing of all AEs will be provided.

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

The overall summary of AEs leading to discontinuation of study intervention will include the frequency (number and percentage) of participants with each of the following, split by treatment arm:

- TEAEs Leading to Temporary Discontinuation of xevinapant/placebo by SOC and PT
- TEAEs Leading to Temporary Discontinuation of IMRT by SOC and PT
- Xevinapant/placebo Related TEAEs Leading to Temporary Discontinuation of Xevinapant/placebo by SOC and PT
- IMRT Related TEAEs Leading to Temporary Discontinuation of IMRT by SOC and PT
- TEAEs Leading to Permanent Discontinuation of xevinapant/placebo by SOC and PT
- TEAEs Leading to Permanent Discontinuation of IMRT by SOC and PT
- Xevinapant/placebo Related TEAEs Leading to Permanent Discontinuation of Xevinapant/placebo by SOC and PT
- IMRT Related TEAEs Leading to Permanent Discontinuation of IMRT by SOC and PT
- TEAEs Leading to Dose Reduction of xevinapant/placebo by SOC and PT

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All deaths, deaths within 30 days after last dose of study intervention, death within 60 days after first dose as well as reason for death, will be tabulated based on information from the "Report of Subject Death" and "Survival Follow-Up" CRFs.

- Number of Deaths
- Number of Deaths within 30 days after last dose of xevinapant/placebo and/or IMRT
- Number of Deaths within 60 days after first dose of xevinapant/placebo and/or IMRT
- Primary Reason of Death
  - Progressive disease and/or disease related condition
  - Event unrelated to study treatment
  - Event related to xevinapant / placebo
  - Event related to IMRT
  - Event related to IMRT and to xevinapant / placebo
  - Unknown

In addition, date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first / last administration, xevinapant dose, and IMRT Actual daily dose planning target volumes (PTV1) and PTV2).

This listing will include:

- AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)
- Flag for death within 30 days of last study intervention
- Flag for death within 60 days of first study intervention

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for serious adverse events (SAEs):

- Incidence of serious TEAEs by SOC and PT
- Incidence of trial drug related serious TEAEs by SOC and PT
- Incidence of radiotherapy related serious TEAEs by SOC and PT

The listings of SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

15.2.3 Other Significant Adverse Events

The events listed on Section 18.4 are defined as CCI as per protocol and safety topics.

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15.3 Clinical Laboratory Evaluation

All laboratory values will be reported in SI units.

Laboratory values (including corresponding normal ranges) from the central lab will be used for summary statistics and shift tables.

In case both central and local labs are collected, summary statistics will be based on central lab collected data, while summaries of worst on-treatment abnormalities will be based on both local and central lab data.

Laboratory results will be graded according to NCI-CTCAE version 5.0. Laboratory parameters which cannot be graded per NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

The definition of baseline measurement is provided in section 9.2.

Values below the detection limit will be imputed by half of the detection limit. If a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g., "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data (hematology, biochemistry, coagulation and urinalysis) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) of raw values and absolute changes from baseline at each on-treatment scheduled visit.

Qualitative data (hematology, biochemistry and coagulation) based on reference ranges will be described according to the categories (i.e., low, normal, high). For urinalysis parameters, the classification Normal, Trace/+, ++, +++, ++++ will be used instead.

Abnormalities classified according to NCI-CTCAE toxicity grading version 5.0 will be described using the worst on-treatment grade. Unless otherwise specified, number of participants with missing measurements will be presented as separate category. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (e.g., hypokalemia) grades at Baseline and postbaseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa. The same applies for non-gradable

parameter, and description of changes from Normal/Low to High and Normal/High to Low will be provided, accordingly. The direction of parameters is defined on Section 18.5.

