STUDY PROTOCOL

A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX)

Investigational Medicinal Product	Xevinapant (also known as Debio 1143)
International Nonproprietary Name	Xevinapant
Study Numbers:	Debio 1143-SCCHN-301 MS202359_0006
EudraCT Number:	2020-000377-25
Current Protocol Version:	V13.0 dated 18 March 2024, including amendments 1-12.0
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Sponsor:	Affiliates of Merck KGaA, Darmstadt, Germany **For all countries, except the US and Canada:** Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293 Darmstadt, Germany **In the US and Canada:** EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA **Local Sponsor for Sites in Japan:** Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
13.0	Global amendment	18 March 2024
12.0	Global amendment	29 February 2024
11.0	Global amendment	02 January 2024
10.0	Global amendment – Urgent Safety Measure	11 April 2023
9.0	Global amendment	10 May 2022
8.1	Local amendment for China	31 January 2022
8.0	Global amendment issued by Merck KGaA, Darmstadt, Germany; see Section 13.10	08 November 2021
7.2	Local amendment for Japan; see Section 13.10	13 October 2021
7.1	Local amendment for Japan; see Section 13.10	20 September 2021
7.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.6	28 June 2021
6.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.5	07 December 2020
5.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.4	06 December 2020
4.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.3	23 July 2020
3.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.2	02 July 2020
2.0	Global amendment issued by Debiopharm; see Section 13.10.1.1.1	12 May 2020
1.0	Original Protocol	02 April 2020

Protocol Version 13.0 (18 March 2024)

Overall Rationale for the Amendment

This amendment corrects a rendering issue that duplicated Table 10-4 in Section 10.2.2.2.

Section # and Name	Description of Change	Brief Rationale
Section 10.2.2.2, Table 10-4	Corrected duplication of Table 10-4 in rendering.	Technical glitch caused table to be repeated.

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ABBREVIATIONS

Abbreviation	Explanation
^{18}F-FDG-PET	Positron Emission Tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	ALanine aminotransferase
ALP	ALkaline Phosphatase
ANC	Absolute Neutrophils Count
AST	ASpartate aminoTransferase
AUC	Area Under the Concentration vs time curve
BIRC	Blinded Independent Review Committee
C	Cycle
CBCDA	Carboplatin
CI	Confidence Interval
C [redacted]	[redacted]
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CRR	Complete Response Rate
CRT	ChemoRadioTherapy
CT-scan	Computed Tomography - Scan
CxDx	Cycle x Day x
CYP	Cytochrome P450
D	Day
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DoR	Duration of Response
ECG	ElectroCardioGram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EFS	Event-Free Survival
eGFR	estimated Glomerular Filtration Rate
END	Elective Neck Dissection
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End Of Study
EOT	End Of Treatment
EPO	Erythropoietin
C [redacted]	[redacted]
E-R	Exposure-Response

Abbreviation	Explanation
ESMO	European Society for Medical Oncology
G	Grade
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD-CDDP	High-Dose Cisplatin
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HRQL	Health-Related Quality of Life
C [redacted]	[redacted]
IAP	Inhibitors of Apoptosis Proteins
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	ImmunoHistoChemistry
IMRT	Intensity-Modulated RadioTherapy
INR	International Normalized Ratio
INN	International Nonproprietary Name
IRB	Institutional Review Board
ITT	Intent-To-Treat
i.v.	Intravenous
IWRS	Interactive Web Response System
LA-SCCHN	Locally Advanced Squamous Cell Carcinoma of the Head and Neck
LRC	LocoRegional Control
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	Not Evaluable
OIS	Overall Imbalance Score
ORR	Objective Response Rate
OPC	OroPharyngeal Cancer
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
C [redacted]	[redacted]
p.o.	Per os (oral)
PR	Partial Response
PRBC	Packed Red Blood Cells
PTV	Planning Target Volume
Q3W	Every 3 Weeks
QoL	Quality of Life
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	RiboNucleic Acid
RP2D	Recommended Phase 2 Dose
RT	RadioTherapy
RT-QA	RadioTherapy Quality Assurance
RTPR	Radiographic Time Point Response
SCCHN	Squamous Cell Carcinoma of the Head and Neck

Abbreviation	Explanation
SAE	Serious Adverse Event
SAF	SAFety set
SAR	Serious Adverse Reaction
SD	Standard Deviation
SMAC	Second Mitochondrial-derived Activator of Caspases
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TNM	Classification of malignant tumors: T=size of the primary tumor, N=regional lymph node involvement, M=distant metastasis
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
C [redacted]	[redacted]

Statement of Compliance

This study will be conducted in accordance with the protocol and in compliance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the ethical principles that have their origin in the Declaration of Helsinki and its subsequent amendments, and applicable local laws and regulations. The Investigator will be responsible for the overall conduct at the study site and adherence to the requirements of the ICH guidelines and all other applicable local regulations.

1. PROTOCOL SUMMARY

1.1. Synopsis

Study title	A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX).		
Study number	MS202359 _0006 (Debio 1143-SCCHN-301)	**Study Phase**	3
Study design	This is a prospective, randomized, double-blind, placebo-controlled, multicenter, 2-arm, parallel-group Phase 3 study comparing the efficacy and safety of xevinapant versus matched placebo, when administered in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy (IMRT) in previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN), suitable for definitive chemoradiotherapy (CRT) (stage III, IVA, IVB; hypopharynx, larynx and/or human papillomavirus [HPV]-negative oropharyngeal cancer [OPC]). Upon confirmation of eligibility, participants will be enrolled and randomized using dynamic allocation in a 1:1 ratio to: **Arm A:** 3 cycles of xevinapant (200 mg/day from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of xevinapant (200 mg/day from Day 1 to 14, per cycle). or **Arm B:** 3 cycles of placebo (Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle). One cycle is composed of 3 weeks. The following stratification factors will be considered for randomization: Region (North America vs Western Europe vs Rest of the world), Primary tumor site (larynx vs other), Lymph node involvement (N0-1 vs N2 vs N3), T size (T4 vs other). Study diagram and flow are provided in Section 1.2.		
Study objectives and endpoints	Primary, secondary, C [redacted] objectives with associated endpoints are presented in the table below. **Synopsis Table 1 - Objectives and endpoints**		

Objectives	**Endpoints**
Primary	
To demonstrate superior efficacy of xevinapant vs placebo when added to CRT in LA-SCCHN.	Event-Free Survival (EFS) as assessed by the Blinded Independent Review Committee (BIRC) defined as the time from randomization to the first occurrence of any of the following events: • Death from any cause. • Progression:

	○ Radiological, assessed per Response Evaluation Criteria in Solid Tumors (RECIST v1.1.) or ○ Clinical, with or without RECIST v1.1-radiologically documented progression, assessed endoscopically. • Primary treatment failure before achieving a complete response (CR): requirement for radical salvage surgery that includes the primary tumor site, with documented viable tumor presenting anatomopathological findings even in the absence of formal RECIST v1.1 radiological progression. • Any radiological or clinical relapse after achieving a CR (locoregionally), including any event defined as locoregional treatment failure, even in the absence of formal radiological progressive disease confirmation: ○ Requirement for radical salvage surgery that includes the primary tumor site, regardless of anatomopathological findings. or ○ Elective neck dissection or biopsy, with positive viable tumor cells on anatomopathological findings at 22 weeks or later after randomization. • Second cancers unless anatomopathological findings exclude squamous histology. Note: Investigator-assessed EFS will be used for supportive analysis.
Secondary	
To assess the efficacy of xevinapant compared to placebo when added to CRT according to additional efficacy endpoints.	Overall survival defined as the time from randomization to death due to any cause.
	Progression-Free Survival (PFS) defined as the time from randomization to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed PFS will be used for supportive analysis.
	Locoregional control defined as the time from randomization to the first occurrence of progression at the site of the primary tumor or the locoregional lymph nodes, either according to RECIST v1.1 or based on clinical assessment (radiological or clinical, as assessed by Investigator). Note: Will be investigated by BIRC as supportive analysis.

		Objective response rate, defined as the proportion of participants with CR or partial response by RECIST v1.1, as assessed by the BIRC. Note: Investigator-assessed response will be used for supportive analysis.
		CR rate, defined as the proportion of participants with CR by RECIST v1.1, as assessed by the BIRC. Note: Investigator-assessed response will be used for supportive analysis.
		Duration of response defined as the time from the first evidence of response (partial or complete, as assessed by the BIRC according to RECIST v1.1) to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed duration of response will be used for supportive analysis.
		Proportion of participants with radical salvage surgery (excluding elective neck dissection, without anatomopathological evidence of residual malignant cells).
		Time to subsequent systemic cancer treatments.
	To compare safety, tolerability, and treatment compliance of xevinapant vs placebo, when added to CRT.	Incidence and severity of adverse events, serious adverse events and adverse events of special interest, changes in laboratory values, vital signs, and electrocardiograms according to NCI-CTCAE v 5.0.
		Extent of exposure of the different treatment agents (i.e., Xevinapant or matched placebo, radiotherapy [RT], chemotherapy) including: • Treatment duration. • Number of cycles. • Actual dose. • Dose intensity. • Relative dose intensity. • Incidence of treatment interruption. • Incidence of treatment reduction. • Incidence of treatment discontinuation.
	To compare the health-related quality of life of xevinapant vs placebo when added to CRT using patient-reported outcome questionnaires.	Changes from baseline in: • Global Health Scale/Quality of Life and Fatigue using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. • Swallowing and Pain using EORTC QLQ-HN35 questionnaire.

	C [redacted]
Study population and sample size	The study population includes adult patients with LA-SCCHN (stage III, IVA or IVB) with histologically confirmed diagnosis in at least one of the following sites: oropharynx (HPV-negative), hypopharynx and larynx. Patients should be previously untreated and suitable for definitive CRT as determined by a multidisciplinary oncology team, as is currently standard clinical practice. This study population will be defined by the inclusion and exclusion criteria below. No protocol waivers will be granted. Upon confirmation of eligibility, participants will be enrolled and randomized. Assuming a 30% screening failure rate, approximately 1000 participants will be screened worldwide at approximately 280 sites and will undergo study related screening assessments to randomize ~700 participants. Note: Additional Chinese participants from China Mainland will be randomized in a China-specific extension cohort.
Inclusion criteria	The following inclusion criteria must be met during screening: 1. Willing and able to sign written informed consent prior to study screening. 2. Male or female ≥ 18 years of age (or based on the country legal age limit for adults) on day of signing the Informed Consent Form (ICF). 3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. 4. Histologically confirmed diagnosis of previously untreated LA-SCCHN patient (stage III, IVA or IVB according to the American Joint Committee on Cancer [AJCC]/TNM Staging System, 8th Ed.) suitable for definitive CRT, of at least one of the following sites: oropharynx, hypopharynx, and larynx. Note: Archival tumor sample to be provided (except for China), if available. 5. Evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by computed tomography scan or magnetic resonance imaging, based on RECIST v 1.1. 6. For OPC patients, primary tumors must be HPV-negative as determined by p16 expression using immunohistochemistry (pathological report should be available). For OPC participants, p16 cutoff for determination of HPV status is defined in the protocol. Note: If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory. 7. Able to swallow liquids or has an adequately functioning feeding tube, gastrostomy or jejunostomy in place 8. No hearing loss by clinical assessment or ≤ grade 2 hearing impairment (according to NCI-CTCAE v.5). 9. Peripheral neuropathy < grade 2. 10. Adequate hematologic, renal, and hepatic function as indicated by: • Estimated glomerular filtration rate ≥ 60 mL/min/1.73m² (using the Chronic Kidney Disease - Epidemiology Collaboration [CKD -EPI] creatinine formula). • Absolute neutrophil count ≥ 1 500 cells/µL. • Platelets ≥ 100 000 cells/µL. • Hemoglobin ≥ 9.0 g/dL (blood transfusions during screening are permitted). • AST and ALT ≤ 3.0 × upper limit of normal (ULN). • Total bilirubin ≤ 1.5 × ULN (up to 2.0 × ULN is allowed if the direct bilirubin level is normal and the elevation is limited to indirect bilirubin).

	11. Women of childbearing potential (according to recommendations of the Clinical Trial Facilitation Group) must have a negative serum pregnancy test at screening and must not be breastfeeding. Women of childbearing potential must agree to use highly effective contraceptive method(s) from ICF signature to 6 months after the last administration of chemotherapy or 3 months after last dose of xevinapant /matched placebo, whichever is the latest. Non-sterilized males who are sexually active with a female partner of childbearing potential must agree to use condom and spermicide from ICF signature to 6 months after the last administration of chemotherapy or 3 months after the last dose of xevinapant /matched placebo, whichever is the latest. Because male condom and spermicide is not a highly effective contraception method, it is strongly recommended that female partners of a male study participant use highly effective contraceptive method(s) (see Section 8.1.3) throughout this period. Male participants must refrain from donating sperm during the clinical study and for 6 months after the last administration of chemotherapy or 3 months after the last dose of xevinapant /matched placebo, whichever is the latest. If not done previously, cryopreservation of sperm prior to receiving chemotherapy or xevinapant/matched placebo is advised to male participants with a desire to have children.
Exclusion criteria	Meeting any of the following criteria at screening will render a participant ineligible for participation in the study: 1. Primary tumor of nasopharynx, paranasal sinuses, nasal, or oral cavity, salivary, thyroid or parathyroid gland pathologies, skin or unknown primary site. 2. Metastatic disease (stage IVC as per AJCC/TNM, 8th Ed.). 3. Prior definitive or adjuvant RT and/or radical surgery to the head and neck region which may jeopardize the primary tumor irradiation plan, or any other prior SCCHN systemic treatment, including investigational agents. 4. Use within 14 days prior to randomization or requirement for ongoing treatment with any drug(s) on the prohibited medication list. 5. Treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of study treatment. 6. Known history of infection with human immunodeficiency virus (HIV). If unknown history of HIV, an HIV screening test is to be performed and participants with positive serology for HIV-1/2 must be excluded. 7 Known chronically active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. If unknown status, the following tests are to be performed and participants with positive serology must be excluded: • HBV screening tests: both HBV sAg and Anti-HepB core IgG. • HCV screening tests: both HCV-antibody and positive viral load HCV-RNA by PCR. 8. Other infections (viral and/or bacterial and/or mycotic) requiring systemic treatment. 9. Live-attenuated vaccinations within 30 days prior to first investigational treatment administration. 10. Ongoing uncontrolled infection requiring intravenous antibiotic therapy within 1 week prior to randomization. 11. Known gastrointestinal disorder with clinically established malabsorption syndrome and major gastrointestinal surgery that may limit oral absorption. 12. Documented weight loss of >10% during the last 4 weeks prior to randomization (unless adequate measures are undertaken for nutritional support), OR plasmatic albumin < 3.0 g/dL. No albumin transfusions are allowed within 2 weeks before randomization. 13. Active gastrointestinal bleeding, or any other uncontrolled bleeding requiring more than 2 red blood cell transfusions or 4 units of packed red blood cells within 4 weeks prior to randomization.

	14. Active uncontrolled inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis, and other autoimmune diseases) requiring ongoing treatment with anti-TNF medication. 15. Any concomitant medication known to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication within 7 days prior to start of treatment. 16. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following: • Ongoing or history of uncontrolled or symptomatic ischemic myocardiopathy within 6 months prior to randomization. • Known left ventricular ejection fraction < 50%, left ventricular hypertrophy, ventricular arrhythmias, bradycardia (heart rate < 50 bpm). • History of myocardial infarction, or severe/unstable angina, within 6 months prior to randomization. • New York Heart Association grade ≥ 3 congestive heart failure. • Congenital long QT syndrome. • Family history of long QT syndrome. • Symptomatic pulmonary embolism within 6 months prior to randomization. • Ongoing or known history of transient ischemic attacks or stroke within 6 months prior to randomization. • QTc using Fridericia's formula (QTcF) interval > 450 ms for males and > 470 ms for females. 17. Symptomatic pulmonary disease requiring continuous or intermittent oxygen supply. 18. History of another malignancy within the last 3 years prior to randomization, with the exception of completely resected non-melanoma cell skin cancer outside the head and neck area or completely resected stage I breast cancer, or completely resected in-situ non-muscular invasive bladder, cervix and/or uterine carcinomas, or T1a squamous cell carcinoma of the esophagus. 19. Known contraindication to undergoing positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG-PET) scans, and/or both contrast-enhanced MRI and contrast-enhanced CT scans. 20. Known allergy to xevinapant, cisplatin, carboplatin, other platinum-based agent or any excipient known to be present in any of these products or in the placebo formulation. 21. Non-compensated or symptomatic liver cirrhosis (Child-Pugh score: B or C). 22. Any ongoing condition or disorder, before randomization, including drug(s) or alcohol abuse, which in the judgment of the Investigator would make the patient inappropriate for entry into the study or precluding his/her ability to comply with study procedures.
Study intervention and dosing scheme	The study intervention includes administration of both investigational treatments and background treatments. In the current protocol, xevinapant (International Nonproprietary Name: xevinapant), matched placebo, cisplatin and carboplatin are investigational treatments. IMRT is considered as background treatment. The following investigational and background treatments will be administered during the study according to randomization: **Arm A:** 3 cycles of xevinapant (200 mg/day from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of xevinapant (200 mg/day from Day 1 to 14, per cycle). or **Arm B:** 3 cycles of placebo (from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle).

In case of toxicity after the first cisplatin dosing, participants can be switched to carboplatin (AUC= 5 or 4 on Day 2 of each subsequent cycle depending on the toxicity observed, see Section 6.1.2.1.2).

Xevinapant, matched placebo and CRT will be administered as per Synopsis Figure 1 and Synopsis Figure 2.

Synopsis Figure 1 - Treatments administered during the combination therapy period

	Combination therapy (CRT and xevinapant/matched placebo) period								
Cycles (a cycle is 3 weeks)	**C1**			**C2**			**C3**		
Study Week	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**
Study Visit Day									
Investigational treatments:									
xevinapant or matched placebo									
HD-CDDP or CBCDA									
Background treatment:									
IMRT									

Abbreviations: C: cycle; **CBCDA:** carboplatin; **CRT**: chemoradiotherapy; **HD-CDDP:** high-dose cisplatin; **IMRT**: intensity-modulated radiotherapy; **W:** week.
One cycle is composed of 3 weeks.

Synopsis Figure 2 - Treatment administered during the monotherapy period

	Monotherapy (xevinapant/matched placebo) period										EOT
Cycles (a cycle is 3 weeks)	**C4**			**C5**			**C6**				
Study Week	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**	**W17**	**W18**	**W19**	**W20**
Study Visit Day											
Investigational treatments:											
xevinapant or matched placebo											
HD-CDDP or CBCDA											
Background treatment:											
IMRT											

Abbreviations: C: cycle**; CBCDA:** carboplatin; **EOT:** end of treatment; **HD-CDDP:** high-dose cisplatin; **IMRT**: intensity-modulated radiotherapy; **W:** week.
One cycle is composed of 3 weeks.

Study duration

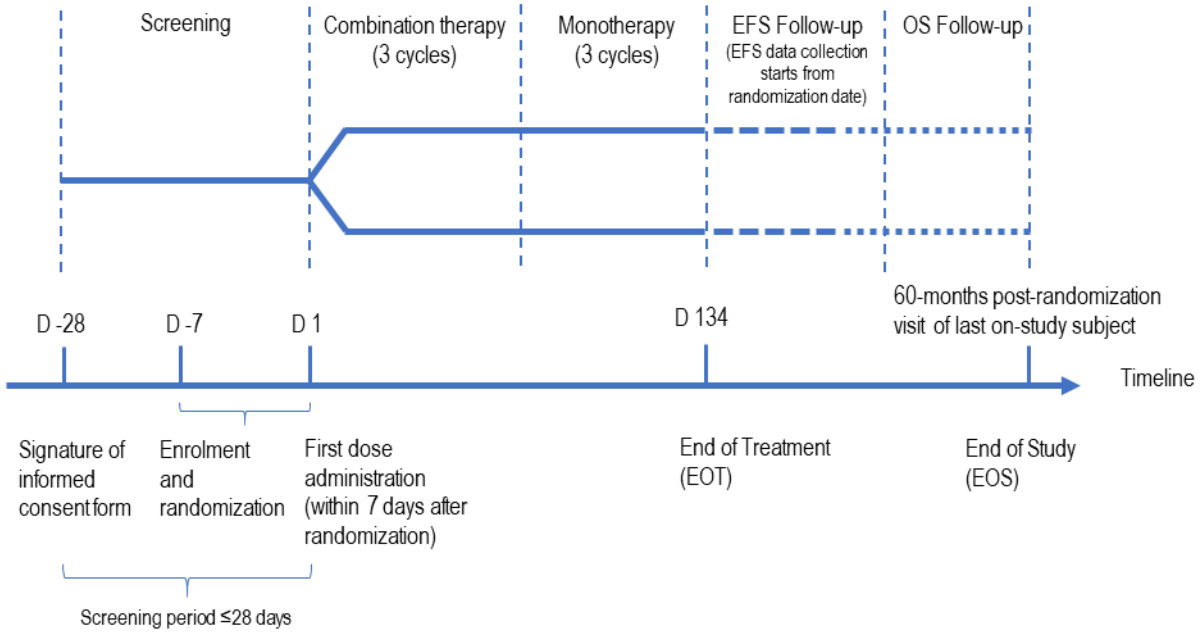
It is expected that the total duration of the study will be around 82 months (6.8 years) (Synopsis Figure 3).

Participant duration	Participants will be followed up until premature discontinuation from study or until the last on-study participant reaches his/her 60-months post-randomization visit, whichever occurs first.
Statistical methods	The following analysis sets will be used for planned analyses: Intent-to-treat, Safety, C [redacted] analysis set. The primary hypothesis on EFS will be evaluated by comparing xevinapant with placebo in combination with CRT using a stratified log-rank test. The stratification factors are tumor size (T4 vs other) and lymph node involvement (N0-1 vs N2 vs N3). Hazard ratio will be estimated using a Cox-proportional hazard regression model adjusted for the randomization stratification factors. Treatment effect on other time-to-event endpoints will be estimated using Cox regression model adjusted for the randomization stratification factors. Estimation of the treatment effect on binary endpoints will be done using a logistic model adjusted for the randomization stratification factors. Descriptive statistics will be provided for safety endpoints. CCI [redacted] Hierarchical fixed sequence testing procedure is applied to control the type I error for the interim analysis and multiple hypotheses testing. The overall type I error is controlled at 0.025 one-sided. An O'Brien & Fleming type α spending is used for the calculation of the significance levels and efficacy boundaries (p-value scale). With CCI [redacted], the clinical study has about 90% power to detect the expected hazard ratio benefit.
Safety and efficacy oversight	An IDMC will be established before the randomization of the first participant to provide safety and efficacy oversight during the study. The review of safety and efficacy data will be performed according to an IDMC Charter that will be prepared before data collection start. All relevant data available from this study will be provided for these reviews. The responsibilities of the IDMC include: • To minimize the exposure of participants to an unsafe therapy or dose. • To make recommendations for changes in study processes where appropriate. • To advise on the need for dose adjustments because of safety issues. • To endorse continuation of the study. It will also be the responsibility of the IDMC to review the efficacy results at the interim analysis.

	At any time during the study when the IDMC recommends major changes, these recommendations will be presented to the Trial Steering Committee. Further details on the membership, responsibilities and working procedures of the IDMC are described in the IDMC Charter, provided as a separate document in the study file.

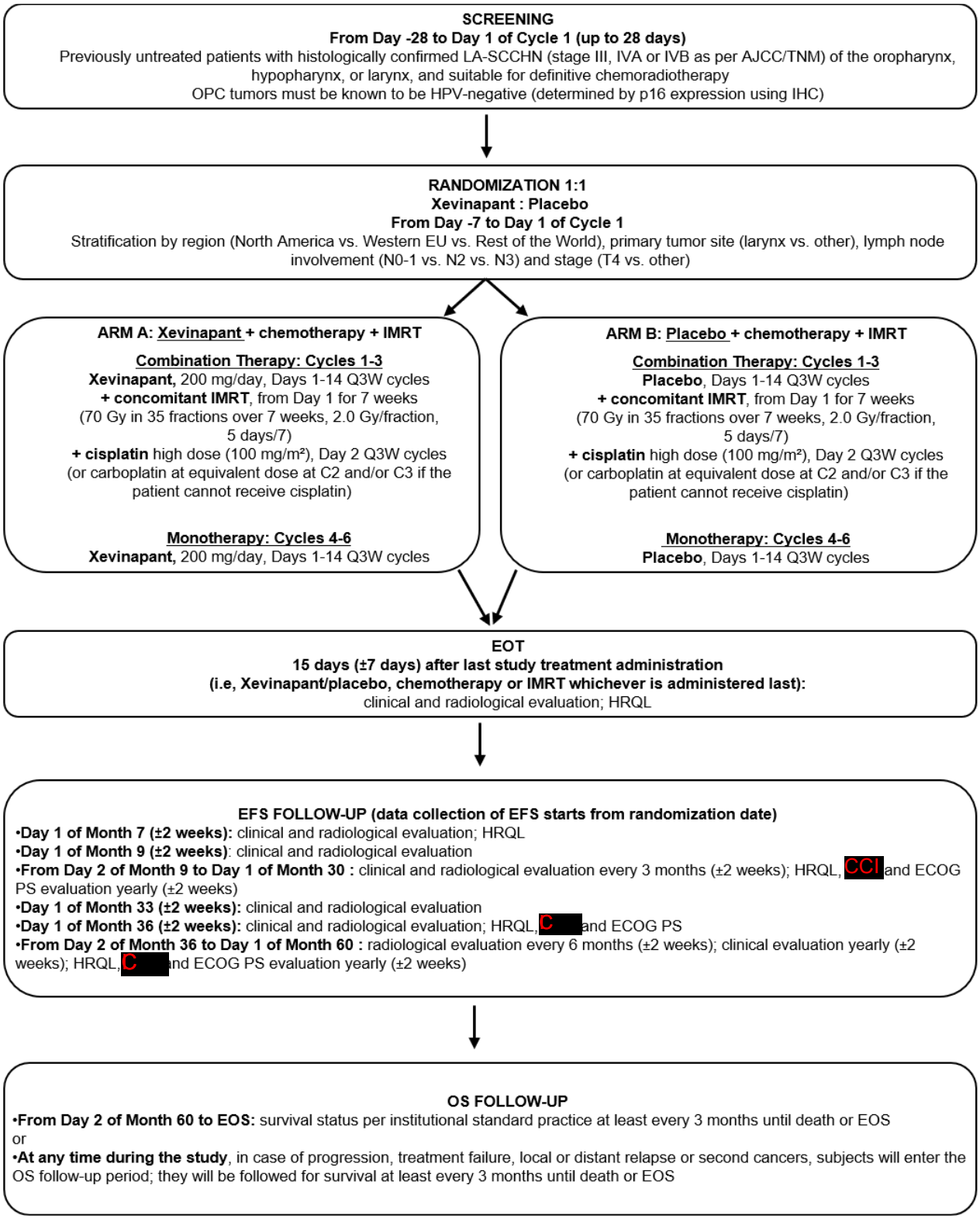
1.2. Study Diagram and Flow

Figure 1-1 Study diagram



Abbreviations: D: day**; EFS follow-up:** Event-Free Survival follow-up; **OS follow-up**: Overall Survival follow-up

Figure 1-2 Study Flow



Abbreviations: AJCC: American Joint Committee on Cancer**; Cx:** Cycle x; **EFS:** event-free survival follow-up; **EOS**: end of study; **EOT**: end of treatment; **EU**: Europe;; **HPV**: human papillomavirus; **HRQL**: health-related quality of life (evaluated with EORTC QLQ-C30, QLQ-HN35 C questionnaires); C **IHC**, immunohistochemistry; **IMRT**: intensity-modulated radiotherapy; **LA-SCCHN**: locally advanced squamous cell carcinoma of the head and neck; **OPC**: oropharyngeal cancer; **OS**: overall survival; **Q3W**: every 3 weeks.

1.3. Schedule of Assessments

The schedule of the normal completion of the study visits/procedures is presented in Table 1-1. The description of each assessment is detailed in Section 8. It may be necessary to perform these assessments at unscheduled timepoints if deemed clinically necessary by the Investigator.

Screening procedures will start once the participant has signed the informed consent form (ICF). The screening period will start at the ICF signature and can last up to 28 days.

^{18}F-FDG-PET, intravenous (i.v.) contrast-enhanced CT-scan or MRI of head and neck, and CT-scan of chest are only accepted if they are performed within 4 weeks before randomization. Dental examination, audiometry, HBV/HCV/HIV tests, and fiberoptic endoscopy performed within 2 weeks before ICF signature do not have to be repeated during screening. If several i.v. contrast-enhanced CT scans/MRI of the head and neck and CT scans of the chest are available before treatment start, the closest imaging prior to randomization will be used as baseline (for each participant, the same radiological method must be used throughout the study). Further details on imaging are provided in Table 1-1, Section 8.2.1.

During screening and after randomization, laboratory assessments and pregnancy tests should be performed either by a local laboratory or by a central laboratory designated by the Sponsor according to instructions provided in Table 8-2 in Section 8.3.7.

Results from central laboratory should be used for defining participant eligibility during screening, except for HBV/HCV/HIV tests that may be performed by a local laboratory within 2 weeks before ICF signature (see above and Table 8-2) and human papillomavirus (HPV) status by p16 IHC that may be obtained locally (see Section 8.1.2).

A participant will be considered eligible to receive the study treatments after he/she has signed the ICF, all eligibility criteria have been met and the IMRT plan has been sent to the Radiotherapy Quality Assurance (RT-QA) Review Center (see Section 11.2.2). Randomization can be performed once the participant is considered eligible. The IMRT plan must be approved by the RT-QA Review Center prior to the start of the IMRT.

Study treatment (on C1D1) should begin within 7 days after randomization.

The End of treatment (EOT) visit will be performed 15 days (± 7days) after last study treatment administration (i.e., xevinapant/placebo, chemotherapy or IMRT whichever is administered last), but prior to the start of any subsequent anticancer therapy (see also Section 7.1).

Study procedures must be performed according to the planned visit schedule within the permitted visit windows. During the treatment period, each study visit day and allowed time windows will be based on the C1D1 date. The treatment diagram and time windows for visits during the treatment period are presented in Table 1-2.

NOTE: Renal function monitoring must also take place 48 hours (± 12 hours) after cisplatin infusion (i.e. at C1D4, C2D4, C3D4) based on local laboratory assessments as shown below (see also Table 1-1):

Local Laboratory Sampling	Schedule for Renal Function Monitoring
Creatinine, eGFR Sodium, potassium, calcium, magnesium	C1D4 (within 48±12 hours from C1D2) C2D4 (within 48±12 hours from C2D2) C3D4 (within 48±12 hours from C3D2)

In case of abnormal renal function parameter(s) or electrolyte disbalance, additional hydration and electrolyte replacement should be considered, as well as cisplatin dose adaptation in the next cycle.

Adequate hydration must be maintained pre- and post-cisplatin infusion according to the following schedule (see Appendix 13.3 for detailed instructions):

Pre-infusion	Post-infusion
2 to 12 hours prior to administration of cisplatin	until minimum 6 hours after the administration of cisplatin

Every attempt should be made to have each participant attend each visit as scheduled. Study visits/procedures performed outside of the allowed visit window will be considered as protocol deviations, with the exception of premature discontinuation from study treatment or withdrawal from the study due to reasons described in Section 7.

The EFS follow-up period must be performed according to the planned visit schedule within the permitted visit windows. Participants without any progression, treatment failure, local or distant relapse, second cancers or death until Month 60 post-randomization, will enter the overall survival (OS) follow-up period after the Month 60 visit (FUP60). They will be followed for survival status only, at least every 3 months, until the End of Study (EOS) (see Section 7.2). Participants who progress according to RECIST v1.1, will enter the OS follow-up period at time of the event and will be followed up for survival status at least every 3 months, until the EOS (see Section 7.2).

In case of premature discontinuation of treatment in participants without disease progression (e.g., unacceptable toxicity), efficacy assessments will continue to be performed until an EFS event has been determined or Month 60 post-randomization, whichever occurs first.

During the EFS follow-up period and OS follow-up period, each study visit day and allowed time windows will be based on the randomization date.

After completion of the follow-up period, participants who have not discontinued the study prematurely will undergo the EOS assessments ([date of the 60 Month visit of the last on-study participant] ± 2 months) and will be considered as having completed the study (see Section 7.2 in case of premature withdrawal).

If the last on-study participant completes the OS follow-up (60 months after randomization), his/her EOS visit will be performed at the same time as his/her 60 Month visit. In case of premature discontinuation from the study, his/her EOS visit will be performed when he/she discontinues from the study.

The EOS visit can be performed by telephone call.

Table 1-1 Schedule of events / flow chart: screening & treatment period

Study Period	Section	Scr	Combination therapy (CRT and Xevinapant/matched placebo) period															Monotherapy (xevinapant or matched placebo) period			EOT visit[1]
Cycles		-	1					2					3					4	5	6	
Visit Label		Scr	C1D1	C1D2	C1D4	C1D8	C1D15	C2D1	C2D2	C2D4	C2D8	C2D15	C3D1	C3D2	C3D4	C3D8	C3D15	C4D1	C5D1	C6D1	EOT
Study Week		-4 to -1 (≤4 weeks)	1	1	1	2	3	4	4	4	5	6	7	7	7	8	9	10	13	16	20
Study Visit Day (from 1st dose administration)		-28 to -1 (≤28 days)	1	2	4	8	15	22	23	25	29	36	43	44	46	50	57	64	85	106	134
Cycle Visit Day		-	1	2	4	8	15	1	2	4	8	15	1	2	4	8	15	1	1	1	-
Visit Window (days)		-	see footnote [2]		±12h			±3d		±12h			±3d		±12h			±3d	±3d	±3d	±7d
Informed consent	8.1, 11.1.1	X																			
Tumor staging	8.1.1	X																			
Archived tumor biopsy[3]	8.5.2	X																			
Medical history	8.1.1	X																			
Demographics, height	8.1.1	X																			
HBV, HCV, HIV tests	8.3.7	X[4]																			
Eligibility	5.1, 5.2	X																			
Randomization[5]	6.3	X																			
Height	8.3.2	X																			
Physical examination, weight	8.3.1, 8.3.2	X	X					X					X					X	X	X	X
ECOG PS	8.3.2	X	X					X					X					X	X	X	X
Vital signs	8.3.2	X	X	X				X					X					X	X	X	X
ECG	8.3.6	X	X			X															
Nutritional status	8.3.3	X						X					X					X			X
Dental examination	8.3.4	X[4]																X			X
Audiometry	8.3.5	X[4]						(X)[10]					(X)[10]					(X)[10]			(X)[10]
Coagulogram	8.3.7	X						X					X					X			X
Blood hematology	8.3.7	X	X[6, 7]			X	X	X[7]			X	X	X[7]			X	X	X	X	X	X
Blood biochemistry – full panel	8.3.7	X	X[6, 7]					X[7]					X[7]					X	X	X	X
Blood biochemistry– minimum panel	8.3.7					X	X				X	X				X	X				
Renal function monitoring[14]					X					X					X						
Pregnancy test[8]	8.1.3, 8.3.7	X	X[6]					X					X					X	X	X	X
Urinalysis	8.3.7	X						X					X					X			X

Study Period		**Scr**	**Combination therapy (CRT and Xevinapant/matched placebo) period**															**Monotherapy (xevinapant or matched placebo) period**			**EOT visit[1]**
Cycles		-	**1**					**2**					**3**					**4**	**5**	**6**	
Visit Label		**Scr**	**C1D1**	**C1D2**	**C1D4**	**C1D8**	**C1D15**	**C2D1**	**C2D2**	**C2D4**	**C2D8**	**C2D15**	**C3D1**	**C3D2**	**C3D4**	**C3D8**	**C3D15**	**C4D1**	**C5D1**	**C6D1**	**EOT**
Study Week	**Section**	**-4 to -1 (≤4 weeks)**	**1**	**1**	**1**	**2**	**3**	**4**	**4**	**4**	**5**	**6**	**7**	**7**	**7**	**8**	**9**	**10**	**13**	**16**	**20**
Study Visit Day (from 1st dose administration)		-28 to -1 (≤28 days)	1	2	4	8	15	22	23	25	29	36	43	44	46	50	57	64	85	106	134
Cycle Visit Day		-	1	2	4	8	15	1	2	4	8	15	1	2	4	8	15	1	1	1	-
Visit Window (days)		-	see footnote [2]		±12h			±3d		±12h			±3d		±12h			±3d	±3d	±3d	±7d
EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires	8.6	X																X			X
[redacted]																					
^{18}F-FDG-PET	8.2.1	X[4]																			X
i.v contrast-enhanced CT-scan or MRI of head and neck AND CT-scan of chest	8.2.1	X[4]																			X[13]
Clinical tumor assessment of ear, nose and throat examination and fiberoptic endoscopy	8.1.1, CCI	X[4]																			X
[redacted]																					
Xevinapant / matched placebo administration	6.1.2.1, Table 1-2		From Day 1 to 14					From Day 1 to 14					From Day 1 to 14					From Day 1 to 14	From Day 1 to 14	From Day 1 to 14	
Participant diary dispensation	8.3.8		X																		
HD-CDDP or CBCDA	6.1.2.2, Table 1-2			X					X					X							
IMRT	6.1.2.3, Table 1-2		5 fractions/week for 7 weeks																		
EFS data collection[11]	8.2		←----------														----------→				
Concomitant medication	6.5		←----------														----------→				
Adverse events	8.3.10, 9		←----------														----------→				
SAEs and late onset AESIs	9.1.4		-																		X

Abbreviations: AESI: adverse event of special interest; **CBCDA**: carboplatin; **CRT**: chemoradiotherapy; **CT-scan**: computed tomography scan; **d**: days; **CxDx:** Cycle x Day x; **ECG**: electrocardiogram; **eCRF**: electronic case report form; **ECOG PS**: Eastern Cooperative Oncology Group Performance Status; **EFS**: event-free survival; **EORTC:** European Organisation for Research and Treatment of Cancer; **EOS**: end of study; **EOT**: end of treatment; C [redacted] C [redacted] **HBV:** hepatitis B virus; **HCV:** hepatitis C virus; **HD-CDDP:** high-dose cisplatin; **HIV:** human immunodeficiency virus; C [redacted] **HPV**: human papilloma virus; **IMRT**: intensity-modulated radiotherapy**; i.v.**: intravenous; **MRI**: magnetic resonance imaging; **OPC:** oropharyngeal cancer**; OS**: overall survival; C [redacted] **^{18}F-FDG-PET**: positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose; **Scr**: screening.

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1. The EOT visit will be performed 15 days (± 7days) after last study treatment administration (i.e., xevinapant/placebo, chemotherapy or IMRT whichever is administered last) but prior to the start of any subsequent anticancer therapy.
2. C1D1 and C1D2 are triggered by the 1st dose administration of xevinapant/matched placebo and HD-CDDP, respectively. These visits should be performed on consecutive days (see also Table 1-2).
3. Participant should be willing to provide an archival tumor sample for exploratory purposes (except for China), if available; it should also be used for HPV status definition by p16 IHC testing (in participants with OPC) if no local report is available. See Sections 8.4.2 and 8.5.2.
4. ^{18}F-FDG-PET, i.v. contrast-enhanced CT-scan or MRI of head and neck, and CT-scan of chest are only accepted if they are performed within 4 weeks before randomization. Dental examination, audiometry, HBV/HCV/HIV tests, and fiberoptic endoscopy performed within 2 weeks before ICF signature do not have to be repeated during screening.
5. Treatment on C1D1 should be initiated within 7 days after randomization.
6. On C1D1, hematologic, renal and hepatic laboratory assessments (as required in inclusion criteria 10, Section 5) and pregnancy status (assessed by urine or serum test) should not be repeated locally if latest results (assessed by central laboratory) are within 7 days prior to the 1st dose administration (see also Table 8-2).
7. On C1D1, C2D1 and C3D1, suitability for chemotherapy administration (see Section 6.1.2.2) should be checked by a local laboratory (see exception on C1D1 in Table 8-2). Suitability for CRT administration must be documented in the participant medical record.
8. Serum pregnancy test during screening will be performed by a central laboratory in women of childbearing potential. Negative pregnancy status should be rechecked locally (serum or urine test) on C1D1 before first dose administration if the assessment was performed more than 7 days before. After C1D1, a urine or serum pregnancy test should be performed by a local laboratory (see also Table 8-2).

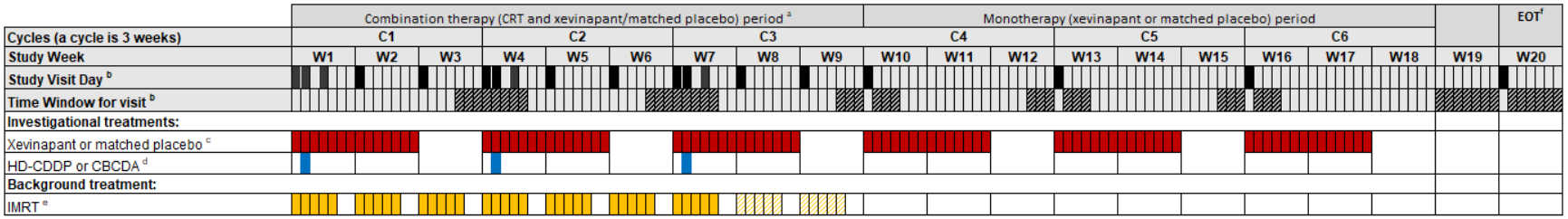
C [redacted]

10. An audiometry must be performed at screening. In addition, a hearing clinical evaluation and an audiometry should be performed at C2D1 and C3D1 if clinically indicated (except for France, see Appendix 13.6) and at any time if clinically indicated as per institutional or national guidelines.
11. After progression (according to RECIST v1.1), at any time during the study, participants will enter the OS follow-up period and will be followed up for survival at least every 3 months until EOS (see Table 1-2and Section 7.2). Survival follow-up can be performed by telephone calls.

C [redacted]

13. Response confirmation is not required. In case of doubt of a clinical locoregional recurrence or distant metastasis before the EOT, imaging by CT/MRI scan should be performed to confirm the disease progression.
14. Renal function monitoring 48 hours (±12 hours) after cisplatin infusion (i.e at C1D4, C2D4 and C3D4) based on local laboratory assessments (see Table 8-2) and hydration recommendation (see Appendix 13.3 for instructions).

Table 1-2 Treatment diagram and time window for visits



Abbreviations: C: cycle; **CBCDA:** carboplatin; **CRT**: chemoradiotherapy; **EOT**: end of treatment; **HD-CDDP:** high-dose cisplatin; **IMRT**: intensity-modulated radiotherapy; **W**: week.

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[a] On days when IMRT and chemotherapy are to be administered, C [redacted] On days when IMRT is to be administered without chemotherapy, xevinapant or matched placebo should be preferably administered before IMRT.

[b] During the treatment period, each study visit day and allowed time windows will be based on C1D1 date. C1D1 and C1D2 are triggered by the 1st dose administration of xevinapant/matched placebo and HD-CDDP, respectively. These visits should be performed on consecutive days.

Stripped gray boxes in the row "Time window for visit" represent days around a specific study visit (represented in gray in the row "Study visit day") where the visit can be rescheduled (see also time windows planned in the schedule of assessments - Table 1-1).

[c] Xevinapant oral solution or placebo: once daily from D1 to D14 of each cycle. Xevinapant/matched placebo should be administered orally, early in the morning, on an empty stomach (no food intake within 2 hours before xevinapant/matched placebo administration). Participants should fast for at least 1 hour after dosing. See also Section 6.1.2.1.

[d] Platinum-based chemotherapy in C1, C2 and C3 (see also Section 6.1.2.2):

HD-CDDP (100 mg/m^2) as an i.v. infusion over at least 90 minutes, on the day after the 1st administration of xevinapant/matched placebo at C1.

For participants not eligible to continue with HD-CDDP at C2 or C3: switch to CBCDA at the next scheduled chemotherapy administration.

[e] IMRT should be delivered in 35 fractions over 7 weeks, 5 planned fractions weekly (solid color). If IMRT is put on hold due to safety or administrative reason, the 7 weeks of IMRT can be administered until Study Week 9 (striped color). See also Section also 6.1.2.3.

[f] The EOT visit will be performed 15 days (± 7days) after last study treatment administration (i.e., xevinapant/matched placebo, chemotherapy or IMRT whichever is administered last), but prior to the start of any subsequent anticancer therapy.

Table 1-3 Schedule of events / flow chart: follow-up visits

Study Period	Protocol Section	EFS FOLLOW-UP															OS FOLLOW-UP	
Study Timing		Year 1			Year 2				Year 3				Year 4		Year 5		FUPx[1] (where x is the number of months post-randomization): At least every 3 months	EOS (date of Month 60 visit of last on-study participant) ±2 months or premature study discontinuation
Visit Label		FUP7	FUP9	FUP12	FUP15	FUP18	FUP21	FUP24	FUP27	FUP30	FUP33	FUP36	FUP42	FUP48	FUP54	FUP60		
Study Month (post-randomization)		7	9	12	15	18	21	24	27	30	33	36	42	48	54	60		
Study Visit Day		D1 of M7 ±2wk	D1 of M9 ±2wk	D1 of M12 ±2wk	D1 of M15 ±2wk	D1 of M18 ±2wk	D1 of M21 ±2wk	D1 of M24 ±2wk	D1 of M27 ±2wk	D1 of M30 ±2wk	D1 of M33 ±2wk	D1 of M36 ±2wk	D1 of M42 ±2wk	D1 of M48 ±2wk	D1 of M54 ±2wk	D1 of M60 ±2wk		
Physical examination, weight	8.3.1, 8.3.2	X																
ECOG PS	8.3.2	X		X		X		X				X		X		X		
Vital signs	8.3.2	X		X		X												
Nutritional status	8.3.3	X		X		X												
Audiometry[2]	8.3.5	(X)																
Coagulogram	8.3.7	X		X		X												
Blood hematology	8.3.7	X		X		X												
Blood biochemistry – full panel	8.3.7	X		X		X												
Pregnancy test	8.3.7	X	X															
EORTC QLQ-C30, EORTC QLQ-HN35 [C] questionnaires	8.6	X		X				X				X		X		X		
[C]																		
^{18}F-FDG-PET[3]	8.2.1	(X on Week 31 ± 2 weeks after 1st dose)																
i.v contrast-enhanced CT-scan or MRI of head and neck AND CT-scan of chest[4]	8.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical tumor assessment of ear, nose and throat examination and fiberoptic endoscopy	8.3.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EFS data collection[1]	8.2	<----------														---------->		
Survival status[1]	8.2	<---------- At least every 3 months ---------->																
Subsequent antineoplastic therapies	6.5	<----------														---------->		
SAEs and late onset AESIs	8.3.10, 9	<----------														---------->		

Abbreviations: AESI: adverse event of special interest; **CT-scan**: computed tomography scan; **D**: day; **ECG**: electrocardiogram; **ECOG PS**: Eastern Cooperative Oncology Group Performance Status; **EFS**: event-free survival; **END:** elective neck dissection; **EORTC:** European Organisation for Research and Treatment of Cancer; **EOS**: end of study; **EOT:** end of treatment; [C] **FUP:** follow-up; [C] **i.v.**: intravenous; **M**: month; **MRI**: magnetic resonance imaging; **OS:** overall survival; **SAE:** serious adverse event; **^{18}F-FDG-PET**: positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose; **wk**: week.

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1. After progression (according to RECIST v1.1) at any time during the study, participants will enter the OS follow-up period and will be followed up for survival at least every 3 months until EOS (see also Section 7.2). Survival follow-up can be performed by telephone calls.

   Participants without any progression, treatment failure, local or distant relapse, second cancers or death until Month 60 post-randomization, will enter the OS follow-up period after the visit of Month 60 (FUP60). They will be followed only for survival status, at least every 3 months until EOS (see also Section 7.2). Survival follow-up can be performed by telephone calls.

   Note: At progression, the participant should complete EORTC QLQ-C30, EORTC QLQ-HN35 [redacted] questionnaires.
2. An audiometry is to be performed only if clinically indicated, as per institutional or national guidelines.
3. If the scan at EOT was negative (see Table 1-1 for schedule) no further ^{18}F-FDG-PET scans should be performed. If the EOT scan was positive AND the participant underwent salvage surgery and END, no further ^{18}F-FDG-PET scans should be performed. If EOT results were inconclusive AND the participant did not undergo salvage surgery and END, the ^{18}F-FDG-PET scan should be repeated 12 weeks after EOT (Week 31±2weeks).
4. Response confirmation is not required.

2. INTRODUCTION

2.1. Study Rationale

Squamous cell carcinoma of the head and neck (SCCHN) is the 6th most common cancer worldwide and more than half of the locally advanced SCCHN (LA-SCCHN) patients will have a tumor relapse or treatment failure within 5 years of treatment (Magnes et al. 2017).

Definitive treatment options for locally advanced (LA)-SCCHN such as surgery can cure some patients, but can also lead to severe limitations in feeding (chewing and swallowing), speaking, and physical appearance that can impair social functioning and cause severe psychological stress (Hernández-Vila 2016; NCCN 2019). Aside from technological improvements in surgical technique and radiation delivery, no major innovations have improved care for patients with LA-SCCHN for years. Despite this, many patients with LA-SCCHN remain ineligible/unsuitable for tumor resection (NCCN 2019; Hernández-Vila 2016).

Among conservative (non-surgical) treatments, the most widely used standard regimen in this setting consists of 100 mg/m^2 cisplatin administered every 3 weeks (Q3W), combined with ~70 Gy radiation delivered in 1.8-2.0 Gy daily fractions. Although associated with increased toxicity compared to radiotherapy (RT) alone, this combination is also associated with increased local control rates and OS (Oun et al. 2018).

Functional impairments particularly affect oropharyngeal cancer (OPC) negative for human papillomavirus (HPV), and non-OPC patients (Ringash et al. 2017). HPV status is considered to be a strong and independent prognostic factor for survival (Ang et al. 2010) and HPV-negative OPC patients are considered to have a worse prognosis. Those patients require more and better tailored options, to improve overall treatment outcomes (Marur et al. 2014; Du et al. 2019).

Therefore, improving SCCHN therapy to enhance treatment outcomes in patients with locally advanced SCCHN, who are suitable for definitive chemoradiotherapy (CRT), without generating increased detriment to patients' quality of life (QoL), is a priority.

Xevinapant is an antagonist of inhibitors of apoptosis proteins (IAPs) that has been shown to have both chemo-radio-sensitizing and immunomodulatory potential. The current Phase 3 study aims to support the approval of xevinapant in untreated LA-SCCHN patients receiving standard of care platinum-based chemoradiation concurrently. Xevinapant may provide an improved therapeutic option for LA-SCCHN patients suitable for definitive CRT who are more likely to experience locoregional failures.

2.2. Background

Epidemiology and clinical presentation

Head and neck cancer include a variety of epithelial tumors originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx, or larynx. Worldwide, head and neck cancer accounts for more than 650,000 cases and 330,000 deaths annually (Bray et al. 2018). In the United States, head and neck cancer accounts for 3% of malignancies, with approximately 53,000 Americans developing head and neck cancer annually and 10,800 dying from the disease (Siegel et al. 2020). In Europe, there were approximately 250,000 cases (an estimated 4% of the cancer incidence) and 63,500 deaths in 2012 (Gatta et al. 2015).