For **WBC differential counts** (neutrophils, lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential % value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:

  derived absolute count does not meet Grade 2-4 criteria, and

  % value < % LLN value, and

  derived absolute count ≥ 800/mm^3
- Neutrophil count decreased

  derived absolute count does not meet Grade 2-4 criteria, and

  % value < % LLN value, and

  derived absolute count ≥ 1500/mm^3

For **calcium**, CTCAE grading is based on Corrected Calcium. Corrected Calcium is calculated from Albumin and Calcium using concurrent measurements as follows

Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the categories listed below. The number and percentage of participants with each of the following during the on-treatment period will be summarized by study intervention group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN

- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot will also be created, with different symbols for different study intervention groups, by graphically displaying two figures with log-scale transformed axes presented as:

- Peak serum ALT (/ULN) vs peak total bilirubin (/ULN) during the on-treatment period including reference lines at ALT = 3×ULN and total bilirubin = 2×ULN
- Peak serum AST (/ULN) vs peak total bilirubin (/ULN) during the on-treatment period including reference lines at AST = 3×ULN and total bilirubin = 2×ULN

A line plot will be produced for participants on the right upper quadrant of the eDISH plot.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a postbaseline TBILI ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided.

Analysis for Parameters with NCI-CTCAE Grade Available

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available. Laboratory values within normal range but considered grade 1 according to NCI-CTCAE will not be graded 1 (Grade 0, instead).

- A summary table of laboratory parameters by NCI-CTCAE grade will include number and percentage of participants with at least one value of Grade ≥ 0, Grade ≥ 3, Grade ≥ 4 during the on-treatment period.
- A shift table will summarize baseline NCI-CTCAE grade versus the worst on-treatment NCI-CTCAE grade. The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary.

  In case of gradings involving baseline measurements (parameters identified with a start [*] below) for the identification of grades during the on-treatment period, the shift table will present baseline normal and abnormal. Additionally, Worst On-Treatment Grade by Baseline Status will be displayed. Normal will include measurements below and within normal range (direction increase), or measurements within and above normal range (direction decrease).

In case of missing baseline values, the on-treatment grades will be generated assuming the baseline was normal.

The above analyses apply to hematology and chemistry evaluations which can be graded per NCI-CTCAE:

- Hematology

  Hemoglobin (HB) (anemia/ hemoglobin increased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased), Eosinophils * (eosinophilia).

- Coagulation

  Activated partial thromboplastin time (aPTT prolonged), Fibrinogen decreased

- Biochemistry

  Albumin (hypoalbuminemia), Alkaline Phosphatase * (alkaline phosphatase increased), Alanine Aminotransferase * (ALT) (ALT increased), Aspartate Aminotransferase * (AST) (AST increased), Total Bilirubin * (blood bilirubin increased), Creatinine/eGRF * (creatinine increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Calcium (hypocalcemia/hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Uric Acid (Hyperuricemia), Magnesium (Hypomagnesemia), Serum Amylase increased, Lipase increased.

Analysis for Parameters with NCI-CTCAE Grade not Available

Hematology, chemistry and urinalysis evaluations which cannot be graded per NCI-CTCAE criteria will be summarized as frequency (number and row percentage) of participants as follows:

- Shifts from baseline normal to at least one result above normal during on-treatment period
- Shifts from baseline normal to at least one result below normal during on-treatment period

This applies to the following parameters:

- Hematology

  Hematocrit (low/high), Mean Corpuscular Hemoglobin (MCH) (low/high), Mean Corpuscular Volume (MCV) (low/high), monocytes (low/high), basophils (high), Erythrocyte (high)

- Coagulation

  Prothrombin time (low/high)

- Biochemistry

  Protein (low), Blood Urea Nitrogen (high), phosphates (low), C reactive protein

- Urinalysis

pH (low/high), specific gravity (low/high), glucose (trace/1+, 2+, 3+, 4+), protein (trace/1+, 2+, 3+, 4+), blood (trace/1+, 2+, 3+, 4+), ketones (trace/1+, 2+, 3+, 4+), leukocyte by dipstick (trace/1+, 2+, 3+, 4+)

Microscopic data, serum and urine pregnancy test results collected during the study will be listed.

The following figures will be provided for hematology, coagulation, serum chemistry parameters,:

- Boxplots of the laboratory values (by study intervention group) by timepoint
- Boxplots of the change from baseline by timepoint

  Where applicable, reference lines for NCI-CTCAE grades should be added to graphical displays.

Listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by study intervention, parameter and assessment date or visit for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and NCI-CTCAE grades.