Most head and neck cancers (90% to 95%) are SCCHN. Approximately two-thirds of those patients are diagnosed with LA-SCCHN (Denaro et al. 2016). Clinical symptoms are varied and include gradually progressing impairment in respiration, swallowing, and speech (Marur et al. 2008). LA-SCCHN is a highly destructive disease, with patients tending to develop local lymph node metastases early, and may develop distant metastases at relatively late stages, even after effective local therapy (Gupta et al. 2016). The most frequent primary tumor sites eligible for definitive non-surgical treatment include the oropharynx, hypopharynx, or larynx.

Risk factors

Alcohol and tobacco abuse are linked to an increased risk for SCCHN cancers, largely due to exposure of the upper aero-digestive tract to carcinogens found in these substances. HPV-negative alcohol and/or tobacco-related SCCHN frequently harbors mutations of the p53 gene and downregulation of the p16 protein. These mutations are linked to poor prognosis and poor survival associated with CRT resistance and treatment failures (Ang et al. 2010). Patients with a smoking history of more than 10 pack-years and HPV-negative OPC have a median OS slightly over 24 months, and the risk of death and cancer relapse increased by 1% for each additional pack-year of tobacco smoking (Pignon et al. 2009; Ang et al. 2010).

OPC patients can be classified as low, intermediate, and high-risk patients, according to the presence of prognostic factors such as HPV status and alcohol or tobacco abuse.

HPV infection, in particular HPV type 16 (p16), is a known risk factor for the development of oropharynx SCCHN, particularly in endemic regions. However, patients with HPV-negative OPC have a worse prognosis compared to HPV-positive patients. HPV-negative tumors in patients with stage III or IV oropharyngeal SCCHN were shown to be associated with a worse OS rate and progression-free survival (PFS) at 3 years. The 3-year rates of OS were 82.4% (95% confidence interval [CI], 77.2 to 87.6) in the OPC HPV-positive subgroup and 57.1% (95% CI, 48.1 to 66.1) in the HPV-negative subgroup while the 3-year rates of PFS were 73.7% (95% CI, 67.7 to 79.8) and 43.4% (95% CI, 34.4 to 52.4), respectively (Ang et al. 2010).

Treatments

Multidisciplinary treatments, including surgery, RT, and chemotherapy alone or in combination represent the treatment options for SCCHN patients depending on the disease stage. LA-SCCHN disease is treated with curative intent and requires multimodality approaches including surgery followed by RT with or without chemotherapy. Organ-preservation approaches combining chemo- and RT are generally favored, with similar results compared to surgery (Wolf 1991). European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines on treatment of SCCHN recommend the use of CRT when the tumor is unresectable or when surgery is not indicated (Grégoire et al. 2010; NCCN 2019).

High-dose cisplatin (100 mg/m^2) administered Q3W with concomitant RT is considered the standard systemic regimen in LA-SCCHN across countries, irrespective of tumor location (Adelstein et al. 2003; Grégoire et al. 2010).

Despite these treatments, at least 50% of patients with LA-SCCHN develop locoregional or distant relapses, which are usually detected within the first 2 years of treatment (Adelstein et al. 2003;

NICE 2004; HAS 2009; Grégoire et al. 2010; AWMF 2012; NICE 2016; AIOM 2018; AWMF 2019). Around 76% of relapses at 5 years are locoregional (Pignon et al. 2009).

The anti-PD-1 agents pembrolizumab and nivolumab have recently been approved in patients with recurrent/metastatic disease (Cohen et al. 2019) and are currently in development in combination with CRT as first-line treatment for LA-SCCHN.

Health-related quality of life

Given the potential serious physical limitations (e.g., difficulties in chewing, swallowing, speaking, tasting, smelling, hearing) and associated psychological distress resulting from LA-SCCHN treatments, improvements in therapy to enhance treatment outcomes without generating incremental detriment to patients' QoL must be priorities in advancing LA-SCCHN therapy. Despite this significant unmet need, prospective assessments of health-related quality of life (HRQL) in SCCHN are scarce and cross-study comparability to inform treatment decisions is limited by heterogeneity in QoL research methods (Ojo et al. 2012).

Clinical development of Xevinapant, an antagonist of IAPs in combination with high-dose cisplatin-based concomitant CRT in LA-SCCHN cancer

Xevinapant is an orally available antagonist of IAPs that has been shown to have chemo-radio-sensitizing, and immunomodulatory potential.

Based on current understanding of the mechanism of action, the value of adding xevinapant to platinum-based conventional CRT in the treatment of previously untreated patients with non-resected LA-SCCHN has been investigated in a Phase 1-2 study (Debio 1143-201).

The Phase 1 part of Debio 1143-201 study (Part A or Debio 1143-201A) determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) to be 200 mg/day xevinapant once daily on Days 1 to 14 of a 3-week cycle, when used concomitantly with high-dose cisplatin-based CRT.

The Phase 2 part of Debio 1143-201 study (Part B or Debio 1143-201B) was a randomized, placebo-controlled, double-blind study. Efficacy results from the 24-month primary analysis have shown antitumor activity of xevinapant: patients treated with xevinapant were around 2.5 times more likely to have locoregional control (LRC) 18 months after completing treatment, compared with patients having received a placebo (see Section 2.3.2 for further details).

Based on the preclinical evidence of xevinapant activity in SCCHN models and the primary analysis results of the Debio 1143-201 study, the current Phase 3 study aims to confirm the value of xevinapant in the treatment of previously untreated LA-SCCHN patients with hypopharynx, larynx and/or HPV-16 negative OPC, who are suitable for definitive CRT and are more likely to relapse locally.

Please refer to the Investigator's Brochure for further details on other non-LA-SCCHN Phase 1 studies and on the Debio 1143-201 study.

2.3. Risk/Benefit Assessment

2.3.1. Known Potential Risks

In line with the postulated radio- and chemo-sensitizing effect of xevinapant, participants receiving xevinapant + CRT combination therapy may experience more frequent and more severe adverse events (AEs) related to CRT. Considering the data from the placebo-controlled study Debio 1143-201, where xevinapant or placebo was administered in association with cisplatin and RT, an increased risk of nausea, mucosal inflammation, dysphagia, weight decrease, radiation skin injury, tinnitus, and grade 3 anemia were observed in both arms with only a slight increase of dysphagia, mucositis, and anemia in the xevinapant arm. Nevertheless, the predominant toxicities were generally mild and/or largely reversible, could be monitored by routine clinical examinations and were manageable by dose delay, dose reduction and/or supportive care.

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Regarding the risk of drug-drug interactions (DDIs), xevinapant is transported by P-glycoprotein (P-gp). Accordingly, strong P-gp inhibitors and inducers are prohibited. In addition, in vitro xevinapant significantly inhibits CYP3A4/5 and P-gp and has the potential to induce and down-regulate CYP3A4/5, 2Cs, 2B6, and to down-regulate 1A2. The clinical relevance of these phenomena is unknown. Accordingly, narrow therapeutic range or sensitive CYP3A substrates are prohibited. Also, narrow therapeutic range or sensitive substrates of P-gp, CYP2Cs, 2B6 or 1A2 should be closely monitored.

CCI [redacted] Preclinical studies also suggest that hepatitis B virus (HBV) titers may be reduced after treatment with SMAC mimetics by promoting the elimination of hepatocytes containing HBV. Candidates for xevinapant studies are therefore tested for HIV, HBV and hepatitis C virus (HCV) serology prior to inclusion. Any patients found to be positive will not be included in xevinapant studies.

Please refer to the current version of the Investigator's Brochure for further details on identified and potential risks.

2.3.2. Known Potential Benefits

Based on the potential for xevinapant to act as a chemo-, immuno- and/or radiosensitizer, the current development strategy for xevinapant focuses only on combination strategies with RT, chemotherapy, CRT or checkpoint inhibitors as accepted standard of care options whenever applicable. Investigated indications include solid tumors such as SCCHN, ovarian/gynecological cancer, non-small cell lung cancer, small cell lung cancer, and/or gastrointestinal cancers as well as potentially other solid tumors.

When xevinapant was administered in combination with CRT in LA-SCCHN patients (study Debio 1143-201B), a statistically significant and clinically relevant improvement was observed in terms of LRC at 18 months and PFS, as well as a trend toward improved OS. The 24-month analysis of the Study 1143-201B demonstrated that the odds for LRC at 18 months after completing treatment is 2.5 times higher in patients (all heavy smokers, ~90% of OPC patients HPV-negative, 85% stage IVa or IVb) treated with xevinapant compared with patients having received a placebo (odds ratio [95%CI]: 2.69[1.13; 6.42]). In addition, a risk reduction of 63% for progression or death was observed in patients having been treated with xevinapant compared with patients having received a placebo, suggesting a highly statistically and clinically significant improvement in PFS (hazard ratio [95%CI]: 0.37[0.18; 0.76]), p=0.007. The PFS rate at 24 months after treatment start was 72% in the xevinapant arm and 41% in placebo arm. Median PFS was not reached in the xevinapant arm at the 24-month analysis cut-off. Results for OS showed a consistent trend (hazard ratio [95%CI]: 0.65[0.32; 1.33]) although they did not reach statistical significance (p=0.243) at the cut-off date. Additional follow-up is ongoing and will provide more mature data (refer to the current version of the Investigator's Brochure for further details).

2.3.3. Risk-Benefit Assessment

To date, safety results on xevinapant given in combination with CRT suggest an acceptable and predictable overall safety profile of the compound. Observed toxicities are mostly low grade, manageable and reversible, and were consistent with those expected in the target population receiving only CRT (with placebo).

To mitigate identified and potential risks related to xevinapant treatment (see Section 2.3.1), the protocol includes close monitoring of participants for known or potential adverse reactions. Regular assessments include but are not limited to gastrointestinal signs and symptoms, renal function, and skin disorders. Laboratory values will be monitored to allow for early detection and treatment of any sign of hematologic toxicity as well as liver or pancreatic function abnormalities.

Electrocardiograms (ECGs) are included in the protocol to allow QTc monitoring, as part of the clinical pharmacovigilance program.

To mitigate the risk of DDIs, a list of prohibited concomitant medications as well as medications that should be used with caution is provided (see Section 6.5).

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Given the current safety and efficacy profile observed in clinical studies, suggesting a positive risk-benefit ratio of xevinapant, further clinical research is warranted.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are presented in Table 3-1.

Table 3-1 Objectives, endpoints and statistical considerations

Objectives	Endpoints	Hypothesis	Primary Analysis Population	Timeframe/Time Point
Primary				

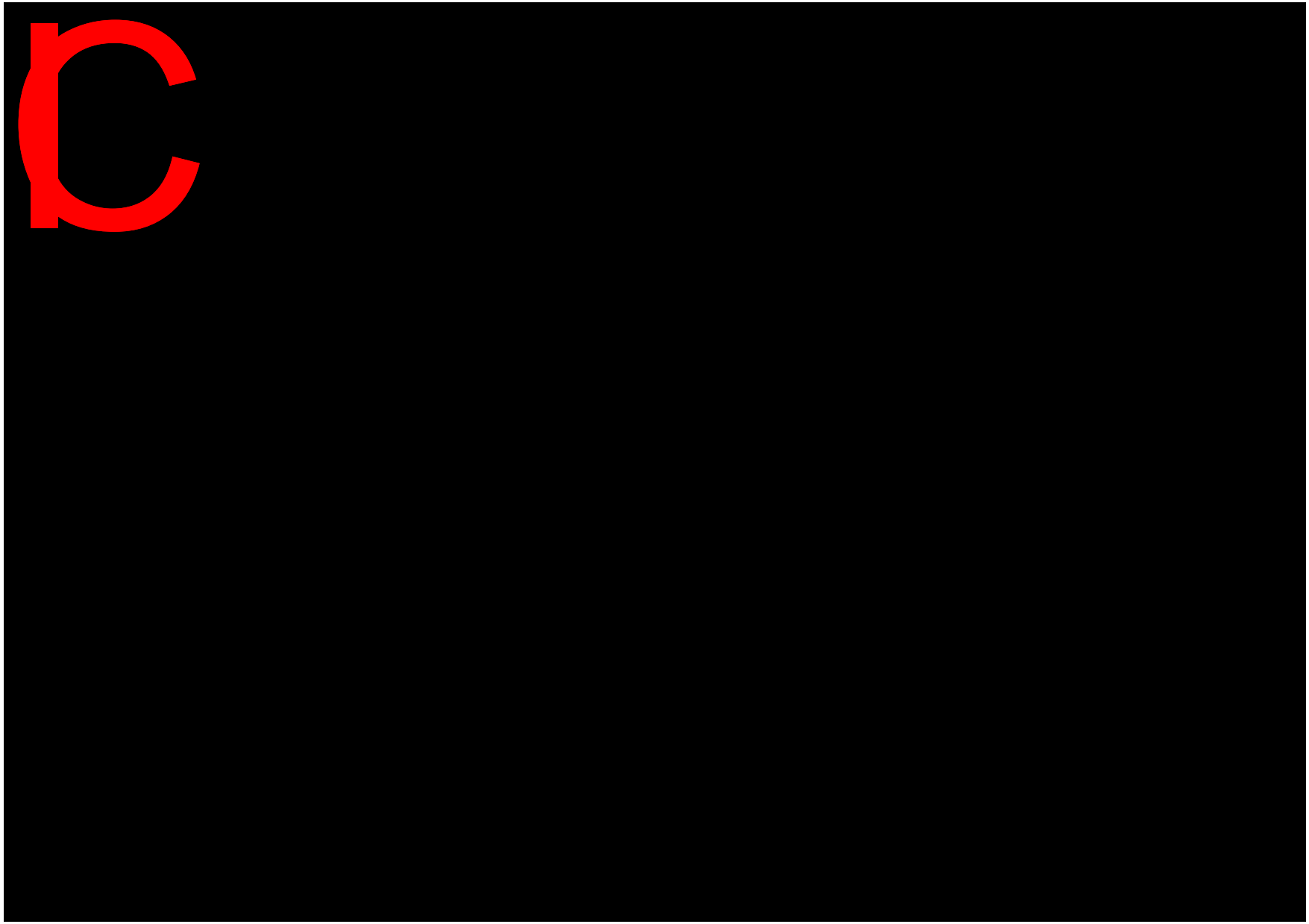
To demonstrate superior efficacy of xevinapant vs placebo when added to chemoradiotherapy (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN)	EFS as assessed by the BIRC defined as the time from randomization to the first occurrence of any of the following events:
	• Death from any cause.
	• Progression:
	  ○ Radiological, assessed per RECIST v1.1
	  or
	  ○ Clinical, with or without RECIST v1.1-radiologically documented progression, assessed endoscopically.
	• Primary treatment failure before achieving a CR: requirement for radical salvage surgery that includes the primary tumor site, with documented viable tumor presenting anatomopathological findings even in the absence of formal RECIST v1.1 radiological progression.
	• Any radiological or clinical relapse after achieving a CR (locoregionally), including any event defined as locoregional treatment failure, even in the absence of formal radiological progressive disease confirmation:
	  ○ Requirement for radical salvage surgery that includes the primary tumor site, regardless of anatomopathological findings
	  or
	  ○ Elective neck dissection or biopsy, with positive viable tumor cells on anatomopathological findings at 22 weeks or later after randomization.
	• Second cancers unless anatomopathological findings exclude squamous histology.
	
	Note: Investigator-assessed EFS will be used for supportive analysis.
		Xevinapant prolongs EFS in previously untreated patients with LA-SCCHN, compared to matched placebo when administered in combination with platinum-based chemotherapy and intensity-modulated radiotherapy (IMRT).	Intent-to-treat	- From randomization to the earliest between any EFS event or EOS.
				- Rate at 9, 12, 18, 24, 30 and 36-months post-randomization.

Objectives	Endpoints	Hypothesis	Primary Analysis Population	Timeframe/Time Point
Secondary				
To assess the efficacy of xevinapant compared to placebo when added to CRT according to additional efficacy endpoints	Overall survival (OS) defined as the time from randomization to death due to any cause.	Xevinapant prolongs OS in previously untreated patients with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to the earliest between death or EOS - Rate at 12, 24, 36, 48 and 60 months post-randomization.
	Progression-free survival (PFS) according to RECIST v1.1 defined as the time from randomization to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed PFS will be used for supportive analysis.	Xevinapant prolongs PFS in previously untreated patients with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to the earliest between PFS event or EOS. - Rate at 9, 12,18, 24, 36, 48 and 60 months post-randomization.
	Locoregional control (LRC) defined as the time from randomization to the first occurrence of progression at the site of the primary tumor or the locoregional lymph nodes, either according to RECIST v1.1 or based on clinical assessment (radiological or clinical, as assessed by the Investigator). Note: Will be investigated by BIRC as supportive analysis.	Xevinapant prolongs LRC in previously untreated patients with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to the earliest between PFS event or EOS. - Rate at 9, 12, 18, 24, 36, 48 and 60 months post-randomization.
	ORR, defined as the proportion of subjects with CR or partial response by RECIST v1.1, as assessed by the BIRC. Note: Investigator-assessed response will be used for supportive analysis.	Xevinapant increases the ORR in previously untreated patients with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to the earliest between progression, start of a new anticancer therapy for this disease or participant EOS. - Rate at 9 and 12 months post-randomization.

Objectives	Endpoints	Hypothesis	Primary Analysis Population	Timeframe/Time Point
	CR rate (CRR) defined as the proportion of participants with CR by RECIST v1.1, as assessed by the BIRC. Note: Investigator-assessed response will be used for supportive analysis.	Xevinapant increases the CRR in previously untreated patietns with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to the earliest between progression, start of a new anticancer therapy for this disease or subject EOS. - Rate at 9 and 12 months post-randomization.
	Duration of response (DoR) defined as the time from the first evidence of response (partial or complete, as assessed by the BIRC according to RECIST v1.1) to the first occurrence of progression (radiological or clinical, as assessed by the BIRC) or death from any cause. Note: Investigator-assessed DoR will be used for supportive analysis.	Xevinapant prolongs DoR in previously untreated participants with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From first evidence of response (partial or complete) to the earliest between DoR event or EOS. - Rate at 6, 12 and 24 months post first evidence of response.
	Proportion of participants with radical salvage surgery (excluding elective neck dissection without anatomopathological evidence of residual malignant cells).		Intent-to-treat	- From randomization to the earliest between radical salvage surgery or EOS. - Rate at 9, 12, 18, 24, 36, 48 and 60 months post-randomization.
	Time to subsequent systemic cancer treatments.		Intent-to-treat	- From randomization to EOS - Rate at 12, 18, 24, 36, 48 and 60 months post-randomization.
To compare safety, tolerability and treatment compliance of	Incidence and severity of adverse events (AE), serious adverse events and adverse events of special interest, changes in laboratory values, vital signs, and electrocardiograms according to NCI-CTCAE v 5.0.		Safety	- From signed informed consent to EOS.

Objectives	Endpoints	Hypothesis	Primary Analysis Population	Timeframe/Time Point
xevinapant vs placebo, when added to CRT	Extent of exposure of the different treatment agents (i.e., xevinapant or matched placebo, radiotherapy, chemotherapy) including: • Treatment duration. • Number of cycles. • Actual dose. • Dose intensity. • Relative dose intensity. • Incidence of treatment interruption. • Incidence of treatment reduction. • Incidence of treatment discontinuation.		Safety	- From first study treatment dose to EOT.
To compare the health-related quality of life of xevinapant vs placebo when added to CRT using patient-reported outcome questionnaires	Changes from baseline in: • CCI [redacted]	Xevinapant is non-inferior for CCI [redacted] at Month 12 post-randomization in previously untreated patients with LA-SCCHN compared to matched placebo when administered in combination with platinum-based chemotherapy and IMRT.	Intent-to-treat	- From randomization to EOS. - At baseline, Study Week 10, 20 and months 7, 12, 24, 36, 48 and 60 post-randomization.

Objectives	Endpoints	Hypothesis	Primary Analysis Population	Timeframe/Time Point
[redacted]				



4. Study Design

4.1. Study Design and Overview

This is a prospective, randomized, double-blind, placebo-controlled, multicenter, two-arm, parallel-group Phase 3 study comparing the efficacy and safety of xevinapant versus matched placebo, when administered in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy (IMRT) in previously untreated patients with LA-SCCHN, suitable for definitive CRT (stage III, IVA, IVB; hypopharynx, larynx and/or HPV-negative OPC).

Once a participant has signed the ICF, an identification number will be assigned to him/her and the study related screening procedures will start. Upon confirmation of eligibility, participants will be enrolled and randomized in a 1:1 ratio, using dynamic allocation to:

- **Arm A:** 3 cycles of xevinapant (200 mg/day from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of xevinapant (200 mg/day from Day 1 to 14, per cycle).

or

- **Arm B:** 3 cycles of placebo (from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100 mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle).

In case of toxicity after the first cisplatin dosing, participants can be switched to carboplatin (AUC=5 or 4 on Day 2 of each subsequent cycle) depending on the toxicity observed, as per Table 6-1.

The schedule of concurrent administration of xevinapant, chemotherapy and IMRT is presented in Table 1-1 and Table 1-2.

Approximately 1000 participants will be screened in order to randomize approximately 700 adult male and female participants.

Note: Additional Chinese participants from China Mainland will be randomized in a China-specific extension cohort (see Section 13.9 for further details).

The following stratification factors will be considered for the randomization:

- Region: North America vs Western Europe vs Rest of the World.
- Primary tumor site: larynx vs other.
- Lymph node involvement: N0-1 vs N2 vs N3.
- T size: T4 vs other.

The study includes the screening period, the treatment period (combination therapy period followed by the monotherapy period, each consisting of 3 cycles), the progression follow-up period (event-free survival [EFS] follow-up) and the OS follow-up period (see Figure 1-1 and Section 1.3 for study schedules of assessments). Each cycle consists of 3 weeks. Participants will be followed up until 386 OS events are observed for the final analysis or the last on-study participant reaches his/her 60-months post-randomization visit or until premature discontinuation from study (see Section 7.2), whichever occurs first.

It is expected that the total duration of the study will be approximately 82 months (6.8 years), (Figure 4-1).

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Special oversight committees will include external Independent Data Monitoring Committee (IDMC), Trial Steering Committee, and Firewall Team. The Firewall Team will be composed of a restricted group of individuals within the Sponsor team who are not directly involved in the study conduct activities.

4.2. Scientific Rationale for Study Design

The target population chosen for the study is of patients for whom a significant benefit from treatment with xevinapant combined with the current standard of care (i.e., cisplatin-based standard CRT) is expected. Patients with unresectable or non-resected LA-SCCHN have the poorest prognosis and predominantly experience locoregional failures.

The primary endpoint of the study is EFS, a widely accepted endpoint in LA-SCCHN studies that was shown to be a surrogate endpoint for OS in studies using CRT, both at the individual and study levels (Michiels et al. 2009; Le Tourneau et al. 2009). OS, a standard assessment of clinical benefit in head and neck patients with cancer, will be followed up for at least 5 years.

In line with the radiosensitizing effect of xevinapant, both the efficacy and safety results of the Phase 2 study (Debio 1143-201B) suggest that xevinapant in combination with CRT result in a LRC and PFS benefit associated with an acceptable safety profile (see Clinical development of xevinapant, an antagonist of IAPs in Section 2.2).

EFS as assessed by Investigators will be used for supportive analysis of the primary endpoint. Randomization is expected to compensate for possible inconsistencies in local assessments, hence minimizing any associated bias.

4.3. Justification for Study Treatment Dose and Regimen

Xevinapant

In Phase 1 studies with xevinapant (Debio 1143-101 to Debio 1143-106), different dose levels (from 5 to 900 mg/day) and schedules (D1-5 every 2 weeks, D1-5 Q3W or D1-14 Q3W) of xevinapant were administered, as monotherapy or in combination with chemotherapy only, with CRT or with immunotherapy (please refer to the current version of the Investigator's Brochure for further details on the Phase 1 and 2 studies). Doses up to 900 mg/day of xevinapant administered as monotherapy were tolerated and no MTD has been reached.

Tumor penetration and target engagement (IAP1 degradation) in the tumor was shown in Phase 2 studies Debio 1143-201 and Debio 1143-SCCHN-202. In the blood, target engagement and potential signs of downstream effects have been observed at all tested dose levels (100, 200 and 300 mg/day [Days 1-14 Q3W]). Xevinapant exposures at RP2D of 200 mg/day were not associated with unacceptable toxicities and enabled near-maximal clinical effect in terms of tumor metrics.

Based on the results of these studies, 200 mg was determined to be the MTD and was defined as the RP2D, administered on D1-14 of each 3-week cycle with concomitant CRT.

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The safety profile observed in combination with CRT in the Phase 2 study indicates that even though some toxicities occurred more often in the xevinapant arm (anemia, mucositis, and dysphagia of grade 3 according to National Cancer Institute -Common Terminology Criteria for Adverse Events [NCI-CTCAE], which were manageable and reversible) compared to the placebo arm, the number of grade 4 events reported was similar in both arms. All events resolved to at least grade 1 soon after CRT completion with identical median times to resolution between arms. One grade 5 treatment-emergent adverse event (TEAE) was reported and occurred in the placebo arm.

Platinum-based chemotherapy

While there is currently no unanimous consensus on the optimal cisplatin regimen, the high-dose regimen of 100 mg/m² Q3W for up to 3 cycles delivered concomitantly with IMRT is generally considered the standard (Szturz et al. 2017), and has been widely adopted whenever patients are eligible for it. Hence, this regimen will be used in this study.

In the Debio 1143-201B Phase 2 study, up to 3 cycles of high-dose cisplatin were safely administered concomitantly with standard fractionated IMRT and xevinapant. The median cisplatin dose delivered was equivalent and high in both arms (288 mg/m^2). Significantly improved anti-tumoral activity was observed in the xevinapant + CRT arm over the placebo + CRT arm (Section 2.3.2). Therefore, the same high-dose cisplatin regimen will be used in the present study in combination with xevinapant and as the comparator arm.

Nevertheless, in the current study, participants who will experience decreased estimated glomerular filtration rate (eGFR) (< 60 mL/min/1.73m² using the Chronic Kidney Disease - Epidemiology Collaboration [CKD -EPI] creatinine formula) after the first cisplatin dosing, can be switched to an equivalent carboplatin doses (area under the concentration vs time curve [AUC] 5.0 Q3W). This regimen is widely accepted and was reported to have similar efficacy in a recent study (Wilkins et al. 2013).

IMRT

The anatomy of the head and neck is complex due to multiple elements of the digestive, respiratory, nervous and endocrine systems located sometimes within millimeters of each other. Due to the complexity of this anatomical region, large and multiple target volumes, and proximity to organs at risk, RT in this region is also complex.

In addition, high-dose fractionated RT (60-72 Gy) is necessary to cure patients. Irradiation of critical normal tissue can cause severe discomfort with increased acute and late morbidity (Marta et al. 2014). Newer techniques have been developed over the past 2 decades to improve delivery of RT with 2 aims. Firstly, to avoid critical normal tissue to decrease toxicity (Jellema et al. 2007). Secondly, to administer a dose to the tumor volume high enough in order not to compromise control rates (Ghosh-Laskar et al. 2016). Techniques were therefore developed to shape the radiation beams more closely to the target volumes to spare critical tissues, hence reducing toxicity.

IMRT was implemented in the mid-1990s but only became widespread in the last decade. Closer shaping to the tumor contour is made possible by aiming multiple photon beams from different directions and with adjusted intensities. This allows better sparing of the organs at risk resulting in less acute and late toxicity, especially xerostomia (Ghosh-Laskar et al. 2016). Nutting et al. published the results of the PARSPORT study (a Phase 3 multicenter randomized controlled study) in 2011. They concluded that sparing the parotid glands with IMRT significantly reduced the incidence of xerostomia and led to recovery of saliva secretion, hence improving QoL (Nutting et al. 2011). According to the NCCN/ESMO guidelines, IMRT is now considered the standard of care for treating SCCHN.

5. STUDY POPULATION

Assuming a 30% screening failure rate, approximately 1000 participants will be screened worldwide at approximately 280 sites and will undergo study related screening assessments to randomize approximately 700 participants.

Note: Additional Chinese participants from China Mainland will be randomized in a China-specific extension cohort (see Section 13.9 for further details).

The study population include adult patients with LA-SCCHN (stage III, IVA or IVB) with histologically confirmed diagnosis in at least one of the following sites: oropharynx (HPV-negative), hypopharynx and larynx. Participants should be previously untreated and suitable for definitive CRT as determined by a multidisciplinary oncology team, as is currently standard clinical practice.

This study population will be defined by the inclusion and exclusion criteria below. No protocol waivers will be granted.

Upon confirmation of eligibility, participants will be enrolled and randomized.

5.1. Inclusion Criteria

The following inclusion criteria must be met during screening:

1. Willing and able to sign written informed consent prior to study screening.
2. Male or female ≥ 18 years of age (or based on the country legal age limit for adults) on day of signing the ICF.
3. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
4. Histologically confirmed diagnosis in previously untreated LA-SCCHN patient (stage III, IVA or IVB according to the American Joint Committee on Cancer [AJCC]/TNM Staging System, 8th Ed.) suitable for definitive CRT, of at least one of the following sites: oropharynx, hypopharynx, and larynx.

   Note: Archival tumor sample to be provided (except for China), if available.
5. Evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by computed tomography scan (CT-scan) or magnetic resonance imaging (MRI), based on RECIST v 1.1.

6. For OPC patients, primary tumors must be HPV-negative as determined by p16 expression using immunohistochemistry (IHC) (pathological report should be available). For OPC participants, p16 cutoff for determination of HPV status is defined in Section 8.1.2.

   Note: If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory.

6. Able to swallow liquids or has an adequately functioning feeding tube, gastrostomy or jejunostomy in place.
7. No hearing loss by clinical assessment or ≤ grade 2 hearing impairment (according to NCI-CTCAE v.5).
8. Peripheral neuropathy < grade 2.
9. Adequate hematologic, renal, and hepatic function as indicated by:
   - eGFR ≥ 60 mL/min/1.73m² (using the CKD-EPI creatinine formula).
   - Absolute neutrophil count (ANC) ≥ 1 500 cells/µL.
   - Platelets ≥ 100 000 cells/µL.
   - Hemoglobin ≥ 9.0 g/dL (blood transfusions during screening are permitted).
   - Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).
   - Total bilirubin ≤ 1.5 × ULN (up to 2.0 × ULN is allowed if the direct bilirubin level is normal and the elevation is limited to indirect bilirubin).
10. Women of childbearing potential (according to recommendations of the Clinical Trial Facilitation Group) must have a negative serum pregnancy test at screening and must not be breastfeeding.

    Women of childbearing potential must agree to use highly effective contraceptive method(s) (see Section 8.1.3) from ICF signature to 6 months after the last administration of chemotherapy or 3 months after last dose of xevinapant/matched placebo, whichever is the latest.

    Non-sterilized males who are sexually active with a female partner of childbearing potential must agree to use condom and spermicide from ICF signature to 6 months after the last administration of chemotherapy or 3 months after the last dose of xevinapant/matched placebo, whichever is the latest. Because male condom and spermicide is not a highly effective contraception method, it is strongly recommended that female partners of a male study participant use highly effective contraceptive method(s) (see Section 8.1.3) throughout this period.

    Male participants must refrain from donating sperm during the clinical study and for 6 months after the last administration of chemotherapy or 3 months after the last dose of xevinapant/matched placebo, whichever is the latest. If not done previously, cryopreservation of sperm prior to receiving chemotherapy or xevinapant/matched placebo is advised to male participants with a desire to have children.

5.2. Exclusion Criteria

Meeting any of the following criteria at screening will render a participant ineligible for participation in the study:

1. Primary tumor of nasopharyngeal, paranasal sinuses, nasal, or oral cavity, salivary, thyroid or parathyroid gland pathologies, skin or unknown primary site.
2. Metastatic disease (stage IVC as per AJCC/TNM, 8th Ed.).
3. Prior definitive or adjuvant RT and/or radical surgery to the head and neck region which may jeopardize the primary tumor irradiation plan, or any other prior SCCHN systemic treatment, including investigational agents (please refer to Section 6.1.1).
4. Use within 14 days prior to randomization or requirement for ongoing treatment with any drug(s) on the prohibited medication list (provided in Sections 6.5.3 and 6.5.4).
5. Treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of study treatment.
6. Known history of infection with HIV. If unknown history of HIV, an HIV screening test is to be performed and participants with positive serology for HIV-1/2 must be excluded.
7. Known chronically active HBV or HCV infection. If unknown status, the following tests are to be performed and participants with positive serology must be excluded:
   - HBV screening tests: both HBV sAg and Anti-HepB core IgG.
   - HCV screening tests: both HCV-antibody and positive viral load HCV-RNA by PCR.
8. Other infections (viral and/or bacterial and/or mycotic) requiring systemic treatment.
9. Live-attenuated vaccinations within 30 days prior to first investigational treatment administration.
10. Ongoing uncontrolled infection requiring intravenous antibiotic therapy within 1 week prior to randomization.
11. Known gastrointestinal disorder with clinically established malabsorption syndrome and major gastrointestinal surgery that may limit oral absorption.
12. Documented weight loss of >10% during the last 4 weeks prior to randomization (unless adequate measures are undertaken for nutritional support), OR plasmatic albumin < 3.0 g/dL. No albumin transfusions are allowed within 2 weeks before randomization.
13. Active gastrointestinal bleeding, or any other uncontrolled bleeding requiring more than 2 red blood cell transfusions or 4 units of packed red blood cells within 4 weeks prior to randomization.
14. Active uncontrolled inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis, and other autoimmune diseases) requiring ongoing treatment with anti-TNF medication.
15. Any concomitant medication known to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication within 7 days prior to start of treatment.

16. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
    - Ongoing or history of uncontrolled or symptomatic ischemic myocardiopathy within 6 months prior to randomization.
    - Known left ventricular ejection fraction < 50%, left ventricular hypertrophy, ventricular arrhythmias, bradycardia (heart rate < 50 bpm).
    - History of myocardial infarction, or severe/unstable angina, within 6 months prior to randomization.
    - New York Heart Association grade ≥ 3 congestive heart failure.
    - Congenital long QT syndrome.
    - Family history of long QT syndrome.
    - Symptomatic pulmonary embolism within 6 months prior to randomization.
    - Ongoing or known history of transient ischemic attacks or stroke within 6 months prior to randomization.
    - QTc using Fridericia's formula (QTcF) interval > 450 ms for males and > 470 ms for females.
17. Symptomatic pulmonary disease requiring continuous or intermittent oxygen supply.
18. History of another malignancy within the last 3 years prior to randomization, with the exception of completely resected non-melanoma cell skin cancer outside the head and neck area or completely resected stage I breast cancer, or completely resected in-situ non-muscular invasive bladder, cervix and/or uterine carcinomas or T1a squamous cell carcinoma of the esophagus.
19. Known contraindication to undergoing positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG-PET) scans, and/or both contrast-enhanced MRI and contrast-enhanced CT scans.
20. Known allergy to xevinapant, cisplatin, carboplatin, other platinum-based agent or any excipient known to be present in any of these products or in the placebo formulation.
21. Non-compensated or symptomatic liver cirrhosis (Child-Pugh score: B or C).
22. Any ongoing condition or disorder, before randomization, including drug(s) or alcohol abuse, which in the judgment of the Investigator would make the participant inappropriate for entry into the study or precluding his/her ability to comply with study procedures.

5.3. Lifestyle Considerations

During the study, participants are asked to refrain from consumption of grapefruit juice, grapefruit-containing products, St John's Wort (= *Hypericum perforatum,* millepertuis) and St John's Wort-containing products because of the risk of DDIs with P-gp resulting in a decrease in xevinapant exposure (see also Section 6.5.3.1).

5.4. Screen Failures

Screen failures are participants who have signed the ICF and for whom a study-specific identification number has been assigned (screened participants) but who were not enrolled because they failed to meet the eligibility criteria or discontinued study participation during the screening period for other reason(s).

In accordance with the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from Regulatory Authorities, only a minimal set of data are collected on screen failures, i.e., demographic data, screening failure reason(s) and any serious adverse event (SAE).

Re-testing of participants in cases of physical and/or laboratory parameters abnormalities will be allowed within 28 days after the signature of ICF (screening period).

Beyond the 28 days after signature of ICF, participants may be re-screened in certain circumstances for enrolment into the study:

- A participant consented to participate, met the eligibility criteria but was delayed in starting due to a change in situation (e.g., family issues, request for attending a private matter, etc.).
- A participant failed eligibility due to an acute event that resolved or was stabilized with medications.
- Reversible causes of screening failure that were adequately treated and/or resolved.
- A participant failed eligibility due to logistical/operational constraints (e.g., assessment could not be done in time due to logistical constraints or had to be repeated but time was limited, laboratory results were delayed, IMRT plan was not approved in time, etc.).

Only one rescreening is allowed.

In case of rescreening, the participant will be required to sign another ICF. A new electronic case report form (eCRF) will be used but the participant number will remain the same. The participant will be flagged in the eCRF as having been re-screened. All assessments should be repeated according to instructions provided for the initial screening (see Section 1.3 and Table 1-1). As with initial screening procedures, ^{18}F-FDG-PET, i.v. contrast-enhanced CT-scan or MRI of head and neck, and CT-scan of chest are only accepted if they are performed within 4 weeks before randomization. Dental examination, audiometry, HBV/HCV/HIV tests, and fiberoptic endoscopy performed within 2 weeks before the last signed ICF do not have to be repeated during screening.

5.5. Strategies for Recruitment and Retention

The target sample size is 700 eligible participants worldwide enrolled from approximately 280 recruiting sites. The following geographic areas are expected to participate: North America, Latin America, Europe, Middle East, and Asia Pacific. Assuming a 30% screen failure rate, approximately 1000 participants will be screened in order to achieve the target number of eligible participants.

Note: Additional Chinese participants from China Mainland will be randomized in a China-specific extension cohort (see Section 13.9 for further details).

Eligible participants will be randomized in a 1:1 ratio to receive xevinapant + CRT (Arm A) or matched placebo + CRT (Arm B). The annual lost to follow-up/dropout rate is expected to be 5% in both arms.

Stratification factors are presented in Section 6.3.

Participants will be recruited from participating investigational sites either by a direct approach from the physician or Health Care Professional or following an enquiry from a referring site or participant. Other measures will be implemented to reach out to potential participants which will include a study-specific website for participants, engagement of Patient Advocacy Groups and selected media coverage, when allowed by local legislation.

Materials focused on participant recruitment and retention will follow local regulations and may include, among others: study posters, participant brochure, patient participation and appointment card, participant's diary and welcome guide.

To assist Health Care Professionals with participant identification a range of materials will also be used such as: Health Care Professionals Brochure, Health Care Professionals Referral Form, Eligibility Checklist, Inclusion/Exclusion card, Health Care Professional study website.

Participants will not be compensated for participation in this study, but travel costs may be reimbursed, when allowed by local regulations. The service of monitoring and managing the participant travel and reimbursement costs will be provided by the study Contract Research Organization (CRO).

6. STUDY INTERVENTION

6.1. Study Intervention Administration

6.1.1. Study Intervention Description

Study intervention or study treatment includes blinded administration of investigational treatments (xevinapant, matched placebo, cisplatin and carboplatin) and background treatments.

The investigational treatment is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In the current protocol, xevinapant, matched placebo, cisplatin and carboplatin are investigational treatments.

Background treatments are medicinal products administered to each of the clinical study participants, regardless of randomization group, to treat the indication which is the object of the study. In the current protocol, IMRT is considered as background treatment.

The following investigational and background treatments will be administered during the study according to randomization (see Section 6.1.2 for dosing and administration details):

- **Arm A:** 3 cycles of xevinapant (200 mg/day from Day 1 to 14, per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week + high-dose cisplatin (100 mg/m^2

on Day 2, per cycle), followed by 3 cycles of monotherapy of xevinapant (200 mg/day from Day 1 to 14, per cycle).

or

- **Arm B:** 3 cycles of placebo (from Day 1 to 14 per cycle) + IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week) + high-dose cisplatin (100mg/m^2 on Day 2, per cycle), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per cycle).

One cycle is composed of 3 weeks.

The administration schedule of xevinapant/placebo, chemotherapy and IMRT is presented in Table 1-1 and Table 1-2.

6.1.2. Dosing and Administration

6.1.2.1. Xevinapant or Matched Placebo

Xevinapant oral solution at 200 mg/day or matched placebo will be administered once daily from Day 1 to Day 14 of a 3-week cycle, during 6 cycles (see Table 1-2).

Xevinapant/matched placebo should be administered orally, early in the morning (except on days C [redacted] where a specific procedure described below applies), on an empty stomach (no food intake within 2 hours before xevinapant/matched placebo administration). Participants should fast for at least 1 hour after dosing. Water is permitted freely before and after xevinapant/matched placebo intake. If necessary, the oral solution will be administered via a nasogastric tube, percutaneous endoscopic gastrostomy, or percutaneous endoscopic jejunostomy tube.

If the participant forgets to take the scheduled dose of xevinapant/matched placebo more than 8 hours after the time of intake, then the participant should skip that dose.

Xevinapant/matched placebo will be dispensed by the medical staff or Pharmacist of the investigational sites. The participant will receive xevinapant or the matched placebo on an outpatient basis.

On days C [redacted] at C1D2, C1D8, C2D2, C3D1, and C3D2, participants should take their doses at the hospital, where the administration of xevinapant or the matched placebo will be supervised and recorded by the medical staff C [redacted] The time of dose administration and the time of blood draw should be recorded in the eCRF and in the participant's diary. In addition, on C1D7, the time of the dose taken at home needs to be recorded in both the eCRF and the participant's diary. On days C [redacted], at C3D8 and C4D1, xevinapant/placebo is taken, and the time of dosing (C3D8 and C4D1) must be recorded both in the eCRF and the participant's diary. On C3D15, the last xevinapant/placebo dose timing (taken at home on C3D14) must be recorded both in the eCRF and the participant's diary.

The treatment schedule of xevinapant or the matched placebo is presented in Table 1-1 and Table 1-2. Participants will be instructed by the medical staff on how to self-administer xevinapant or the matched placebo at home. The participant should inform the medical staff of any missed or delayed doses. In addition, a Participant Diary will be provided to participants to record

xevinapant/matched placebo intakes at home. Please refer to Sections 6.4 and 8.3.8 for further details.

6.1.2.1.1. Concurrent Administration to Chemotherapy and IMRT

On days when IMRT and chemotherapy are to be administered (see Table 1-2), CCI [redacted] chemotherapy should be administered preferably before IMRT.

On days when IMRT is to be administered without chemotherapy (see Table 1-2 and Section 6.1.2.3), xevinapant or matched placebo should be preferably administered before IMRT.

If chemotherapy or IMRT are put on hold or discontinued, please refer to Section 6.1.2.1.2 to adapt xevinapant administration accordingly.

6.1.2.1.2. Dose Modification, Interruption and Discontinuation of Xevinapant/ Matched Placebo Treatment

For participants who do not tolerate the study treatment, adjustments to the study treatment are permitted to allow the participant to continue on-study treatment.

The guidelines for xevinapant/matched placebo dose modifications for toxicities considered at least possibly related to study treatment are outlined in Table 6-1 and Table 6-2 , for combination therapy and monotherapy, respectively. These dose modifications are recommendations unless otherwise specified as mandatory. All dose modifications should be based on the worst preceding toxicity (NCI-CTCAE v5.0). Additionally, non-treatment-related events or unexpected toxicities may require interruption of study treatment at the discretion of the Investigator.

For each participant, a maximum of 2 dose reductions of xevinapant/matched placebo will be allowed during the study.

The volume of the oral solution equivalent to each dose level is the following:

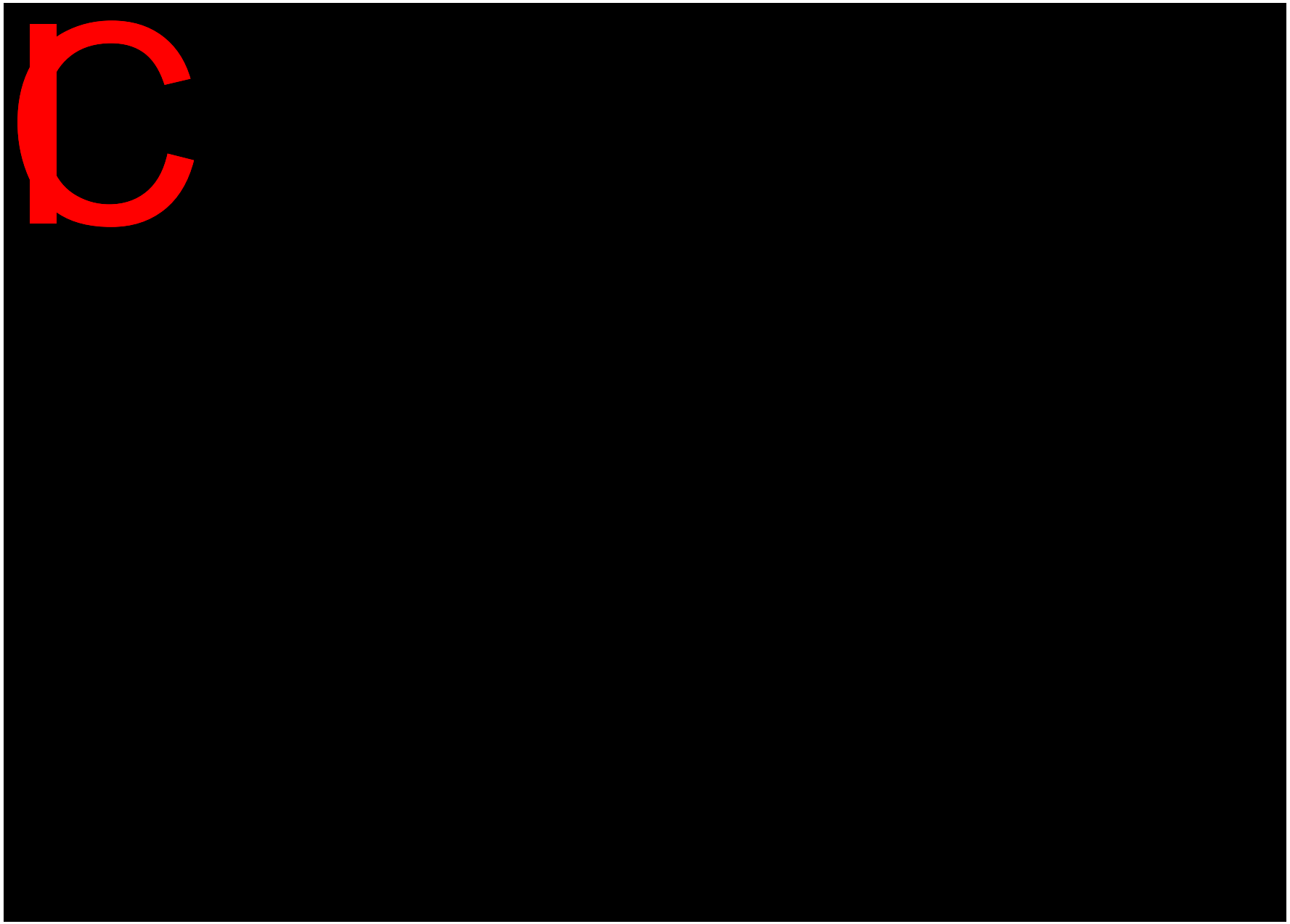
- Planned dose (level 0): CCI [redacted] corresponds to 200 mg/day of xevinapant
- Dose level -1: CCI [redacted] corresponds to 150 mg/day of xevinapant
- Dose level -2: CCI [redacted] corresponds to 100 mg/day of xevinapant

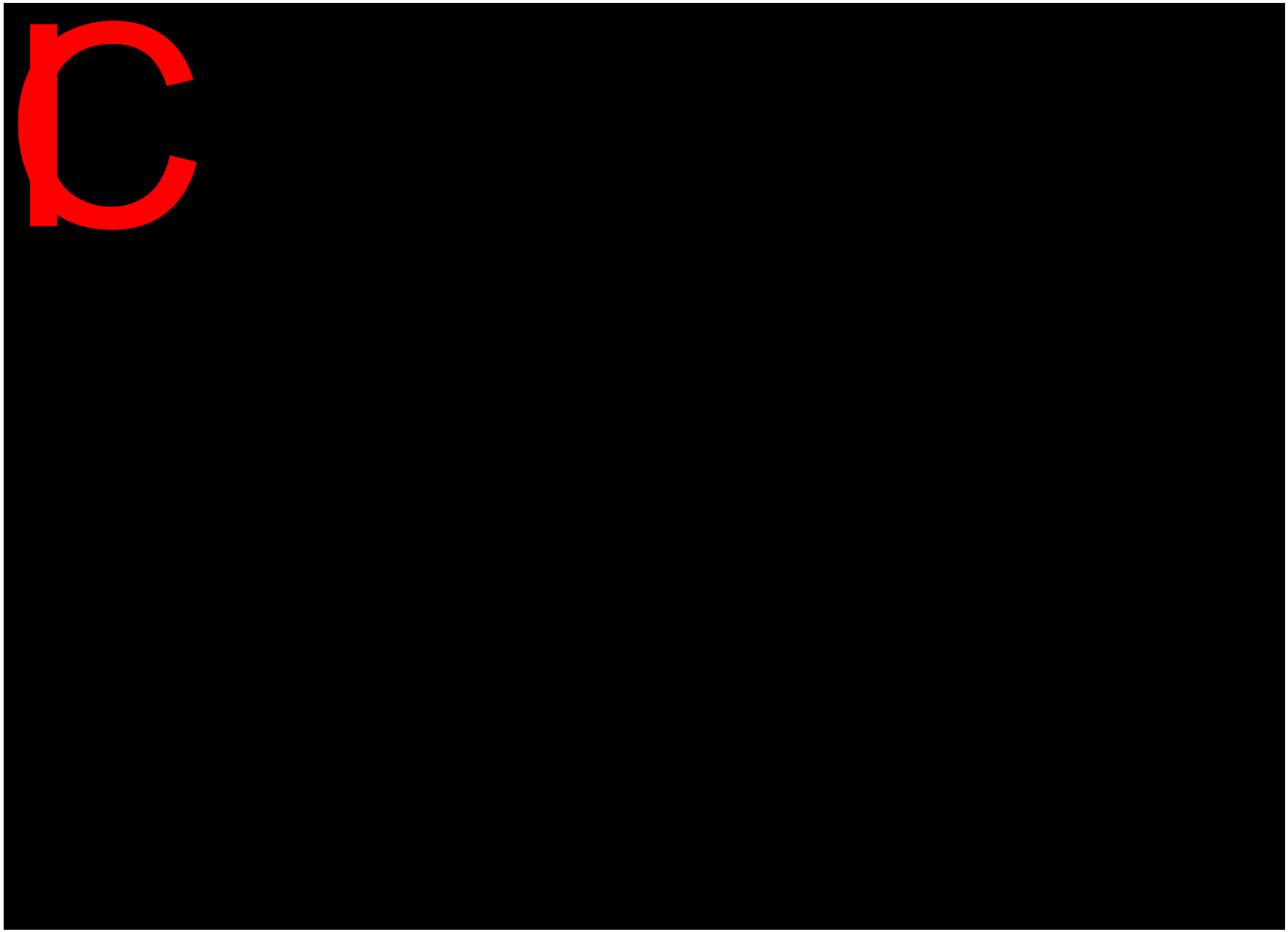
General rules for xevinapant/matched placebo administration throughout the treatment period (C1 to C6) are:

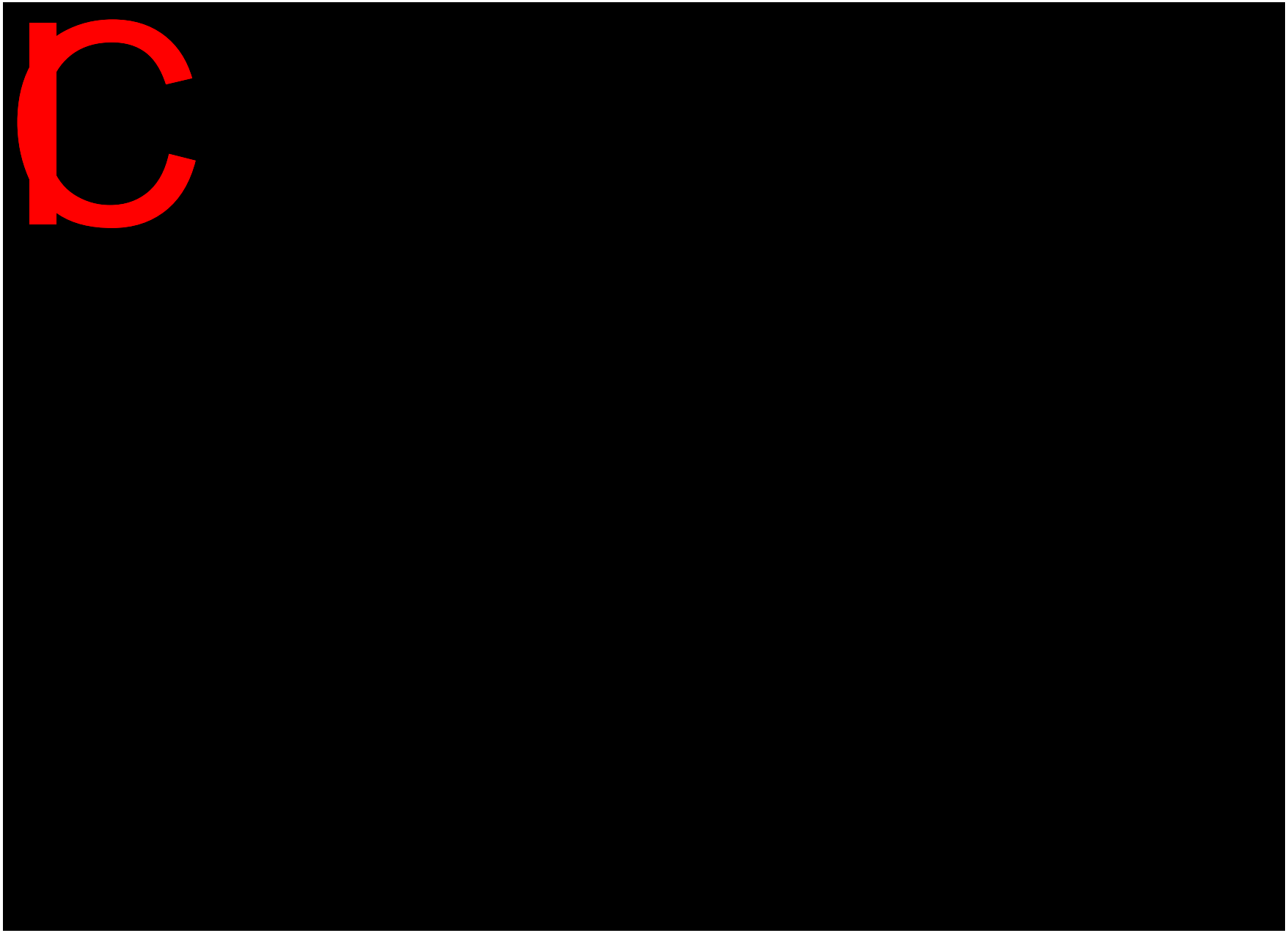
- The number of treatment days with xevinapant intake should not exceed 14 days per cycle.
- In case of tolerability issues, up to 2 sequential xevinapant dose reductions of CCI [redacted] (CCI [redacted] of oral solution) per step will be allowed, down to a minimum dose of CCI [redacted] CCI [redacted] of oral solution). If further dose reduction is required, the participant must be permanently discontinued from xevinapant/matched placebo administration (other ongoing treatments can continue, see Sections 6.1.2.2 and 6.1.2.3).
- If the onset of several toxicities leads to conflicting recommendations as described in Table 6-1 the most conservative dose adjustment among all toxicities presented must be followed.

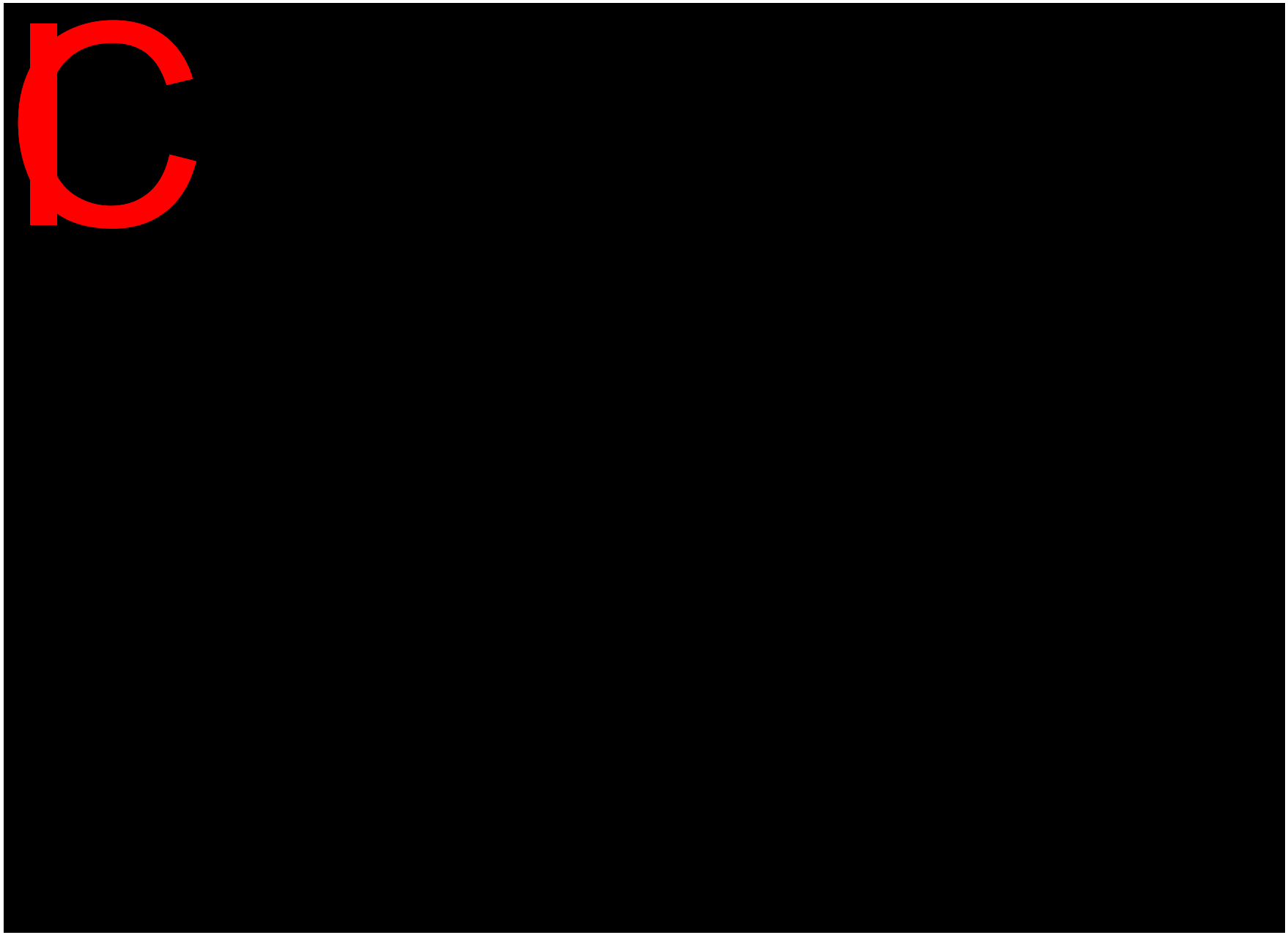
- **No re-escalation** of xevinapant/matched placebo dose after dose reduction will be allowed during the study. Once xevinapant or matched placebo dose has been reduced, participant will keep receiving the same dose until the EOT, or until further dose reduction or permanent treatment discontinuation, if required due to tolerability issues.
- Xevinapant doses/matched placebo that were omitted on a specific day should **NOT** under any circumstances be administered any other day in addition to the scheduled intake.
- No additional dose should be re administered after vomiting; the participant must wait for the next scheduled intake.
- If during the monotherapy part of the treatment, a participant requires a xevinapant/matched placebo dose interruption of more than 21 consecutive days due to study treatment-related toxicities, the Investigator should consider discontinuing the treatment. If a participant is discontinued from the monotherapy treatment, the EOT visit should be performed.
- Chemotherapy discontinuation will **NOT** result in xevinapant/matched placebo discontinuation.
- During the combination treatment period, if IMRT is interrupted, xevinapant/matched placebo should be interrupted. If IMRT is restarted, xevinapant/matched placebo should be resumed at the next originally scheduled intake day of xevinapant/matched placebo, provided other rules of dose interruption are not met (see Section 6.1.2.3). If IMRT is permanently discontinued due to safety issues, then xevinapant/matched placebo administration should be maintained, and the participant can enter the monotherapy period. Otherwise, xevinapant/matched placebo treatment should be discontinued permanently, the EOT visit should be performed, and the participant should stay on study for follow-up as per protocol. IMRT may be interrupted for up to a maximum of 10 treatment days in total.
- Participants who prematurely discontinue from all treatments, i.e., chemotherapy, IMRT and xevinapant/matched placebo, in the absence of an EFS event will undergo the EOT visit and then enter the EFS follow-up period according to schedule.

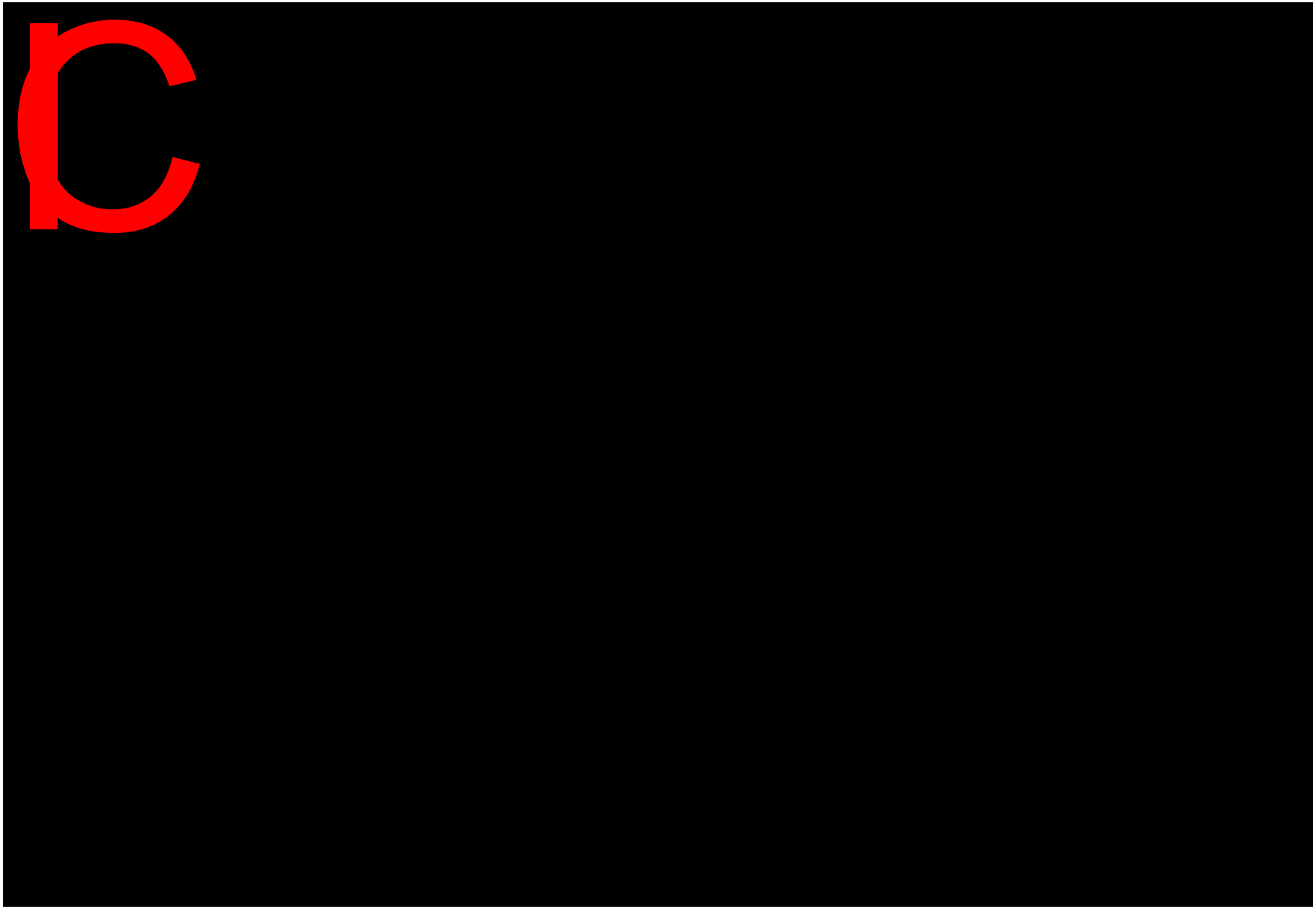
Any dose modification and dose interruption including the reason must be recorded on the Dosage Administration Record eCRF.