15.4 Vital Signs

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The following vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) for raw values and changes from baseline at each scheduled visit:

- Body temperature (°C)
- Systolic and diastolic blood pressure (mmHg)
- Respiration rate (bpm)
- Pulse rate (beats/min)
- Weight (kg)

The maximum on-treatment changes of vital sign measurements from Baseline will be grouped as follows:

	Baseline Value	Change from Baseline
Body temperature increase	< 37 °C; 37 – < 38 °C; 38 – < 39 °C; 39 – < 40 °C; ≥ 40 °C	< 1 °C, 1 – < 2 °C, 2 – < 3 °C, ≥ 3 °C
Pulse rate increase from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
Pulse rate decrease from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm

SBP increase from baseline	< 140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
SBP decrease from baseline	< 140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP increase from baseline	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP decrease from baseline	< 90 mmHg; ≥ 90 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate increase from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm
Respiration rate decrease from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

For each participant, the worst on-treatment value (i.e., lowest and highest when applicable) will be calculated. For the definition of baseline values, see section 9.2. Missing values will define a separate category.

The following summaries will be prepared for vital sign parameters as grouped above:

- Maximal shifts from baseline (changes in categories)

A participant data listing will present data for all vital signs. Worst on-treatment values (highest and/or lowest values depending on vital sign), and changes from Baseline in the highest categories as defined in the table above will be identified.

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15.6 Other Safety or Tolerability Evaluations

ECG summaries will include all ECG assessments collected at Baseline and during the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

For those participants with missing QTcF value, it will be derived as:

$$QTcF\ (msec) = \frac{QT\ (msec)}{\sqrt[3]{\frac{60}{HR\ (beats/min)}}}$$

In case of abnormal ECG findings, triplicate ECG readings will be performed including the already abnormal ECG reading. If there are multiple assessments at the same visit and time point, the average value will be calculated for each parameter and used for the analysis. At Screening, if several ECGs (scheduled and unscheduled) are performed, the results recorded on the latest day before first dose will be used and averaged. At post-baseline visits/time points, values will be averaged based on their observed visits/time points according to time windows defined in Section 9.7.

The following analyses will be performed for each applicable ECG parameter (heart rate, RR, PR, QRS, QT, QTcF and interpretation) study intervention group:

- Descriptive statistics at Baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of participants with notable ECG values according to the following categories by scheduled visit.
    - HR < 50 bpm, < 40 bpm, < 30 bpm
    - HR increase from baseline > 20 bpm, > 30 bpm, > 40 bpm
    - PR > 200 ms and > 220 ms
    - PR increase from baseline > 30 bpm
    - QRS > 110 ms
    - QT/QTcF > 450 ms, > 480 ms, > 500 ms
    - QT/QTcF increase from baseline > 30 ms, > 60 ms

ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized at Baseline and during the on-treatment period.

A shift table from baseline to the worst on-treatment observation in ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant, missing and total) will also be provided.

Complete ECG profiles will be provided in a subject listing for participants with at least one notable ECG value or one notable ECG increase as defined above. For these participants, all ECG parameter values collected during the study will be provided.

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed by the Clinical PK/PD Group, Merck Healthcare KGaA, Darmstadt, Germany, or by a CRO selected by the Sponsor.

All descriptive summaries of PK data will be performed on the PKAS.

16.1.1 Descriptive Statistics of PK Concentration Data

PK concentrations will be descriptively summarized using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median) and maximum (Max).

Descriptive statistics will only be calculated for n>2 in which a measurement of BLQ represents a valid measurement and will be taken as zero for summary statistics of PK concentration data. In case n ≤2, individual data will be presented (min, max) in summary tables.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. PK concentrations will be carried over with full precision as provided in the source data without any rounding applied to CDISC SDTM PC and ADaM ADPC domains.

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

n	0 decimal place
Mean, Min, Median, Max, SD:	3 significant digits
CV%:	1 decimal place

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized using: n, Mean, SD, CV%, Min, Median, Max, geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval (CI) for the GeoMean (LCI 95% GM, UCI 95% GM). In case of any PK parameters related to time (e.g. t_{max}), only n, Min, Median, and Max may be reported.

Descriptive statistics will only be calculated for a PK parameter when n>2. In case n≤2, individual data will be presented (min, max) in summary tables.

PK parameters read directly from the measurements (i.e. C_{max}, C_{trough}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. Descriptive statistics of PK parameter data will be calculated using full precision and rounded for reporting purposes only.