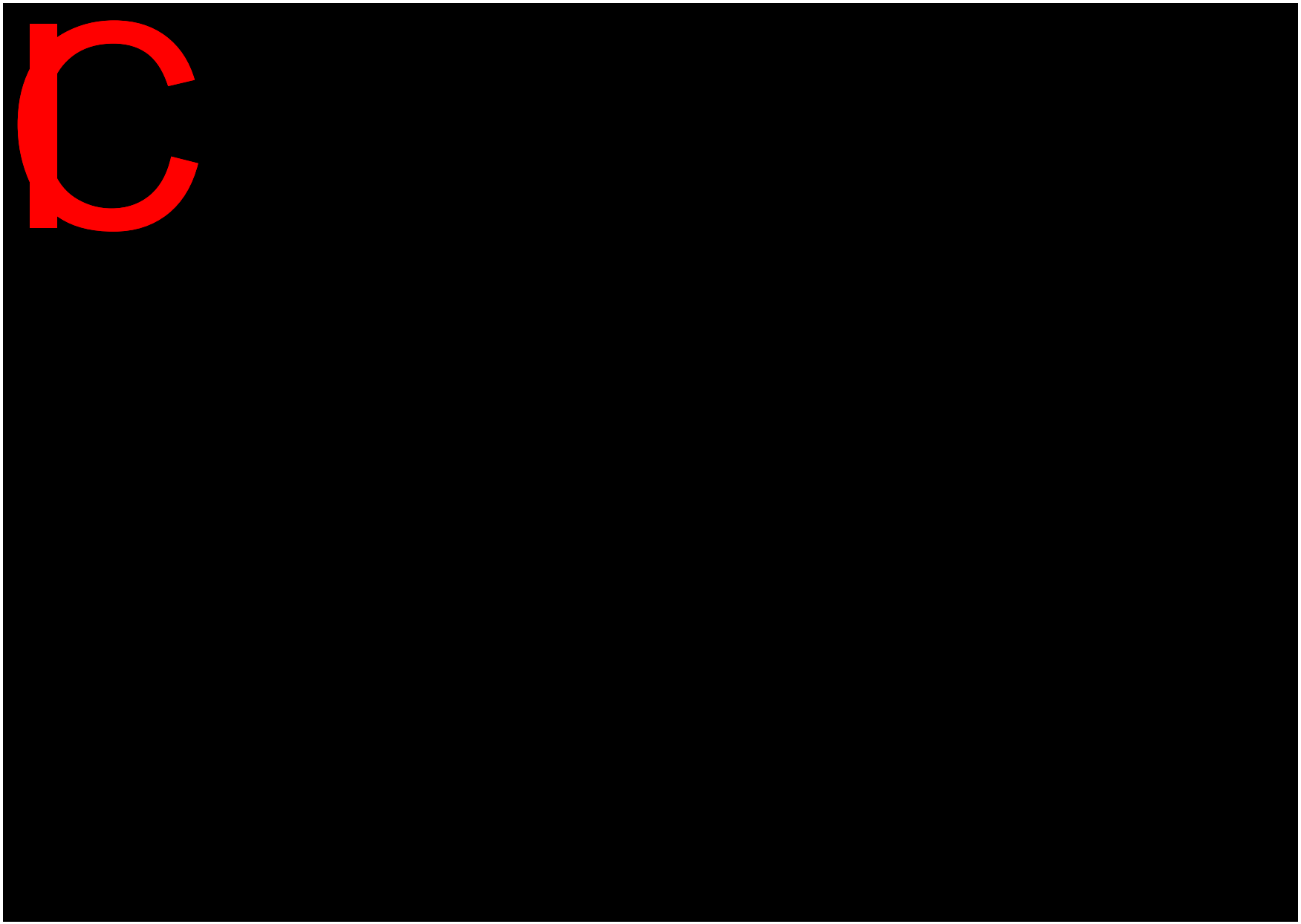


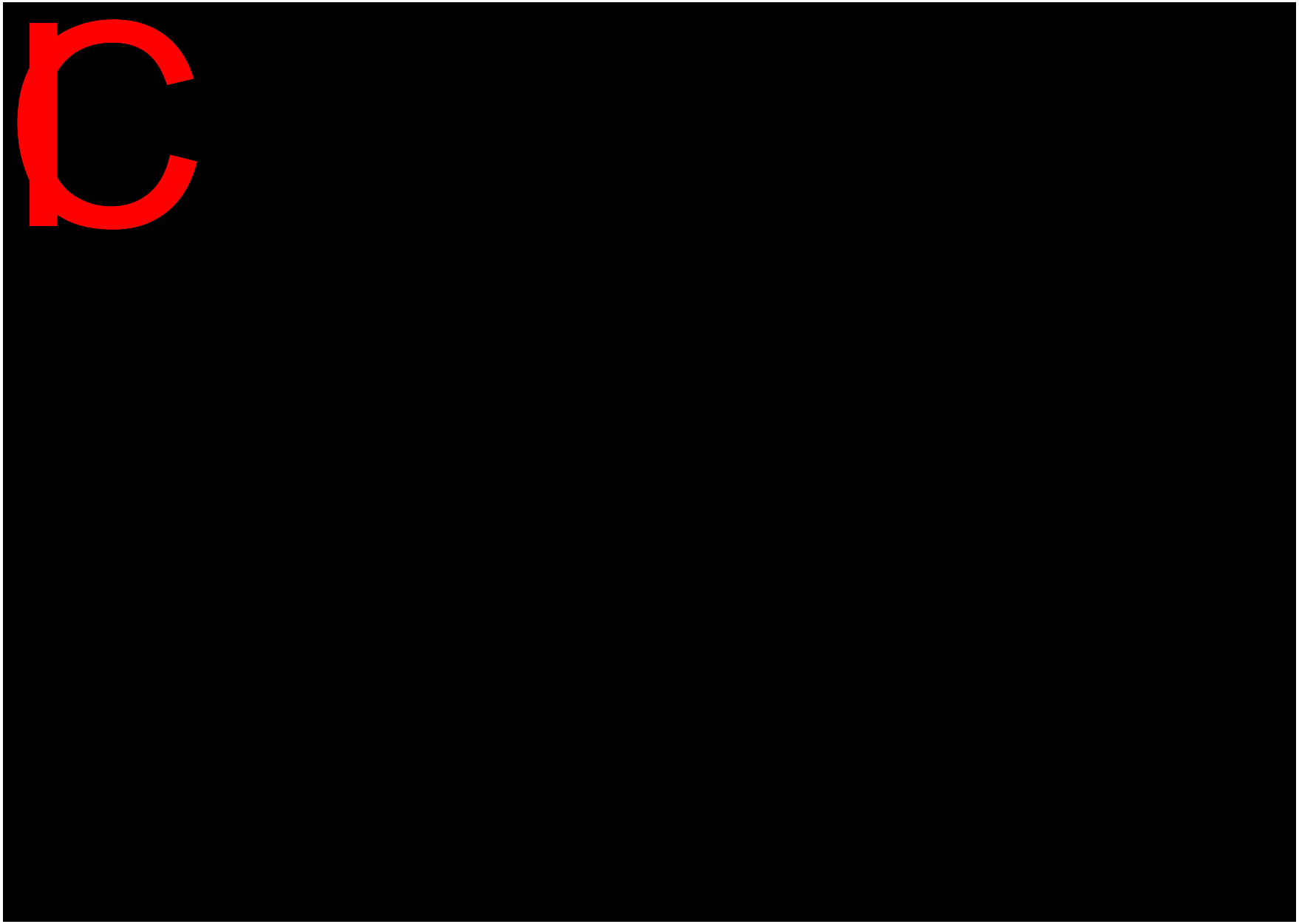


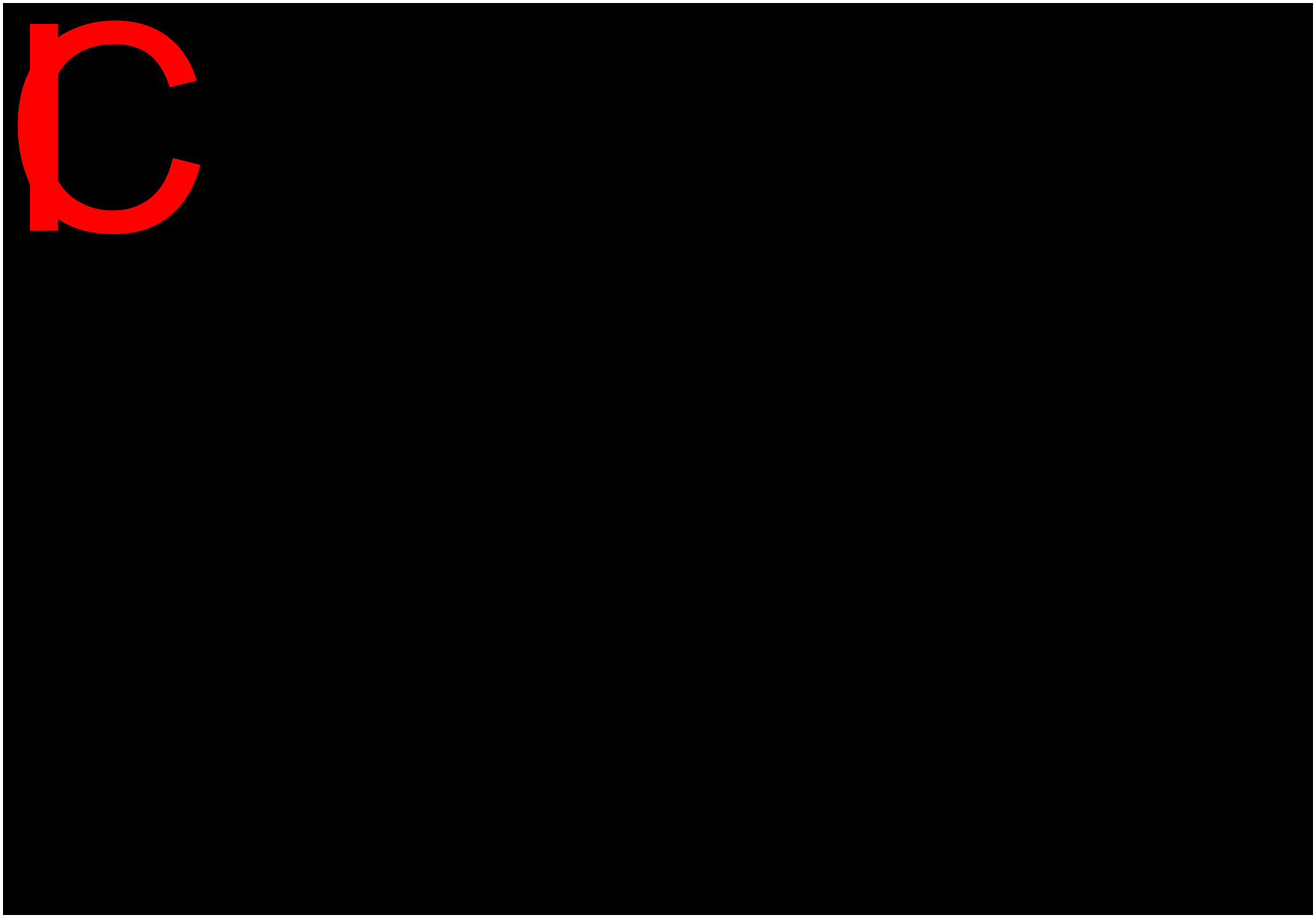




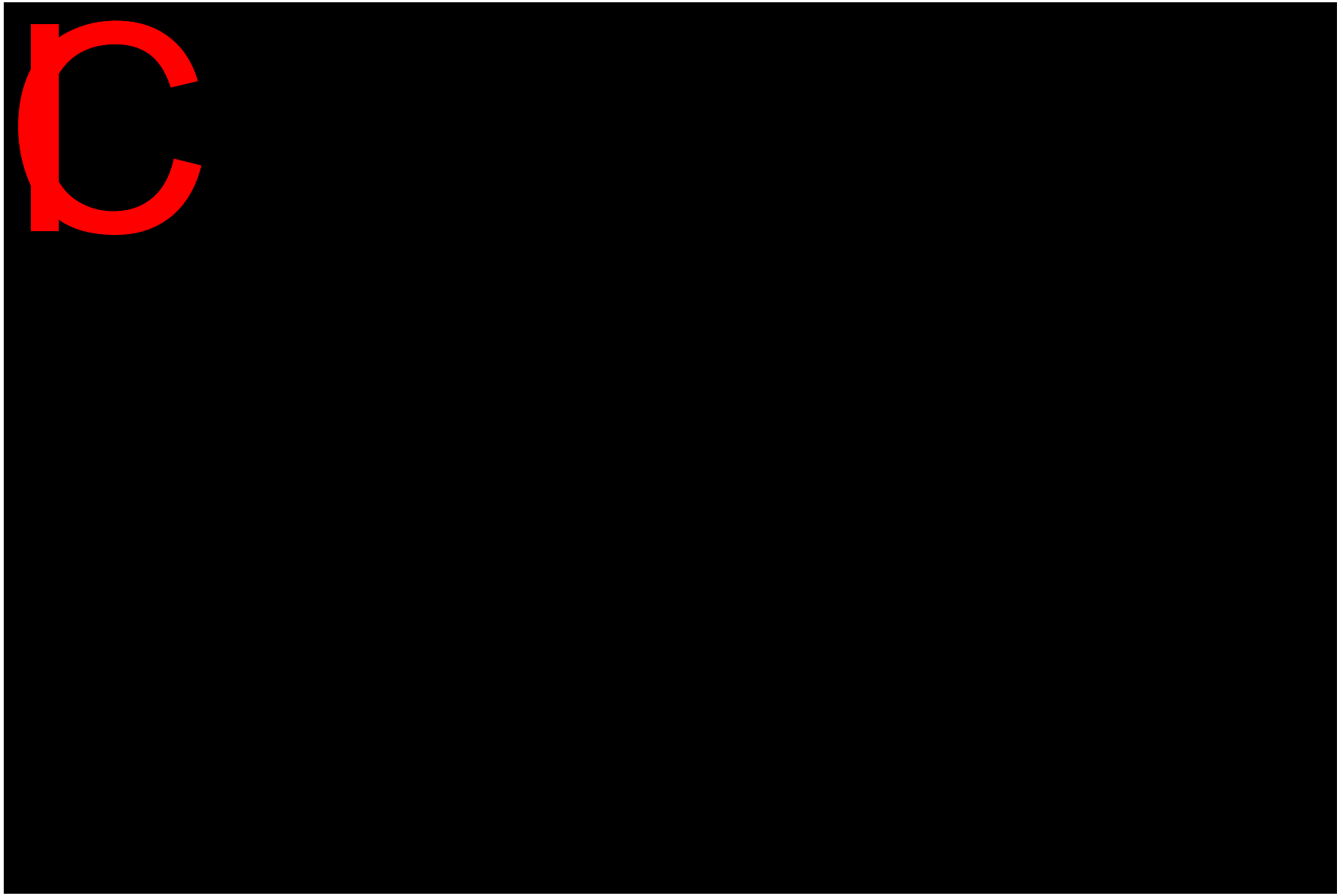


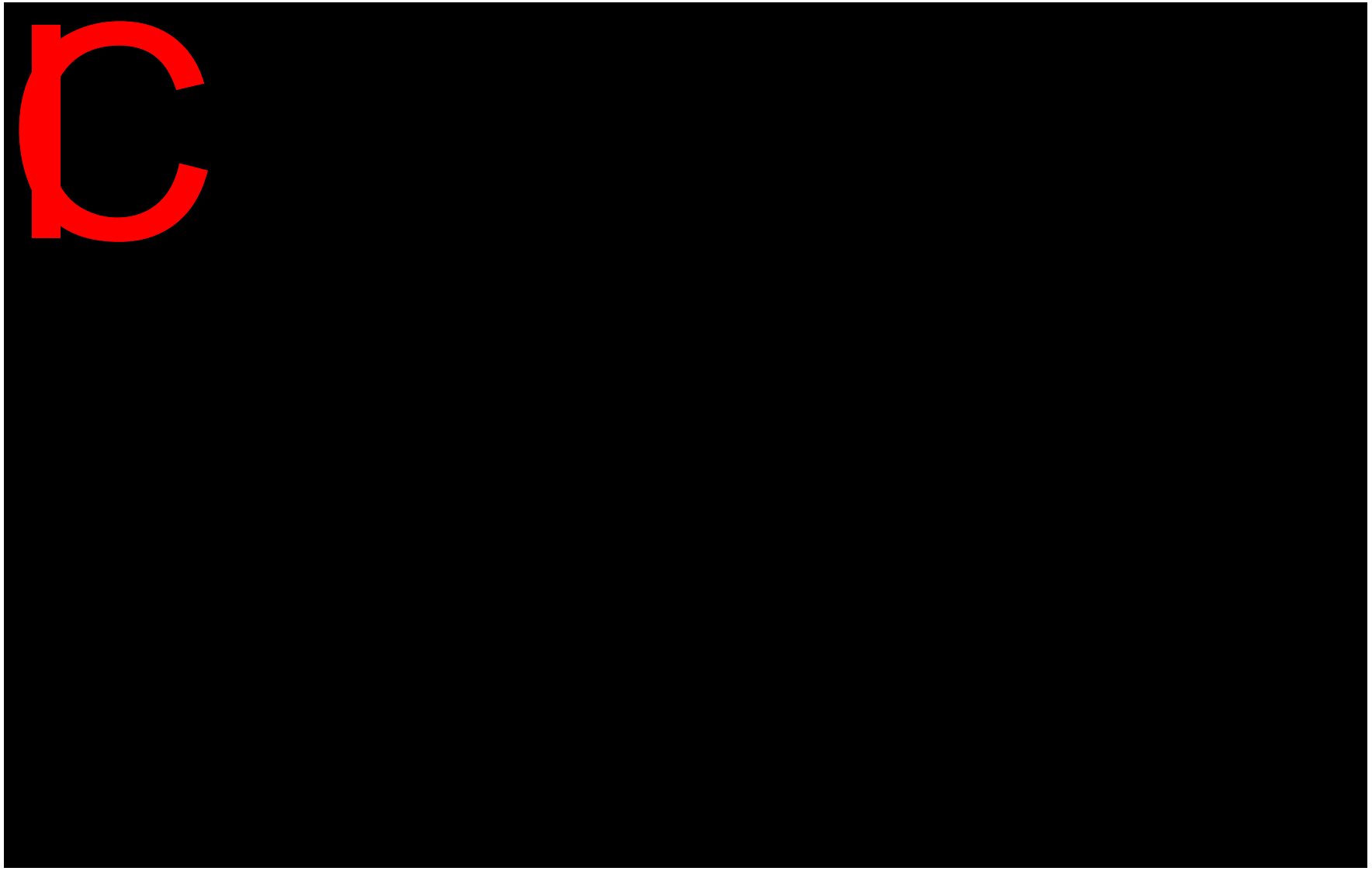






[redacted]





6.1.2.1.3. End of Xevinapant/Matched Placebo Treatment

Xevinapant/matched placebo treatment will be administered until the 6 cycles of therapy (i.e., 3 cycles of combination therapy followed by 3 cycles of monotherapy) are completed or until any of the study intervention discontinuation criteria described in Section 7.1 occur.

Note: If IMRT is permanently discontinued due to severe or intolerable toxicities as per Investigator's discretion, then the participant can enter the monotherapy period.

Discontinuation from study treatment does not mean discontinuation from the study. Procedures to be followed in the event of a study treatment discontinuation are presented in Section 7.1.

Procedures for discontinuation from study (not only study treatment) are described in Section 7.3.

6.1.2.2. Chemotherapy

All participants will receive high-dose cisplatin (100 mg/m^2) intravenously over at least 90 minutes on Day 2 Q3W up to a maximum of 3 cycles in total (see administration schedule in Table 1-1 and Table 1-2). If body surface area is >2.00 m^2, total administered dose will be capped at a maximum of 200 mg. Please consult and follow cisplatin administration instructions provided in your local label. The infusion has to be administered with pre- and post-infusion hydration +/- mannitol and/or diuretics, according to institutional guidelines. Any pre-existing dehydration should be corrected. Please refer to Appendices 13.2 and 13.3 for additional information on cisplatin administration and suggested hydration regimen.

[redacted]

eGFR (using the CKD-EPI creatinine formula) should be ≥60 mL/min/1.73m^2 before administration of cisplatin at C1D2; re-treatment conditions as specified in Table 6-1 should be met.

Participants should receive at least one dose of cisplatin on C1D2.

Standard antiemetic prophylaxis for high-dose cisplatin containing regimens are mandatory starting on Day 1 of each chemotherapy containing cycle. Standard antiemetics guidelines (administration of pre- and post-treatment 5-HT3 receptor antagonists, neurokinin-1 receptor antagonists and dexamethasone [or any other corticosteroid at equivalent dose i.v.] according to the 2016 MASCC and ESMO guideline (Roila et al. 2016)]) are provided in Section 6.5.1; however the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved.

Note: Dose and schedule of dexamethasone coupled with its wide availability in various forms established it as the agent of choice in the 2016 MASCC and ESMO guideline. If an equivalent dose of corticosteroids is used according to institutional guidelines, the risk of increased toxicity to corticosteroids should be carefully monitored. Elevations of plasma levels may be triggered by xevinapant inhibition of CYP3A4.

The participant can switch to carboplatin in C2 and/or C3 as per the dose modifications outlined in Table 6-1 (NCCN Chemotherapy Order Templates 2020). Please consult and follow the carboplatin administration instructions provided in your local label.

No pre- or post-treatment hydration or forced diuresis is required for carboplatin administration.

6.1.2.2.1. Dose Modification, Interruption and Discontinuation of Chemotherapy

Permitted cisplatin dose levels:

- Planned dose (level 0): corresponds to cisplatin 100 mg/m^2
- Dose level -1: corresponds to cisplatin 75 mg/m^2 (-25% from prior dose level: capped at 150 mg total dose)
- Dose level -2: corresponds to cisplatin 50 mg/m^2 (-25% from prior dose level: capped at 100 mg total dose)

For participants switching to carboplatin: carboplatin AUC = 5 mg·min/mL or AUC = 4 mg·min/mL is allowed.

Please refer to Table 6-1 for instructions on dose modifications, interruption, and discontinuation of chemotherapy in case of toxicity suspected to be related to study treatment.

Toxicity related to chemotherapy administration includes but is not limited to nausea, vomiting, renal toxicity (with an elevation of blood urea nitrogen and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), peripheral neuropathy, ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus) and hyperuricemia. Much more severe and prolonged toxicity has been observed in participants with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed anemia is expected.

Chemotherapy dose adjustments at the start of a cycle should be based on the nadir of hematologic counts or maximum non-hematologic toxicity from the previous treatment cycle. chemotherapy infusion may be delayed to allow for sufficient recovery time.

6.1.2.2.2. End of Chemotherapy

Chemotherapy will be administered until completion of the 3 cycles of platinum-based therapy planned in the study or until any of the study intervention discontinuation criteria described in Section 7.1 occur.

Note: Chemotherapy discontinuation will not result in xevinapant/matched placebo discontinuation or study treatment discontinuation.

Dose modifications, interruption, including switching from cisplatin to carboplatin, and permanent discontinuation of any of the components of the study intervention is to be recorded in the Dosing Case Report Form (CRF) of each component of the study intervention. For each action, the reason must be recorded.

Discontinuation from study treatment does not mean discontinuation from the study. Procedures to be followed in the event of a study treatment discontinuation are presented in Section 7.1.

Procedures for discontinuation from study (not only study treatment) are described in Section 7.3.

6.1.2.3. Radiotherapy

Standard fractionation IMRT (as fully described in the IMRT manual) is to be started on C1D1 after administration of xevinapant/matched placebo (see administration schedule in Table 1-1 and Table 1-2). On days where all treatment components should be administered, IMRT should be preferably administered after xevinapant/matched placebo and chemotherapy.

IMRT will be delivered per Table 6-3 and the following:

- To the PTV and high-risk clinical target volume: 70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/week. Missed treatments due to holidays or logistic reasons can be compensated by delivering the missed fraction before or after the end of the combination treatment period (i.e., up to Week 9 after administration of first dose) (see Section 6.1.2.3.1).
- Elective irradiation (low-risk) to locoregional areas, 56 Gy (1.6 Gy/fraction per day, 5 fractions per week [5/7 days]).

Table 6-3 Radiation therapy scheme

	Total dose in Gy	Dose in Gy	Number of days	
PTV 70	70	2	35	5 fractions per week over 7 weeks
PTV 56	56	1.6	35	5 fractions per week over 7 weeks

Abbreviations: PTV: Planning target volume.

The RT-QA Review Center (Section 11.2.2) will centrally review the IMRT treatment plan(s) to ensure compliance with protocol guidelines and provide feedback to the site.

The IMRT treatment plan for each participant must be submitted electronically to the RT-QA Review Center as soon as possible and no later than 5 business days prior to the start of IMRT. The digital data must include treatment planning of CT-scan, structure, plan, and dose files (please refer to the RT-QA Manual/Guide). The RT-QA Review Center will evaluate IMRT delivery and any critical/major deviations from the submitted plan during study treatment period. RT-QA Review Center approval of the IMRT plan is requested before starting the first fraction administration.

6.1.2.3.1. Treatment Interruption

IMRT interruption is strongly discouraged; any interruption must be clearly indicated in the treatment record and reasons should be documented.

IMRT may be interrupted for up to a maximum of 10 treatment days in total to allow resolution/improvement of radio-chemo toxicities such as grade 4 mucositis measured by physical or functional examination, or grade 4 radiodermatitis (see section 6.1.2.3.2 for management of those toxicities).

Treatment interruption due to a non-medical reason should be minimized as much as possible and should not exceed 2 consecutive treatment days per interruption (Radiologists 2020). In case

of interruption for technical reasons (e.g., malfunction or revision of the treatment machine), continued treatment must be ensured, and the use of another unit is recommended. For units that have different energy levels, it is recommended to perform the dosimetry on an alternative device.

If a fraction has to be compensated, it can be administered after the planned 35 fractionation days (cycle 1 to 3) or it can be compensated during the 35 fractionation days. If compensated during the 35 fractionation days, the fractions should be at least 6 hours apart. Xevinapant / placebo administration should not be compensated. In any case, there must be no more than 5 days of treatment in a given week.

If IMRT is permanently discontinued due to severe and intolerable toxicities as per Investigator's judgment, then xevinapant/matched placebo monotherapy administration should be maintained, and the participant can enter the monotherapy period.

6.1.2.3.2. Management of Acute "in Radiation Field" Toxicity

If dermatitis, mucositis, or dysphagia occurs, the possibility of IMRT interruption should be assessed according to their severity. Institutional guidelines on prophylaxis and dental hygiene will be followed for management of skin and mucosal toxicity.

For any other degree of minor toxicity, the necessary support measures must be taken to ensure treatment continuity (Peterson et al. 2015).

In the event of mucositis, the following recommendations will be considered:

- Rapid escalation of analgesics using the World Health Organization cancer pain relief ladder (WHO 2018).
- Enteral or parenteral nutritional support according to the institutional guideline. Enteral nutritional support is strongly recommended if weight loss is ≥ 5%. If the weight loss is ≥ 10%, the use of a nasogastric or gastrostomy tube must be implemented as quickly as possible (Elad 2019).

The management of radiation dermatitis should be based on the severity of symptoms, as determined by Radiation Therapy Oncology Group and should follow the recommendations by the Supportive Care Guidelines Group.

6.1.2.3.3. End of Radiotherapy

Radiotherapy will be administered until completion of the IMRT dose and schedule (see Table 6-3) planned in the study or until any of the study intervention discontinuation criteria described in Section 7.1 occur.

Discontinuation from study treatment does not mean discontinuation from the study. Procedures to be followed in the event of a study treatment discontinuation are presented in Section 7.1.

Procedures for discontinuation from study (not only study treatment) are described in Section 7.3.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Acquisition and Accountability

The investigational treatments (xevinapant/matched placebo, cisplatin, and carboplatin; see Section 6.1) will be provided to the Investigators by and under the responsibility of the Sponsor, who will also ensure release of the investigational treatments as per current Good Manufacturing Practice (GMP) guidelines. Any documentation required by local Health Authorities for import of the investigational treatments will be appropriately submitted.

The Investigator, Pharmacist or other authorized personnel at each study site will inventory and acknowledge receipt of all shipments of investigational treatments. The investigational treatments accompanied by analytical reports when appropriate, must be kept in a locked area with access restricted to designated study personnel.

Investigational treatment acquisition, dispensing, accountability and reconciliation will be managed through an Interactive Web Response System (IWRS).

The Investigator/Pharmacist at each study site will keep accurate records of the investigational treatment (and other study-related drugs) dispensed. Specific procedures for investigational treatment preparation, handling, storage, and accountability will be detailed in the Pharmacy Manual, provided by the Sponsor to each study site.

During the study, whenever appropriate, partially used and unused investigational treatments will be counted and returned in the original packaging to the Sponsor or destroyed with Sponsor written permission. The Sponsor's monitor/representative will review drug accountability records and ensure investigational treatment return to depot for destruction if not destroyed on site.

Any discrepancies between the investigational treatments returned and the expected balance must be documented.

Unused investigational treatments must not be discarded or used outside of the frame of the present study.

When the above tasks are delegated to a Pharmacist, the Investigator remains ultimately responsible for the maintenance of accurate drug dispensing records.

6.2.2. Formulation, Appearance, Packaging, and Labeling

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines.

6.2.2.1. Formulation, Appearance, Packaging

Table 6-4 Formulation, appearance and packaging of investigational treatments: xevinapant and platinum-based chemotherapy

Product	Potency	Appearance	Packaging
Xevinapant[a] or Placebo[a]	CCI mg/mL Not applicable	Oral solution	CCI [redacted]
Cisplatin	1 mg/mL	Concentrate for solution for infusion	Package contains 1 vial (50 mL) of cisplatin concentrate for solution for infusion. Each package is labeled as appropriate to comply with local regulations.
Carboplatin	10 mg/mL	Concentrate for solution for infusion	Package contains 1 vial (15 mL or 60 mL) of carboplatin concentrate for solution for infusion. Each package is labeled as appropriate to comply with local regulations.

a The formulation will be specified in the Pharmacy Manual.

6.2.2.2. Labeling

Medication labels will comply with the legal requirements of each country and will be printed in the local language. The storage conditions for the investigational treatments will be described on the medication label.

6.2.3. Product Storage and Stability

Xevinapant oral solution or placebo should be stored under controlled temperature at 2°C to 8°C (36°F to 46°F). Do not freeze. Keep medication in its original container.

Cisplatin and carboplatin should be stored according to the drug label.

Any additional storage requirements will be further detailed in the Pharmacy Manual provided by the Sponsor to each study site.

6.2.4. Preparation

For oral (p.o.) administration of 200 mg of xevinapant oral solution or placebo: oral intake by the participant directly from the CCI [redacted]

For enteral administration of 200 mg of xevinapant oral solution or placebo: withdrawal of the required volume by the participant using a 5 mL syringe. Note: CCI [redacted] the use of larger syringes is not feasible.

In case of dose reduction, p.o. and enteral administration of 150 mg/7.5 ml or 100 mg/5 ml (for xevinapant) or placebo: withdrawal of the required volume by the participant using a 5 ml syringe. Note: CCI [redacted], the use of larger syringes is not feasible.

6.3. Measures to Minimize Bias: Randomization and Blinding

To ensure that treatment assignment is unbiased and concealed from participants and Investigator staff, randomization will be performed using the following procedure.

All participants will be centrally assigned to randomized study intervention using an IWRS. A web address and a manual for the IWRS will be provided to each site. The Investigator or authorized person will be responsible for activating the IWRS.

During screening or at C1D1 and upon confirmation of eligibility, the participant will be randomized to one of the 2 study arms in a 1:1 ratio. Each medication kit will be identified by a unique medication number. To avoid unintentional unblinding, those numbers will be assigned following a randomized sequence. At the D1 visit of each cycle, the IWRS will assign 2 kit numbers per participant.

Eligible participants will be randomized in a 1:1 ratio to receive xevinapant + CRT (Arm A) or matched placebo + CRT (Arm B). The following stratification factors will be considered for the randomization:

- Region: North America vs Western Europe vs Rest of the World.
- Primary tumor site: larynx vs other.
- Lymph node involvement: N0-1 vs N2 vs N3.
- T size: T4 vs other.

The randomization mechanism will have 2 stages:

- First stage: randomization will be either to “balanced part” (with probability 0.2) or “adaptive part” (with probability 0.8).
- Second stage: randomization will be based on the result of the first stage. If randomization from the first stage is:
    - to the “balanced part”: treatment assignment will be in a 1:1 ratio to either xevinapant + CRT (Arm A) or matched placebo + CRT (Arm B), regardless of the stratification factors.
    - to the “adaptive part”: a dynamic allocation will be carried out following the methodology proposed by Pocock et al. (Pocock et al. 1975; Lebowitsch et al. 2012). An Overall Imbalance Score (OIS, using the range measure) will be calculated based on levels of individual stratification factors of participants both for the scenario when xevinapant + CRT will be assigned and scenario when placebo will be assigned. Based on the values of OIS for each arm, probabilities for assignment will be derived:
        - If OIS is the same for both arms, then the randomization will be 1:1 to either xevinapant + CRT or placebo + CRT.
        - If OIS is different between the 2 arms, then assignment to the treatment leading to the highest OIS will have a probability of 0.2 and assignment to treatment leading to lower OIS will have a (complementary) probability of 0.8.

This two-stage process was introduced to add a random factor to the treatment allocation while minimizing the imbalance between treatments and preventing perfectly deterministic allocation and allocation concealment.

The 1st xevinapant/matched placebo administration should be performed within 1 week maximum following randomization.

If the participant fails to be randomized, the screening failure reason should be recorded in the eCRF (see also Section 5.4).

In the event a participant is randomized but does not begin treatment, that participant's randomization number will not be reassigned.

Randomization codes will be kept confidential and maintained blinded to the Investigators/site personnel, CRO and Sponsor team until the database is locked for primary analysis. However, randomization codes will be disclosed to the third party laboratory in charge of bioanalytical assays [redacted] to prevent analyses of placebo participants' samples while allowing [redacted] samples analysis within the samples stability period. Furthermore, the IDMC and supporting independent statistical data center will be unblinded to treatment especially for the interim analysis. The IDMC will first share recommendation(s) based on the results of the interim efficacy analyses to the Firewall Team and jointly discuss results, as needed, for final Sponsor decision according to the protocol, keeping all individuals involved in the study conduct blinded to preserve its integrity.

Emergency unblinding

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. Only medical reasons should trigger an emergency unblinding.

The Investigator will be able to break the blind through the IWRS system without prior approval from the Sponsor. The IWRS will be programmed with blind-breaking instructions and will automatically notify the Sponsor in case of unblinding.

The date and reason of blind break must be recorded in the source documentation and CRF. The Investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable.

Xevinapant/matched placebo must be discontinued after emergency unblinding.

6.4. Study Intervention Compliance

Participants' compliance to each component of the study intervention (i.e., xevinapant/matched placebo, chemotherapy and IMRT) will be verified by direct visual supervision by the Investigator or his/her designee when administered at the hospital.

When xevinapant/matched placebo administration is taken at home, compliance will be monitored via a participant dosing diary (see Section 8.3.8) to be filled out after each intake. Participants will be instructed to return used and unused xevinapant or the matched placebo vials to the site to allow drug accountability by the medical staff.

Compliance will be assessed by the timepoint/schedule, sequence of administration, number of cycles, dose intensity, volume/amount administered and duration of administration.

For each component of the study intervention (i.e., xevinapant/matched placebo, chemotherapy and IMRT) the reasons for dose modification, interruption and discontinuation must be recorded in the CRF.

6.5. Prior, Concomitant, and Subsequent Therapy

Any medication or therapy received after the ICF signature and prior to the first dose of study treatment, whether or not such medication/therapy is continued at the time of starting study treatment, is considered as prior therapy.

Any therapy started between the first dose of study intervention and the EOT is considered concomitant therapy.

Any antineoplastic therapies (e.g., medication, surgery, any further RT) started between the EOT and the EOS are considered subsequent therapies.

All prior, concomitant and subsequent antineoplastic therapy (medication or procedures) must be recorded in the Prior, Concomitant, and Subsequent antineoplastic medication eCRF. Further instructions will be provided in the eCRF completion guidelines.

6.5.1. Permitted Concomitant Medications

6.5.1.1. Antiemetics

The specific antiemetic regimen is at the discretion of the Investigator, provided adequate control is achieved. Related information should be reported in the eCRF. For participant receiving cisplatin, antiemetic therapy including dexamethasone (or any other corticosteroid at equivalent dose i.v.), 5-HT_3 serotonin receptor antagonists and neurokinin-1 receptor antagonists can be administered as per 2016 MASCC and ESMO guideline (Roila et al. 2016).

For instance, the Investigator can consider the following regimen:

Day of cisplatin administration (Day 1 of cisplatin = Day 2 of each treatment cycle):

- 5-HT_3 serotonin receptor antagonists i.v., at the appropriate antiemetic dose for highly emetogenic regimens. If ondansetron is used with xevinapant/matched placebo, participant should be monitored closely (see also Section 6.5.2).
- Dexamethasone: 12 mg or any other corticosteroid at an equivalent dose orally (to be taken 30 minutes prior to chemotherapy).
- Aprepitant: oral 125 mg at least 30 minutes prior to infusion.

Day 2-3 after cisplatin administration: Dexamethasone 8 mg + aprepitant 80 mg/day ± 5-HT_3 serotonin receptor antagonist

Day 4 after cisplatin administration: Dexamethasone 8 mg

For participants receiving carboplatin, antiemetic therapy including dexamethasone (or any other corticosteroid at an equivalent dose i.v.) and 5-HT_3 serotonin receptor antagonists may be administered as per 2016 MASCC and ESMO guideline (Roila et al. 2016).

Note: Dose and schedule of dexamethasone coupled with its wide availability in various forms established it as the agent of choice in the 2016 MASCC and ESMO guidelines. If an equivalent dose of corticosteroids is used according to institutional guidelines, the risk of increased toxicity to corticosteroids should be carefully monitored. Elevations of plasma levels may be triggered by xevianapant inhibition of CYP3A4.

6.5.1.2. SARS-CoV-2 Vaccination

In case a participant is to be vaccinated for SARS-CoV-2 during the study treatment period, the following actions should be considered:

- Administer only approved vaccines.
- Consider choosing an appropriate type of SARS-CoV-2 vaccine for the participant and consult with an infectious disease expert if desired.
- Non-replicating viral vector-based vaccines and mRNA-based vaccines are not considered live-attenuated vaccines (exclusion criterion #9) and can be administered during the study.
- If possible, choose the right time for the vaccination avoiding administering the dose of SARS-CoV-2 vaccine during the leukocytes nadir periods due to the chemotherapy.
- Report all SARS-CoV-2 vaccine name, and if available, the batch number on the ConMed page in eCRF.

6.5.2. Medications to be Used with Caution with Xevinapant or Matched Placebo

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI [redacted]

[redacted].

6.5.3. Prohibited Concomitant Medications

6.5.3.1. Prohibited Medications with Xevinapant or Matched Placebo

Live-attenuated vaccinations during treatment with xevinapant/matched placebo and up to 90 days after the end of treatment are prohibited.

Other preparations and medications such as those listed below are strictly prohibited in combination with xevinapant or matched placebo.

6.5.3.1.1. Food and Herbal Preparations

Grapefruit juice and grapefruit-containing products (P-gp inhibitors) may lead to increased xevinapant exposure.

St John's Wort (= *Hypericum perforatum*, millepertuis) and St John's Wort-containing products (P-gp inducers) may lead to decreased xevinapant exposure.

CCI [redacted]

[redacted]

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[redacted]	
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6.5.3.2. Recombinant Human Erythropoietin and Derivates

Recombinant human erythropoietin (EPO) is not allowed throughout the entire duration of the study.

Preclinical and clinical studies showed that autocrine or paracrine erythropoietin signaling can enhance cancer invasion in SCCHN and negatively affects patient outcome in terms of OS and local-regional PFS (Henke et al. 2003; Lambin et al. 2009).

To investigate whether EPO signaling might play a direct role in SCCHN progression, Mohyeldin A. et al examined the immunohistochemical expression of EPO and EpoR proteins in biopsy samples obtained from oral cavity, oropharyngeal, hypopharyngeal, and laryngeal lesions of patients not previously treated with recombinant human EPO (Mohyeldin et al. 2005). The analysis revealed high levels of both EPO and EpoR expression in the carcinomas examined. In normal tissues, EpoR staining was low and limited to the basal epithelial layer. Strong EpoR staining was seen throughout the dysplastic epithelium, in invasive carcinoma cells, and in lymph node metastases.

6.5.3.3. Prohibited or Concomitant Use of Traditional Chinese Medicines

Any traditional Chinese medication with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted during study treatment. Traditional Chinese medicines for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator. Any traditional Chinese medicines or herbal supplement, if known to be strong inhibitors/inducers of CYP3A4 or inhibitors of P-gp, will not be permitted. Use of traditional Chinese medicines as part of next line of anticancer treatment should be documented as such.

6.5.3.4. Prohibited Medications and Medications to be Used with Caution with Cisplatin or Carboplatin

Prohibited medications

Platinum-based cytotoxic agents may reduce the digestive absorption of phenytoin and fosphenytoin, resulting in reduced epilepsy control and risk of exacerbation of convulsions. Therefore, both phenytoin and fosphenytoin are prohibited during the combination therapy period.

Granulocyte-Colony Stimulating Factors (G-CSF) are not allowed throughout the screening period and for prophylaxis. Nevertheless, for participants presenting with febrile neutropenia who have risk factors for infection-related complications or poor clinical outcome, therapeutic G-CSF including secondary prophylaxis should be considered (Becker et al. 2020). Features associated with poor outcome include age >65 years, sepsis syndrome, ANC <100 neutrophils/m^3, anticipated prolonged (>10 days) neutropenia, pneumonia or other clinically documented infection, invasive fungal infections, and hospitalization at the time of fever.

Medications to be used with caution

Please consult and follow the instructions provided in your local label.

6.5.3.5. Use of Other Investigational Agents and Devices

Treatment with an investigational agent other than xevinapant/placebo, treatment or use of an investigational device within 4 weeks of the first dose of study treatment or during study treatment are prohibited.

6.5.3.6. Use of Anticancer Treatments

Treatment with other anticancer treatments within 4 weeks of the first dose of study treatment or during study treatment is prohibited.

6.5.4. Rescue Therapy and Supportive Care

6.5.4.1. Rescue Therapy

Not applicable

6.5.4.2. Supportive Care

6.5.4.2.1. Nutritional Support

All participants should be screened for nutritional risk and early enteral nutrition. Nutrition status should be evaluated Q3W during the treatment period.

A percutaneous endoscopic gastrostomy or nasogastric tube can be placed prophylactically necessary depending on the participant's nutritional status and/or swallowing capabilities according to the Investigator's judgment.

6.5.4.2.2. Dental Care

Patients with head and neck cancers are at risk of oral and dental complications after RT because of treatment-induced xerostomia and salivary gland dysfunction, which are associated with increased dental caries.

In addition, RT to the dental hard tissues is associated with bone demineralization and trismus of the masticatory muscles. Using IMRT and limiting the RT dose to the teeth have been shown to decrease both xerostomia and damage to the teeth (Adam S. Garden 2017; NCCN 2019). Dental/oral evaluation and management can help decrease dental caries and associated problems such as dentoalveolar infection and osteoradionecrosis.

The recommended dental/oral evaluations before, during, and after RT are summarized below.

A dental/oral treatment plan should be implemented before RT and should include the following:

- Eliminating potential sources of infection.
- Performing any dental extractions preferably at least 2 weeks before RT.
- Treating active dental caries and periodontal disease.
- Treating oral candidiasis.
- Educating participants about preventive strategies.

Some of the strategies to decrease oral and dental complications include:

- Decrease dry mouth (e.g., by using salivary substitutes and stimulation).
- Decrease dental caries (e.g., by using topical fluoride).
- Decrease dentoalveolar infection (e.g., with frequent evaluations to detect and treat disease promptly).
- Decrease osteoradionecrosis (e.g., by extracting teeth before RT).

- Decrease trismus of the masticatory muscles (e.g., by using custom mouth-opening devices to maintain range of motion).
- Have participants undergo evaluations during and after treatment to help minimize complications.

During and after treatment, the goals of dental/oral management include:

- Managing xerostomia.
- Preventing trismus.
- Detecting and treating oral candidiasis.

Additional goals after treatment include:

- Preventing and treating dental caries.
- Preventing post-radiation osteonecrosis.
- Preventing oral candidiasis.

Dental/oral evaluation can be performed by the dental clinic team of the site or by an external dentist.

6.5.4.2.3. Pain

The management of pain should be done according to severity and recommended drugs as per institutional guidelines. Please, review Table 6-5 before using concomitant medications.

7. STUDY INTERVENTION DISCONTINUATION, END OF STUDY AND EARLY STUDY TERMINATION

7.1. Study Intervention Discontinuation

Study treatments (i.e., xevinapant/matched placebo, cisplatin/carboplatin and IMRT) must be discontinued under the following circumstances:

- Disease progression, including clinical progression as judged by the Investigator, treatment failure, local or distant relapse, second cancers, or start of any new anticancer treatment including salvage surgery (see EFS definition in Table 3-1 for further details).
- Participant withdrawal of consent for treatment.

  Participants may voluntarily withdraw consent at any time. If such withdrawal occurs, every effort should be made by the Investigator to determine the primary/underlying reason for this decision, which should be recorded in the EOT eCRF. The participant should be encouraged to remain on study to be followed for survival and/or efficacy assessments.
- Unacceptable toxicity/AEs, that result in a significant risk to the participant's safety.

  Participants who are removed from study treatment due to AEs are to be treated and followed up for these AEs according to standard medical practices.

- Any protocol deviation that results in a significant risk to the participant's safety.
- Pregnancy.
- Investigator decision in the participant's best interest.

  The primary reason for this decision (e.g., lack of efficacy, AE) must be recorded in the eCRF.
- Early study termination by the Sponsor, Steering Committee, the Investigator, the IEC/IRB or the Regulatory Agencies (Section 7.4).

7.2. End of Study

The EOS will be triggered once 386 OS events are observed or the last on-study participant has reached his/her 60-months post-randomization visit. At this timepoint (± 2 months), all participants who have not previously discontinued from the study prematurely will undergo the EOS assessments and will be considered as having completed the study.

7.3. Premature Study Withdrawal (Participant Level)

Premature withdrawal from the study can be triggered by:

- Participant withdrawal of consent for study participation.

  Participants may voluntarily withdraw consent at any time. If such withdrawal occurs, every effort should be made by the Investigator to determine the primary/underlying reason for this decision and that should be recorded as reason in the End of Study eCRF i.e., if the underlying reason for the decision is toxicity (e.g., AE) this should be recorded as such and the Investigator has to follow up the participant until the AE or SAE is resolved.
- At the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons (e.g., disruption of operations due to natural disasters, interruption of laboratory or facility accreditation, participant moving to another country, resignation of key staff).

  The primary reason for this decision must be recorded in the CRF.
- Participant lost to follow-up (Section 7.5).
- Death.
- Early study termination by the Sponsor, Steering Committee, the Investigator, the IEC/IRB or the Regulatory Agencies (Section 7.4).

Should a participant be withdrawn from the study, EOS assessments should be performed prior to any further therapeutic intervention whenever possible. Results of these assessments are to be recorded in the eCRF, together with a description of the reasons for study discontinuation.

7.4. Early Study Termination by the Sponsor, Steering Committee, the Investigator, the IEC/IRB or the Regulatory Agencies

The study may be prematurely terminated by the Sponsor, Steering Committee, the Investigator, the IEC/IRB or the Regulatory Agencies at any time, for the following reasons:

- Medical or ethical reasons impacting the continuation of the study.
- Difficulties in recruiting participants.
- Ineffectiveness of the study medication.
- Onset of adverse reactions of investigational drug that are unacceptable and unknown to date with regards to their nature, severity and duration; or an unexpected incidence of any unacceptable adverse reaction.
- Business reasons.

If the study is prematurely terminated, the Investigator must promptly inform the study participants and ensure that they receive appropriate therapy and follow-up. All assessments described in Section 7.1 for premature withdrawal of the participant should be followed. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests.

The Investigator will be responsible for informing the IRB and/or IEC of the early termination of the study. If the IEC/IRB terminates the study or suspends its approval, the Investigator should promptly inform the Sponsor and provide a detailed written explanation of the termination.

Please refer to Section 7.3 for study discontinuation at the participant level.

7.5. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for the EOS assessments within the permitted EOS visit window and is unable to be contacted by the study site staff.

The site should make every effort to regain contact with the participant and reschedule the missed visit as quickly as possible. These contact attempts should be documented in the participant's medical record or study file. Participants lost to follow-up will not be replaced.

7.6. Participant Replacement

Participants will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Please refer to Section 1.3, Table 1-1 and Table 1-2 for the schedule of assessments. It may be necessary to perform these assessments at unscheduled timepoints if deemed clinically necessary by the Investigator.

8.1. Screening Procedure

Once a participant has signed the ICF (see Section 11.1.1), an identification number will be assigned to him/her and the study related screening procedures will start. The screening period will last up to 28 days before the start of the treatment (C1D1).

Protocol waivers or exemptions are not allowed.

A participant will be randomized into the study after he/she has signed the ICF, all eligibility criteria have been met and the IMRT plan has been sent to the RT-QA Review Center (see Section 11.2.2). The IMRT plan must be approved by the RT-QA Review Center prior to the start of the IMRT.

The central laboratory assessments needed for participant eligibility are specified in Table 8-2. Local laboratory results only for HBV/HCV/HIV tests (obtained within 2 weeks before ICF signature) and HPV status (also see Section 8.1.2) may be accepted if report is available. If the previous central laboratory results are older than 7 days, the hematologic, renal and hepatic laboratory assessments should be rechecked by a local laboratory before the first dose administration.

No participant replacement will be allowed. All randomized participants will be included in the Intent-to-treat (ITT) population.

8.1.1. Baseline Disease Characteristics and Assessments

Baseline participant and disease characteristics will be assessed during the 28-day screening period.

The following should be performed prior to randomization to confirm eligibility and disease staging: demographics, vital signs, physical examination, weight, height, ECOG performance status (ECOG PS), ECG, nutritional status, dental examination, audiometry, coagulogram, laboratory tests (see Section 8.3.7 for further details), ^{18}F-FDG-PET, i.v. contrast-enhanced CT-scan or MRI of head and neck, CT-scan of chest, and fiberoptic endoscopy.

Medical history includes tobacco and alcohol consumption history and habits.

Tumor staging should be established using the AJCC/TNM Staging System, 8th Ed., based on radiological imaging. Please refer to Section 8.2.1 for further details on radiological imaging.

If several ECGs (scheduled and unscheduled) are performed during the screening, the most recent results should be recorded in the eCRF.

^{18}F-FDG-PET, i.v. contrast-enhanced CT-scan or MRI of head and neck, and CT-scan of chest are only accepted if they are performed within 4 weeks before randomization. Dental examination, audiometry, HBV/HCV/HIV tests, and fiberoptic endoscopy performed within 2 weeks before ICF signature do not have to be repeated during screening.

Results from the central laboratory should be used for defining participant eligibility during screening, except for:

- HBV/HCV/HIV tests that may be performed by a local laboratory within 2 weeks before ICF signature (see Section 8.3.7).
- HPV status by p16 IHC that may be obtained locally (see Section 8.1.2).

8.1.2. HPV Status in Participants with OPC

In participants with OPC, primary tumors must be HPV-negative, determined by p16 IHC.

p16 cutoff for determination of HPV status is defined as following: For HPV status of OPC participants, p16 expression by IHC is scored as positive if a total H-Score ≥ 210 or ≥ 70% of the tumor cells with 3+ staining intensity in nucleus and cytoplasm. H-Score should be calculated by the formula: H = [% weak (1+)x1] + [% moderate (2+)x2] + [% strong (3+)x3].

Results obtained prior to the participant's consent to participation in the study are acceptable, provided a report is available. If no report is available for HPV status by p16 IHC, the assessment can be done locally on an archived tumor sample.

If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central pathology laboratory designated by the Sponsor. In this case, randomization into the study can only occur after confirmation of HPV-negative status has been communicated to the site.

The results of existing local data must be captured on the appropriate eCRF upon enrolment into the study after the participant has signed the ICF.

8.1.3. Highly Effective Contraceptive Measures and Pregnancy Test

To be enrolled in the study women of childbearing potential and men with female partners of childbearing potential must agree to use highly effective contraceptive measure(s) from ICF signature to 6 months after completing chemotherapy treatment or 3 months after last dose of xevinapant/matched placebo, whichever is the latest (see inclusion criteria 11 in Section 5).

Non-sterilized males who are sexually active with a female partner of childbearing potential must agree to use condom and spermicide from ICF signature to 6 months after last administration of chemotherapy or 3 months after last dose of xevinapant/matched placebo, whichever is the latest (see inclusion criteria 11 in Section 5). Because male condom and spermicide is not a highly effective contraception method it is strongly recommended that female partners of male study participants use highly effective contraceptive method(s) throughout this period.

Contraceptive measures which are considered highly effective comprise combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner and sexual abstinence.

If a hormonal contraception is chosen, the use of a barrier method (preferably male condom) is mandatory due to potential risk of CYP3A4/5 induction by xevinapant that may reduce hormonal contraception efficacy.

Abstinence is acceptable only if it is consistent with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of birth control.

Females without childbearing potential, defined as those who are surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are post-menopausal (defined as 12 months with no menses without an alternative medical cause) and have a follicle-stimulating hormone level in the laboratory normal range for post-menopausal phase at screening, do not need a pregnancy test.

Serum pregnancy test (β-HCG) will be conducted during screening by a central laboratory in women of childbearing potential (see Table 8-2). On C1D1, negative serum pregnancy status should be rechecked locally by serum or urine test only if the previous central laboratory result is older than 7 days. After C1D1, serum or urine tests should be performed locally according to schedule presented in Table 1-1 and Table 1-2

Should a pregnancy still occur, all study treatments should be discontinued immediately.

The Sponsor should be notified of any pregnancy that occurs in female participants or partners of male participants during participation in studies with xevinapant by submitting a specific pregnancy form. Any reports of pregnancy in participants or partners of participants will be followed up as described in Section 9.4.2.

8.2. Efficacy Assessments

Assessment of tumor response to treatment will be assessed locally and centrally according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) but will also take into consideration clinical, anatomopathological, and functional assessments of the tumor, as described in Appendix 13.5.

Tumor assessment and HRQL questionnaires or assessments should be continued until disease progression (as per RECIST v1.1) occurs or Month 60 post-randomization, whichever occurs first.

Participants who progress (as per RECIST v1.1) will enter the OS follow-up period at the time of the event and will be followed up for survival status at least every 3 months, until the EOS (see Section 7.2).

In case of premature discontinuation of treatment in participants without disease progression according to RECIST v1.1 (e.g., unacceptable toxicity), efficacy assessments will continue to be performed until an EFS event has been determined or Month 60 post-randomization, whichever occurs first.

8.2.1. Radiological Assessment

For each participant, the same radiological method for head and neck and for chest must be used throughout the study. The schedule of collection of i.v. contrast-enhanced CT-scan or MRI of head and neck (which cover the orbits), CT-scan of the chest and ^{18}F-FDG-PET scan (from the skull base to the proximal upper legs) is provided in Table 1-1 and Table 1-2.

^{18}F-FDG-PET/CT-scan is preferred to facilitate pre-and post-treatment evaluation of metabolic response and the need for post-treatment neck dissection. If physical examination and imaging suggest residual disease at the primary site, a biopsy will be performed to confirm residual disease; otherwise, participants will undergo serial follow-up.

Additional imaging assessments may be performed at any time during the study at the Investigator's discretion to support the efficacy evaluations for a participant. Clinical progressive disease (PD) is recommended to be confirmed by imaging and/or endoscopy (i.e., biopsy).

If an off-schedule imaging assessment is performed because progression is suspected, subsequent assessments should be performed in accordance with the original imaging schedule.

Measurability of the tumor at baseline

At baseline, participants may be included with measurable disease or with only evaluable, non-measurable disease according to RECIST v1.1 and as assessed by the Investigator. Measurable disease is defined as the presence of at least one measurable nodal or non-nodal lesion. The assessment of participants at baseline according to RECIST v1.1 is covered in Appendix 13.5.

Non-measurable disease means that only non-measurable lesions exist at baseline. Guidance on how participants with only non-measurable disease at baseline will be evaluated for response and progression based on RECIST v1.1 is also defined in Appendix 13.5.

In this study, radiological response confirmation is not required either for partial or complete response.

For the purposes of the primary endpoint and to minimize bias, a BIRC will perform an independent assessment based on all efficacy imaging reading, review of selected clinical data and anatomopathological results.

Hence, all study imaging performed, including any off-schedule imaging performed, and anatomopathological assessments should be submitted to the designated imaging vendor for quality control and review by the BIRC, promptly after acquisition.

8.2.2. Clinical Assessment

All participants will be assessed at the EOT visit (20 [±1] weeks) with clinical/radiological exams on:

- ^{18}F-FDG-PET/CT scans for determining the overall clinical outcomes and the need for nodal dissection (^{18}F-FDG-PET/CT should be ordered before examination under anesthesia with endoscopy, biopsies, and tonsillectomy, to help identify potential primary sites before any intervention occurs).
- Ear, nose and throat, and fiberoptic endoscopy.

These clinical assessments are to be performed according to the schedule presented in Table 1-1 and Table 1-2

If the EOT scan was positive AND the participant underwent salvage surgery and END, no further ^{18}F-FDG-PET scans should be performed. If EOT results were inconclusive AND the participant did not undergo salvage surgery and END, the ^{18}F-FDG-PET scan should be repeated 12 weeks after EOT (Week 31±2weeks).

Clinical PD must be verified by imaging and/or biopsy, wherever possible. The presence or absence of residual viable tumor cells will be determined via a histopathological examination.

Negative ^{18}F-FDG-PET at baseline, with a positive ^{18}F-FDG-PET at EOT is a sign of PD based on a new lesion if considered related to the disease under study (a confirmatory biopsy should be performed whenever possible). Further details of the interpretation of ^{18}F-FDG-PET in this study are supplied in Appendix 13.5.

In case of doubt of a clinical local-regional recurrence or distant metastasis before the EOT, imaging by CT/MRI scan should be performed to verify disease progression.

During the follow-up period the participants will undergo ear, nose and throat examination, fiberoptic endoscopy and MRI and/or chemotherapy as per the schedule presented in Table 1-2.

Clinical assessment process:

If the primary site is cleared of residual disease but residual disease at the cervical nodal basin is suggested by imaging/clinical evaluation, then END will be performed unless a cytologic sampling of the node is negative. Post-treatment “planned” neck dissection will be defined as being performed for residual disease and before 22 weeks after randomization.

Positive neck specimens removed before 22 weeks after randomization will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection at 22 weeks and beyond will be considered regional failures.

Such post-treatment consolidation neck dissections will encompass only the areas initially involved in the side of the neck in question (typically the involved area(s) and the adjacent immediate level). The extent of neck dissections performed for nodal recurrence, nodal progression, or salvage of disease at the primary will be determined by the treating surgeon.

Any treatment intervention in relation to the disease under study, including biopsies, END or surgery on the primary tumor as well as the anatomical site(s) and histopathology results must be reported in the eCRF.

If histopathology results or other clinical data are not consistent with the radiology report, then this information will be taken into account for the determination of tumor status according to the decision tree below (Figure 8-1).

8.3. Safety Assessments

Safety assessments will be performed according to the schedule in Table 1-1 and Table 1-3 and are further described below.

8.3.1. Physical Examination

The examination will include general appearance, sclera, cardiovascular system, pulmonary system, neurologic system, skin and gastrointestinal system. Abnormalities are to be recorded as medical history if started prior to the ICF signature or as an AE if started on or after ICF signature.

8.3.2. Vital Signs and ECOG Performance Status

Weight (to the nearest 0.1 kilogram or pound), height, ECOG performance score (see Appendix 13.1) and vital signs will be collected. Height will be measured at screening only.

Vital signs will include systolic/diastolic blood pressure (in sitting position after 10 minutes of supine rest), heart rate (after 10 minutes of supine rest), respiratory rate, and temperature.

8.3.3. Nutritional Status

Swallowing/nutritional status is to be done to determine if nasogastric tube, percutaneous endoscopic gastrostomy, or percutaneous endoscopic jejunostomy tube placement is needed.

An examination under anesthesia is recommended, including a direct laryngoscopy, bronchoscopy, esophagoscopy, and nasopharyngoscopy. At this point a biopsy can be taken if not yet readily available and if necessary.

A feeding tube is strongly recommended if the participant has swallowing disorders and / or weight loss. A feeding tube is mandatory if the participant has grade 3 dysphagia.

8.3.4. Dental Examination

A dental examination is to be performed by the site's dental clinic team according to institutional guidelines or by an external dentist (see Section 6.5.4.2.2).

8.3.5. Audiometry

An audiometry must be performed at screening. In addition, hearing clinical evaluation and audiometry should be performed at C2D1 and C3D1 if clinically indicated (except for France, see Appendix 13.6) and at any time if clinically indicated as per institutional or national guidelines. During the follow-up period, an audiometry is to be performed only if clinically indicated, as per institutional or national guidelines.

8.3.6. Electrocardiograms

A standard single 12-lead ECG will be recorded after 10 minutes of supine rest according to the schedule shown in Table 8-1.

Table 8-1 ECG collection plan

Study visit or cycle	Day	Time relevant to dosing
Screening	-28 to -1	n.a.
Cycle 1	1	Predose[a]
		0.5-2 hours postdose[b]
		4-6 hours postdose
	8	Predose[a]
		0.5-2 hours postdose[b]

n.a.: not applicable.

a To be performed prior to blood sampling.

[redacted]

If several ECGs (scheduled and unscheduled) are performed during the screening, the latest results should be recorded and used.

If ECGs are performed at the same time point as blood sampling (C safety laboratory tests), ECG readings should be taken prior to C sampling.

All ECG readings will be performed locally by the Investigator, or a cardiologist will be consulted if clinically indicated.

Additional ECGs can be performed if clinically indicated.

Abnormal ECG findings

In case of **abnormal** ECG findings (e.g., QTcF prolongation >30 ms compared to baseline, or QTcF interval >500 milliseconds, Torsade de pointes, ventricular tachycardia, ventricular fibrillation, flutter or any other new cardiac abnormality), triplicate ECG readings will be performed. If the abnormal ECG finding is confirmed after triplicate ECG readings, the participant should be referred to a local cardiologist.

Significant QTcF prolongation is defined as an interval >500 milliseconds (ms) or an interval which increases by 60 ms over baseline.

Management of participants with significant QTcF prolongation

If the QTcF prolongation is confirmed by **either** criterion (i.e., QTcF interval >500 ms **or** >60 ms increase from baseline) the following actions will be taken (see also Table 6-1):

- The treatment with xevinapant/matched placebo must be interrupted.
- The participant will be monitored including assessment of electrolytes in plasma (potassium calcium and magnesium), treated appropriately and closely followed (ECGs at least 3 times per week) until resolution to within 30 ms from baseline or QTcF <480ms.
- Stop any concomitant medication known to cause QTc prolongation.
- The participant will be referred to a cardiologist.
- The medical monitor will be consulted prior to administering further xevinapant/matched placebo doses.
- If the QTcF interval does not return to within 30 ms of baseline or <480 ms within 14 days, xevinapant/matched placebo must be permanently discontinued.
- For cisplatin/carboplatin, at the first occurrence, action taken for these agents is based on the Investigator's judgment. At the second occurrence, consider permanent discontinuation.