PK parameters will be provided with full precision, without any rounding applied to CDISC SDTM PP and ADaM PP domains.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI, SD:	3 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 General Specifications for PK Concentration Data

Pre-dose samples that occur before drug administration will be assigned a time of 0 hours, as if the sample had been taken simultaneously with the study intervention administration. The same applies to the pre-dose sample of a multiple dose study.

Predose or trough samples which have been taken after the subsequent dosing will be reported as a protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and PK parameter estimation.

Values that are BLQ will be taken as zero for summary statistics of PK concentration data, PK parameter estimation, and for graphical presentations.

Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as “N.R.”. A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

If important protocol deviations occurred likely to affect the PK profile of participants as specified in Section 10.2.1, the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participants listings and flagged; a reason for exclusion will be detailed in the CSR (e.g., a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® Version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters.

PK parameters will be calculated using the actual elapsed time since dosing. In cases where the actual sampling time is missing, calculations may be performed using the nominal time. Details (e.g. number of samples, participants affected) will be described in the CSR. In case actual dosing time is missing, scheduled time might be used for noncompartmental analysis after performance of adequate plausibility checks and agreement with the Sponsor. Decision and rationale should be included in the CSR. Otherwise, there will be no further imputation of missing data.

The following plasma PK parameters will be calculated for xevinapant [and metabolite(s), if applicable] where appropriate:

Symbol	Definition	Calculation
C_{max}	Maximum observed concentration over the dosing interval.	Observed concentration of sample collected at 0.5 to 4 hours postdose
C_{trough}	The concentration observed at the end of a dosing interval immediately before next dosing.	Observed concentration of predose sample

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration and dose units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

16.1.5 Presentation of PK Concentration and PK Parameter Data

16.1.5.1 Listings and Tables

The following PK tables will be produced (PK Analysis Set):

- Descriptive statistics of concentrations by analyte, day, and scheduled time, for all subjects combined and for racial subgroups (Asian, Chinese, Japanese)
- Descriptive statistics of PK parameters by analyte and day, for all subjects combined and for racial subgroups (Asian, Chinese, Japanese)

The following PK Listings will be produced (Safety Analysis Set):

- Individual concentrations by analyte, day, and scheduled time
- PK sampling date and time, nominal time, actual time, and analyte concentrations by participant, sorted in chronological order
- Individual PK parameters by analyte and day
- Data excluded from PK descriptive summaries

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[redacted]

17 References

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18 Appendices

18.1 Appendix 1 – External DMC Analysis

The external DMC will assess the safety and available PK data of the investigational treatment to safeguard the interests of study participants. The external DMC will also monitor the overall conduct of the clinical study to protect its validity and credibility.

The external DMC will perform a safety review after 12 participants have been randomized, treated, and followed up until the end of the combination therapy period and hereafter every 4 months during recruitment and twice a year after recruitment has been completed if not otherwise requested earlier by the Sponsor or the external DMC. The external DMC will also take into consideration available PK data when assessing safety. For further details, refer to the external DMC Charter.

Ongoing data cleaning will be performed, as described in the Integrated Data Review Plan.

Analysis Sets

Screening Analysis Set (SCR): The Screening analysis set includes all participants who provided informed consent, regardless of the participant's randomization and study intervention status in the study.

Safety Analysis Set (SAF): The DMC Safety Analysis Set will include all participants who received at least 1 dose of study intervention at the time of the data export. For the first DMC meeting triggered by the 12 first randomized participants followed up until the end of the combination therapy period, the DMC SAF will also include the participants subsequently enrolled but with a shorter treatment period.

Participants will be analyzed according to the actual treatment.

General Specifications for Data Analyses

Same specifications described in Section 9 and Section 9.1 will be used for DMC analysis.

Planned Analyses

For DMC meeting 1 delivery only listings will be provided:

- Listing of TEAEs Leading to Discontinuation of Xevinapant/Placebo or IMRT - Safety Analysis Set as described in Section 15.1.2
- Listing of Serious TEAEs - Safety Analysis Set as described in Section 15.1.1
- Listing of all TEAEs with Grade >= 3 and SAEs - Safety Analysis Set Set as described in Section 15.1.1

- Listing of Discontinued Subjects as described on Section 10.1
- Listing of Important Protocol Deviations - Safety Analysis Set as described in Section 10.2.1
- Listing of Demographic Data - Safety Analysis Set as described in Section 11.1
- Listing of Disease History - Safety Analysis Set as described in Section 11.3
- Listing of Treatment Exposure - Safety Analysis Set as described in Section 13
- Listing of Hematology Values by Subject - Safety Analysis Set as described in Section 15.3
- Listing of Biochemistry Values by Subject - Safety Analysis Set as described in Section 15.3
- Listing of ECG values for subjects with abnormal findings - Safety Analysis Set as described in Section 15.6
- Listing of ECG values for subjects with clinically significant findings - Safety Analysis Set as described in Section 15.6

For External DMC meeting 2 onwards delivery will include the following analyses:

- Study Subject Data
    - Disposition of participants and discontinuations using the SCR analysis set, presenting the overall summary by actual treatment arm and overall as described in Section 10.1
    - Figure Time to treatment discontinuation - Safety Analysis Set
    - Summary of Timeliness/Cleanliness of Data - Safety Analysis Set
    - Important Protocol Deviations - Safety Analysis Set as described in Section 10.2.1
    - Stratum by IWRS different from stratum by eCRF– Safety Analysis Set
    - Demographic Characteristics - Safety Analysis Set as described in Section 11.1
    - Disease History – Safety Analysis Set as described in Section 11.3
    - Concomitant Medications - Safety Analysis Set as described in Section 12
    - Xevinapant/ Placebo - Dose Reductions – Safety Analysis Set as described in Section 13

- Xevinapant/ Placebo and IMRT – Therapy delays – Safety Analysis Set as described in Section 13

- Safety Data

  - Overview of Treatment Emergent Adverse Events (TEAEs)- Safety Analysis Set as described in Section 15.1.1

  - Overview of TEAEs Leading to Discontinuation of Treatment- Safety Analysis Set as described in Section 15.1.1

  - Listing of TEAEs Leading to Discontinuation / Dose Reduction of Treatment - Safety Analysis Set as described in Section 15.1.2

  - TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT) - Safety Analysis Set as described in Section 15.1.1

  - Forest Plot for Tier 1/3 TEAEs- Safety Analysis Set as described in Section 15.1.1

  - Tier 2/3 TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT) - Safety Analysis Set as described in Section 15.1.1

  - Serious TEAEs by SOC and PT - Safety Analysis Set as described in Section 15.1.1

  - TEAEs (by worst grade >=3, >=4, =5) by SOC and PT - Safety Analysis Set as described in Section 15.1.1

  - Xevinapant/Placebo and/or IMRT related TEAEs (by worst grade >=3, >=4, =5) by SOC and PT - Safety Analysis Set as described in Section 15.1.1

  - Overview of tEAEs of Special Interest - Safety Analysis Set as described in Section 15.2.3

  - TEAEs of Special Interest by SOC and PT - Safety Analysis Set as described in Section 15.2.3

  - Listing of Late onset AESI - SAF Analysis Set as described in Section 15.2.3 (if more than 20 events will be presented switch to a table for Late Onset AEs by of special interest - Safety Analysis Set)

  - Overview of late onset AEs of Special Interest - Safety Analysis Set as described in Section 15.2.3TEAEs frequency and worst grade occurring in >=5% subjects in either Treatment Arm - Safety Analysis Set as described in Section 15.1.1

  - TEAEs Leading to Death by SOC and PT - Safety Analysis Set as described in Section 15.1.1

- TEAEs Leading to Permanent Discontinuation of xevinapant/placebo by SOC and PT - Safety Analysis Set as described in Section 15.1.2
- TEAEs Leading to Permanent Discontinuation of IMRT by SOC and PT - SAF Analysis Set as described in Section 15.1.2
- Deaths by Primary Reason - Safety Analysis Set as described in Section 15.2.1
- Listing of Serious TEAEs - Safety Analysis Set as described in Section 15.1.1
- Listing of all TEAEs with Grade >= 3 and SAEs - Safety Analysis Set as described in Section 15.1.1
- Hematology - Baseline and Worst On-Treatment Value - Safety Analysis Set as described in Section 15.3
- Hematology - Shift in Toxicity Grading from Baseline to Highest NCI-CTCAE on treatment Grade - Safety Analysis Set as described in Section 15.3
- Hematology - Boxplot for PARAM1 Values by Time Point and Treatment Group - Safety Analysis Set as described in Section 15.3
- Hematology - Summary by Worst On-treatment Value - Safety Analysis Set as described in Section 15.3
- Hematology: Subjects with at least one abnormal and/or NCI-CTCAE grade >=1 result, listing - Safety Analysis Set
- Biochemistry - Baseline and Worst On-Treatment Value - Safety Analysis Set as described in Section 15.3
- Biochemistry - Shift in Toxicity Grading from Baseline to Highest NCI-CTCAE on treatment Grade - Safety Analysis Set as described in Section 15.3
- Biochemistry - Boxplot for PARAM1 Values by Time Point and Treatment Group - Safety Analysis Set as described in Section 15.3
- Biochemistry - Summary by Worst On-treatment Value - Safety Analysis Set as described in Section 15.3
- Biochemistry: Subjects with at least one abnormal and/or NCI-CTCAE grade >=1 result, listing - Safety Analysis Set
- eDISH Plot - Safety Analysis Set as described in Section 15.3
- Line plot (for those patients who are in the upper right quadrant) - Liver Function Test - Safety Analysis Set as described in Section 15.3

- Subjects with QTcF values >=500 msec and QTcF changes from baseline >60 msec at the same visit - Safety Analysis Set
- Subjects with noteworthy QTcF values - Safety Analysis Set
- Subjects with noteworthy QTcF change from baseline - Safety Analysis Set
- Listing of Concomitant Medications - Safety Analysis Set as described in Section 12
- Listing of Adverse Events - Safety Analysis Set as described in Section 15.1
- Listing of TEAEs leading xevinapant/placebo permanent discontinuation - Safety Analysis Set
- Listing of TEAEs leading IMRT permanent discontinuation - Safety Analysis Set
- Listing of ECG values for subjects with abnormal findings - Safety Analysis Set as described in Section 15.5
- Listing of ECG values for subjects with clinically significant findings - Safety Analysis Set as described in Section 15.5
- Listing of Vital Signs - Safety Analysis Set as described in Section 15.4
- Listing of subjects with at least one QTcF change from baseline value > 30 msec - Safety Analysis Set

18.2 Appendix 2 – HRQOL scoring

18.2.1 Appendix 2.1 – EORTC QLQ-HN35 scoring

Refer to: H&N35 Scoring 2.0.pdf

18.2.2 Appendix 2.2 – EORTC QLQ-C30 scoring

Refer to: EORTC QLQ-C30.pdf

18.2.3 Appendix 2.3 – EQ-5D-5L scoring

Refer to: EQ-5D-5LUserguide-08-0421.pdf

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18.5 Appendix 4 - NCI-CTCAE grading for Laboratory Parameters

Laboratory Assessment	Parameters	Name in NCI-CTC	Direction(s) of abnormality
Hematology	Hemoglobin	Anemia/Hemoglobin increased	Low/High
	Lymphocytes	Lymphocyte count decreased / increased	Low/High
	Neutrophils	Neutrophil count decreased	Low
	Platelets	Platelet count decreased	Low
	Eosinophils	Eosinophila [a]	High
Coagulation	Activated Partial Thromboplastin Time	Activated Partial Thromboplastin Time prolonged	High
	Fibrinogen	Fibrinogen decreased	Low
Biochemistry	Albumin	Hypoalbuminemia	Low
	Alkaline Phosphatase	Alkaline Phosphatase increased [a]	High
	Alanine Aminotransferase (ALT)	Alanine Aminotransferase increased [a]	High
	Aspartate Aminotransferase (AST)	Aspartate Aminotransferase increased [a]	High
	Total Bilirubin	Blood bilirubin increased [a]	High
	Creatinine	Creatinine increased [a]	High
	eGFR	Chronic kidney disease	Low
	Potassium	Hypokalemia / Hyperkalemia	Low / High
	Sodium	Hyponatremia / Hypernatremia	Low / High
	Calcium	Hypocalcemia / Hypercalcemia	Low / High
	Glucose	Hypoglycemia / Hyperglycemia	Low / High
	Uric Acid	Hyperuricemia	High
	Magnesium	Hypomagnesemia/Hypermagnesemia	Low / High
	Amylase	Serum amylase increased	High
	Lipase	Lipase increased	High

[a] on treatment grading dependent on baseline grading

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