If the prolongation is confirmed by **both** criteria (i.e., QTcF interval > 500 ms **and** > 60 ms increase from baseline) the following actions will be taken:

- The treatment with xevinapant/matched placebo and cisplatin/carboplatin must be permanently discontinued.
- The participant will be monitored including assessment of electrolytes in plasma (potassium calcium and magnesium), treated appropriately and closely followed (ECGs at least 3 times per week) until resolution to within 30 ms to baseline.
- Stop any concomitant medication known to cause QTc prolongation.
- The participant will be referred to a local cardiologist.

8.3.7. Laboratory Tests: Hematology, Biochemistry, Urinalysis, Pregnancy Tests

Laboratory assessments and pregnancy test should be performed by a central laboratory designated by the Sponsor and/or by a local laboratory, according to instructions in Table 8-2 below.

These laboratory assessments are to be performed according to the schedule presented in Table 1-1 and Table 1-2

On C1D1, hematologic, renal and hepatic laboratory assessments required for inclusion (see criteria 9 -Section 5), and for defining suitability for cisplatin administration (see Table 8-2 and Section 6.1.2.2) should be assessed by a central laboratory. If the previous central laboratory results are older than 7 days, the hematologic, renal and hepatic laboratory assessments should be rechecked by a local laboratory before the first dose administration.

On C1D1, negative serum pregnancy status should also be rechecked locally by serum or urine test only if the previous central laboratory result is older than 7 days.

On C2D1 and C3D1, suitability for chemotherapy administration (see Table 8-2 and Section 6.1.2.2) should be evaluated based on local laboratory values irrespectively of the samples sent to the central laboratory.

Renal function must be monitored 48 hours (±12 hours) after cisplatin infusion (i.e C1D4, C2D4, C3D4) based on local laboratory values of creatinine, eGFR, sodium, potassium, calcium, and magnesium.

The initial pregnancy test should be performed on serum during screening period by a central laboratory (Table 8-2 and Section 8.1.3). Subsequent pregnancy tests will be performed locally using urine or serum according to the schedule in Table 1-1 andTable 1-2, or if clinically indicated.

Table 8-2 Assessments to be performed by a central laboratory or by a local laboratory according to study visit

Visit	Central laboratory designated by the Sponsor	Local laboratory
During screening	○ HBV/HCV/HIV tests if no local results obtained within 2 weeks before ICF signature ○ HPV status by p16 IHC if no available report and test not available locally ○ Blood hematology (Table 8-3) ○ Blood biochemistry (Table 8-3) ○ Serum pregnancy test ○ Urinalysis (Table 8-3)	○ Local results within 2 weeks before ICF signature accepted for HBV/HCV/HIV tests ○ HPV status by p16 IHC if no available report

Visit	Central laboratory designated by the Sponsor	Local laboratory
C1D1	All hematology and biochemistry assessments (full panel) mentioned in Table 8-3.	The following assessments should be performed locally if the previous central laboratory results are older than 7 days: ○ Laboratory assessments specified in inclusion criteria 9 and assessments required to evaluate suitability for cisplatin: eGFR, ANC, platelet counts, hemoglobin, AST, ALT, total bilirubin ○ Serum or urine pregnancy test If central laboratory assessments for eGFR, ANC, platelet counts, hemoglobin, AST, ALT and total bilirubin were performed within 7 days before C1D1, they should not be repeated locally on C1D1.
C2D1 and C3D1	○ All hematology and biochemistry assessments (full panel) mentioned in Table 8-3. ○ Coagulogram (Table 8-3) ○ Urinalysis (Table 8-3)	○ Laboratory assessments required to evaluate suitability for chemotherapy administration: eGFR, platelet counts, ANC, hemoglobin rate ○ Serum or urine pregnancy test
All visits after randomization, except C1D1; C2D1 and C3D1	Hematology, coagulogram, blood chemistry and urinalysis assessments (Table 8-3), to be performed according to schedule presented in Table 1-1 and Table 1-2	Serum or urine pregnancy test
Renal function monitoring 48 hours (±12 hours) after cisplatin infusion (C1D4, C2D4, C3D4)	n.a.	Creatinine, eGFR Sodium, potassium, calcium magnesium

Abbreviations: ALT: alanine aminotransferase; **ANC:** absolute neutrophil count; **AST**: aspartate aminotransferase; **CxDx**: cycle x Day x; **eGFR:** estimated glomerular filtration rate; **HBV**: Hepatitis B virus; **HCV**: Hepatitis C virus; **HIV**: Human immunodeficiency virus; **HPV**: human papillomavirus; **ICF:** informed consent form; **IHC**: immunohistochemistry; **n.a.**: not applicable.

Blood samples for hematology, biochemistry and coagulogram assessments should be taken before treatment administration., Blood sample for coagulogram should be collected C [redacted] (see schedule of relevant visits in Table 1-1).

Details on all laboratory procedures, collections, shipment of samples and reporting of results, alerting of extreme values and notable values by the central laboratory are provided to Investigators in the laboratory manual of extreme values.

The Investigator is responsible for reviewing all laboratory reports for participants during the study and evaluating any abnormalities for clinical significance.

If a local laboratory is used, the local laboratory values will have to be recorded on the Local Laboratory Results eCRF if clinically significant.

Furthermore, local laboratory assessments may also be performed according to medical needs (e.g., during medical emergencies, or for treatment-related decisions, etc.) when the Investigator needs quick results to make treatment decisions.

Clinically significant laboratory abnormalities occurring since the ICF signature are to be recorded in the eCRF as AEs.

Further details on sample collection, handling and shipment will be provided in the laboratory manual.

Table 8-3 Assessments to be performed by a central laboratory designated by the Sponsor

Virology	HBV: HBV sAg and Anti-HepB core IgG HCV: HCV-antibody and HCV-RNA by PCR HIV1/2	
Hematology	White blood cell count (total and differential) Red Blood cell count, Hemoglobin Platelet count ANC	
Coagulogram	Prothrombin Time or INR, if applicable (e.g., under oral anticoagulation medication) Activated partial thromboplastin time Fibrinogen	
Blood Biochemistry (full panel)	Creatinine and eGFR[a] Total protein Albumin Total bilirubin (If >ULN: direct bilirubin should also be measured) ALP AST ALT C-reactive protein	Amylase Lipase Sodium Potassium Calcium Magnesium Urea Uric acid
Blood Biochemistry (minimum panel)	Creatinine Total bilirubin (If >ULN: direct bilirubin should also be measured) ALT AST ALP	Sodium Potassium Amylase Lipase Urea
Urinalysis	Dipstick test for:	
	Red blood cells Protein Glucose	Leucocytes Ketones
Pregnancy test	Serum pregnancy test (β-HCG) during screening in women of childbearing potential, local serum or urine tests thereafter.	

Abbreviations: ALP: alkaline phosphatase; **ALT:** alanine aminotransferase; **ANC:** absolute neutrophil count; **AST**: aspartate aminotransferase; **β-HCG**: Human chorionic gonadotropin; **eGFR**: estimated glomerular filtration rate; **HBV**: hepatitis B virus; **HCV**: hepatitis C virus; **HIV**: human immunodeficiency virus; **INR**: International normalized ratio; **sAg:** surface antigen**; ULN**: upper limit of normal.

a eGFR should be calculated using the using the Chronic Kidney Disease - Epidemiology Collaboration [CKD -EPI] creatinine formula.

8.3.8. Participant Diary

Xevinapant/matched placebo will be dispensed by the medical staff or Pharmacist of the investigational sites. The participant will receive xevinapant or the matched placebo on an outpatient basis.

On days C [redacted] C1D2, C1D8, C2D2, C3D1, C3D2, participants should take their doses at the hospital, where the administration of xevinapant or the matched placebo will be supervised and recorded by the medical staff both in the eCRF and in the participant's diary. In addition, the time of C1D7 dose taken at home needs to be recorded in both the eCRF and the participant's diary. On days C [redacted], at C3D8 and C4D1, xevinapant/placebo is taken, and the time of dosing (C3D8 and C4D1) must be recorded both in the eCRF and the participant's diary. On C3D15, the last xevinapant/placebo dose timing (taken at home on C3D14) must be recorded both in the eCRF and the participant's diary.

The treatment schedule of xevinapant or the matched placebo is presented in Table 1-1 and Table 1-2. Participants will be instructed by the medical staff on how to self-administer xevinapant or the matched placebo at home. The participant should inform the medical staff of any missed or delayed doses.

The paper diary will be dispensed to the participants according to the schedule presented in Table 1-1. They will be instructed on how to record xevinapant/matched placebo administration (i.e., date and time of the xevinapant intake should be recorded in the diary).

Participants should record any skipped or miss-timed doses in their diary.

Participants will be asked to bring the diary with them to their study visits. The diary will be collected and reviewed by site staff after the completion of each visit.

8.3.9. Concomitant and Subsequent Neoplastic Medications

Information about prior, concomitant, and subsequent therapies is provided in Section 6.5.

8.3.10. Adverse Event Monitoring

All AEs (including AESIs during the treatment period) will be collected from the time of ICF signature until the EOT visit. From the EOT visit until the EOS visit, only SAEs and late onset AESIs will be collected.

Please refer to Section 9 for further details on AE collection.

8.5. Biological Specimen Collection

8.5.1. Estimated Volume of Blood Samples

For each participant enrolled, the estimated volumes of biological specimens collected during the study is listed in Table 8-4.

Table 8-4 Biological specimens collected during the study

Sample type	Type of assessment	Volume/Size
Blood/plasma	Hematology, biochemistry, pharmacokinetics, pharmacogenetics	180 mL

8.6. Health-Related Quality of Life Assessments

HRQL data will be collected to investigate the effects of xevinapant + CRT on participants' reported well-being compared to placebo + CRT.

The EORTC QLQ-C30 version 3.0, the EORTC QLQ-HN35 [redacted] will be administered electronically:

- The EORTC QLQ-C30 questionnaire captures QoL dimensions that are relevant for oncologic participants independently of the cancer type.
- The EORTC QLQ-HN35 is a disease-specific supplementary module designed to capture dimensions that affect the QoL of head and neck cancer participants.
- [redacted]

Further details on the questionnaires are provided in Appendix 13.4.

Administration of the HRQL questionnaires

[redacted] EORTC QLQ-HN35 and EORTC QLQ-C30 questionnaires will be administered according to the schedule shown in Table 1-1 and Table 1-2 The participant should also complete the EORTC [redacted] questionnaires at the time of progression.

The baseline HRQL assessment should be performed prior to randomization.

Questionnaires should be completed by participants prior to any clinical tumor assessment and/or receiving results of any test, including disease status. Particular attention should be devoted to maximizing compliance.

A nominated person in each center must be assigned to take responsibility for administration of HRQL forms. Participants should receive a short electronic training at screening, before completing the questionnaires. Participants should complete the questionnaires in a quiet, private area and any form of influence on their answers (e.g., conferring with friends, relatives, study personnel) should be avoided in order to ensure participant's privacy and absence of bias.

Completion of all 3 questionnaires is expected to take less than 25 minutes in total.

9. ADVERSE EVENTS

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

Investigators will seek information on AEs at each safety evaluation. All AEs whether reported by the participant or noted by authorized study personnel, will be recorded in the participant's medical

record and on the AE CRF. Their nature, severity, duration, and treatment, together with the Investigator's opinion as to their relationship to the drug, will be recorded. The Investigator will also indicate how the signs of the condition evolved.

As needed, Sponsor may ask for copies of certain medical records (e.g. autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation associated to AEs. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor.

9.1. Definitions and Assessment Criteria

9.1.1. Definition of Adverse Events

The ICH Guidelines for GCP E6 (R1) defines an AE as: Any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Thus, any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit should be considered as an AE, except if considered as associated with the underlying disease (for more details, see the paragraph below “Events that do not meet the definition of an AE”).

Any abnormal laboratory test results or other safety assessments such as ECG findings, vital sign measurements), including those that worsen from baseline, and assessed to be clinically significant in the medical and scientific judgment of the Investigator, should be reported as an AE. Abnormal laboratory values that require an intervention such as a treatment or a change in the study treatment should also be reported as an AE.

If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, urine red blood cell count increased).

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal finding or other abnormal safety assessment that is associated with the underlying study disease, disease progression/recurrence unless judged by the Investigator to be more severe than expected for the participant’s condition.
- Diagnostic testing and procedures: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures should not be reported as AEs or SAEs.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Lack of efficacy is not considered as an AE.

9.1.2. Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect in offspring of the participant.
- Is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether or not expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note: Inpatient hospitalization is considered to have occurred if the participant has had to stay overnight at the hospital.

The criterion for prolongation of hospitalization is also defined as an extra night at the hospital than planned. Hospitalization may not constitute sufficient grounds to be considered as a SAE if it solely for the purpose of diagnostic tests (even if related to an AE).

Pre-planned hospitalization: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if an event occurs during the pre-planned hospitalization that prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level.

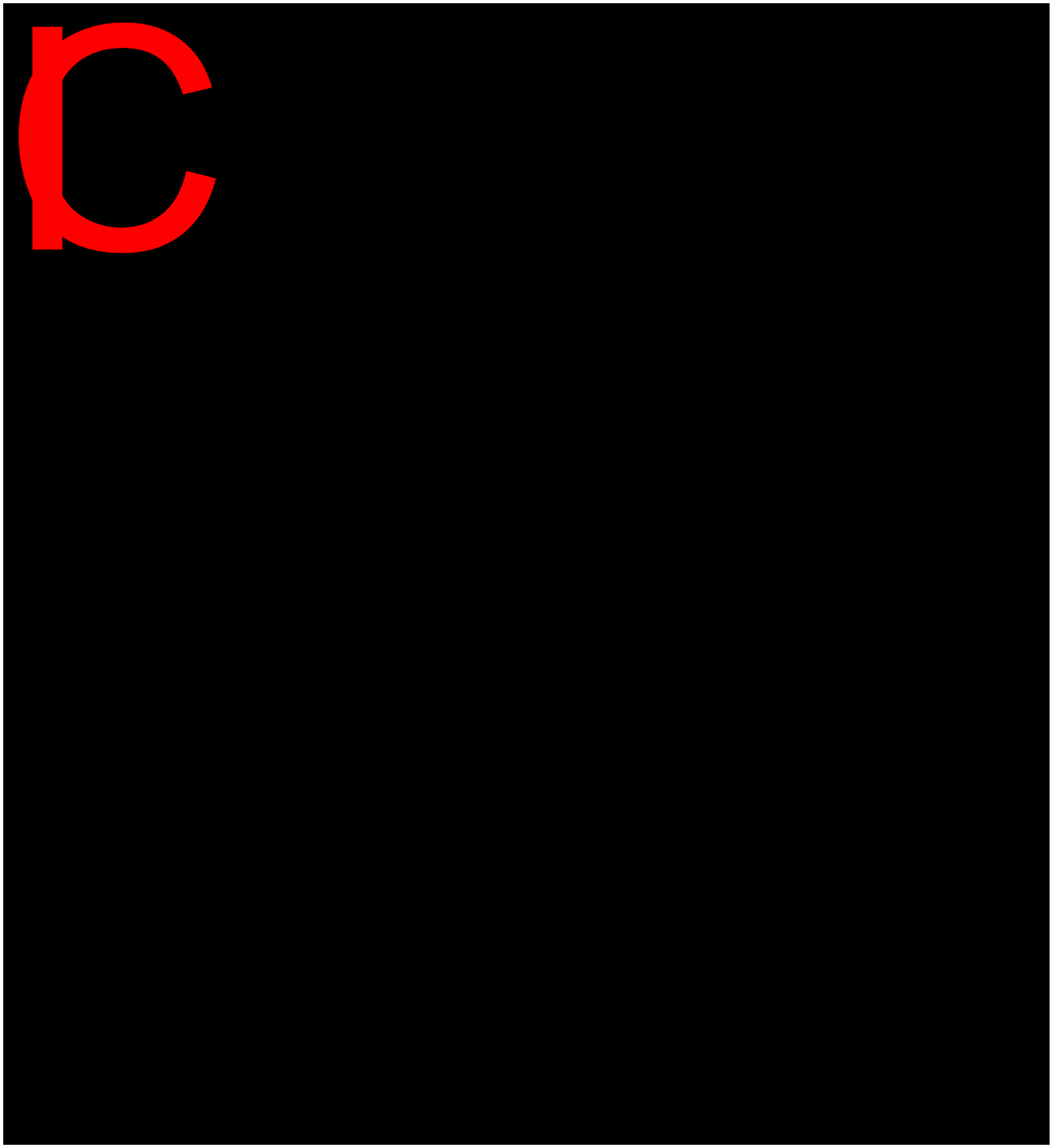
Social admissions: hospitalizations for social reasons, for example, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

9.1.3. Definition of Adverse Events of Special Interest

An AESI is a noteworthy event of the particular study treatments (xevinapant/placebo, chemotherapy and IMRT) that can be appropriate to monitor closely. An AESI may be serious or non-serious and an AESI could include events that might be potential precursors or prodromal symptoms for more serious medical conditions in susceptible individuals.

The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the study treatment administration (xevinapant/placebo, chemotherapy and IMRT).

All AESIs during the treatment period should be recorded promptly in the eCRF. In addition, AESIs that are also SAEs should be reported to the Sponsor within 24 hours.



9.1.4. Definition of Adverse Event Reporting Period

All AEs (including AESIs during treatment period) will be collected from the time of signature of ICF until the EOT visit. From the EOT visit until the EOS visit, only SAEs and late onset AESIs will be collected.

9.1.5. Assessment of Relationship with Study Treatment(s)

The Investigator or designee will determine the relationship between the AE and each study treatment according to the guidance below.

Table 9-1 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the study treatments (xevinapant/placebo, chemotherapy, and IMRT) based on facts, evidence, science-based rationales, and clinical judgment?	
Reasonable causal relationship	The temporal relationship of the AE/SAE to **study treatment** administration **(xevinapant/placebo, chemotherapy and IMRT)** makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
No reasonable causal relationship	The temporal relationship of the AE/SAE to **study treatment** administration **(xevinapant/placebo, chemotherapy and IMRT)** makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Abbreviations: AE: adverse event; **IMRT:** intensity-modulated radiotherapy; **SAE:** serious adverse event.

The Investigator's assessment of causality for individual AE reports is part of the study documentation process.

Regardless of the "Yes" or "No" causality assessment for individual AE reports, Sponsor or designee will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable Regulatory Authorities.

9.1.6. Assessment of Severity of Adverse Events

AEs will be graded by the Investigator according to NCI-CTCAE, v5.0 criteria. The alternative definitions for grade 1, 2, 3, and 4 events mentioned in Table 9-2 should be used when the observed or reported AE is not in the NCI-CTCAE classification.

Table 9-2 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternative Description
1	Mild	Awareness of sign or symptom, but easily tolerated; Transient or mild discomfort (<48 hours); no interference with the participant's daily activities; no medical intervention/therapy required.
2	Moderate	Discomfort enough to cause mild to moderate interference with normal daily activities; No or minimal medical intervention/therapy required.
3	Severe	Considerable interference with the participant's daily activities; medical intervention/therapy required; hospitalization possible.
4	Very severe, life-threatening or disabling	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable.
5	Death related to adverse event	

9.2. Procedures for Recording Adverse Events

All AEs, whether expected or not, should be recorded immediately in the source document, and described on the AE form of the eCRF.

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the CRF. Avoid colloquialisms and abbreviations. There is one eCRF for recording AEs or SAEs. Only one medical concept should be recorded in the event field on the Adverse Event CRF.

9.2.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases).

However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE in the CRF. If it is an SAE, each individual event should be reported on a separate form. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.2.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE in the CRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events in the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

9.2.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between participant evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event CRF.

A recurrent AE is one that occurs and resolves between participant evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the Adverse Event CRF.

9.2.4. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require a treatment, study drug to be held or discontinued, more frequent follow-up assessments, further diagnostic investigation, etc.). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

9.2.5. Deaths

All deaths occurring during the study will be reported on the death page of the eCRF.

Deaths that are attributed by the Investigator as solely due to disease progression (death due to cancer under study) are not considered as SAEs. Conversely, medical events leading to death should be reported as SAEs if they cannot be determined to be exclusively due to the progression of the cancer under study or if they do not correspond to the expected pattern of progression of the disease under study.

All other deaths are considered SAEs. They will be recorded on both the Death and SAE page of the eCRF:

- The SAE verbatim term of the event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept.
- If the cause of death is unknown and cannot be ascertained at the time of reporting, the verbatim term "Unexplained Death" should be recorded.
- The Investigator must notify all other deaths within 24 hours of awareness (refer to Section 9.3).

9.3. Procedure for Reporting Serious Adverse Events to the Sponsor

Notification of SAEs until the EOS visit will not depend on their relationship with study treatments: all SAEs and Serious Adverse Reactions (SARs) will be recorded until the EOS visit or until the study discontinuation/termination, whichever is the latest.

The Investigator must notify the Sponsor **of all SAEs within 24 hours of awareness** by completing the AE form provided in the eCRF. Once the AE is selected as a SAE and the form is saved in the eCRF, an email notification will be sent automatically to the Sponsor's Pharmacovigilance department. If for any reason the eCRF is not available, as a backup option, the SAE can be declared by email at SafetyReporting@SyneosHealth.com using the paper "SAE report form".

If for any reason, the eCRF and email are not available, the paper "SAE report form" can be sent by fax to +**1-877-464-7787** with the provided fax cover page entitled "Serious Adverse Event Report transmittal form".

Email and fax reporting should be followed by the completion of the AE form in the eCRF as soon as possible.

The processes are fully described in separate guidelines and will be provided to Investigators with the protocol.

9.3.1. Follow-up of Serious Adverse Events

All SAEs, regardless of severity, must be followed up:

- To resolution (the participant's health has returned to the baseline status or all variables have returned to normal),

  or

- Until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event),

  or

- Until the event is otherwise explained regardless of whether the participant is still participating in the study.

Some events, such as metastases, are often ongoing; however, once these events have been determined by the Investigator to be stable or chronic, he/she may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor of any follow-up information in the eCRF page within 24 hours of new information awareness.

Any AEs that are unresolved at the participant's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF.

Sponsor or designee retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.3.2. Procedure for SAE Communication

If required by applicable local regulations, the Investigator will promptly notify the relevant IRB/IEC (in addition to the Sponsor) of any SAE (including post-study SAEs and follow-up information) that occurred at their site or was brought to their attention by the Sponsor. The Investigator will verify that the IRB/IEC acknowledges receipt of the notification.

In case of Suspected Unexpected Serious Adverse Reaction (SUSAR), unusual increase in the frequency of the severity of expected SAEs or new safety data which could have an impact on the overall expectedness of Serious Adverse Reaction or change in the safety profile of the study treatment(s) that require the informed consent to be updated, the Sponsor will prepare a safety report according to regulatory requirements relating to safety reporting.

This report will be communicated by the Sponsor to all Investigators involved in clinical studies with xevinapant.

9.4. Other Events Requiring Immediate Reporting

9.4.1. Overdose

For this study, an overdose is defined as follows:

- For xevinapant: any dose higher than 200 mg/day.
- For cisplatin: any dose higher than 100mg/m^2 per cycle.
- For carboplatin: any dose higher than AUC = 5 per cycle.

Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the participant should be observed closely for signs of toxicity. Overdoses should be recorded as an AE.

Any AEs associated with an overdose should be recorded as separate AEs in addition of the AE "Overdose".

If an overdose on a Merck KGaA, Darmstadt, Germany investigational product (Debio-1143 or matched placebo) occurs during the course of the study, the Investigator or other site personnel must inform appropriate Sponsor representatives immediately and no later than 24 hours after becoming aware of the event.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor's participant safety data entry site.

For overdoses associated with an SAE, the standard SAE reporting timelines apply.

For other overdoses, reporting must occur within 30 days.

9.4.2. Pregnancy

All pregnancies occurring from signing informed consent until 9-months visit should be reported to Merck KGaA, Darmstadt, Germany.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive method.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

Elective abortions without complications should not be handled as AEs.

Pregnancies should be followed up until the final outcome and documented event if the participant was discontinued from the study.

If any pregnancy occurs, the Investigator must:

- Discontinue study treatments (i.e., xevinapant/matched placebo, cisplatin/carboplatin and IMRT).
- Complete the pregnancy report form and send it within 24 hours of awareness by email at SafetyReporting@SyneosHealth.com or by fax to +**1-877-464-7787**.

For the follow-up information, an updated pregnancy report form should be sent within 24 hours in the same way as the initial notification.

Any serious outcomes experienced by the parent and/or the fetus/child should be reported as SAEs using the SAE report form.

This procedure applies to pregnancies in female participants as well to those in female partners of male participants. Information on the pregnancy of a participant's partner must be obtained directly from the participant's partner. Therefore, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the participant's partner.

10. STATISTICAL CONSIDERATIONS

This section describes the statistical analyses and associated procedures intended to be performed during the analysis of the data collected during this clinical study. A detailed description of the statistical analyses will be provided in the statistical analysis plan.

The key elements of the statistical analysis plan are summarized in Table 10-1. A comprehensive description is provided in Section 10.4.

Table 10-1 Summary of Statistical Analysis Plan

Study Design Overview	This is a prospective, randomized, double-blind, placebo-controlled, multicenter, two-arm, parallel-group Phase 3 study comparing the efficacy and safety of xevinapant versus matched placebo, when administered in combination with platinum-based standard fractionation IMRT in previously untreated LA-SCCHN patients suitable for definitive CRT.
Treatment Assignment	Eligible participants will be randomized in a 1:1 ratio to receive xevinapant + CRT (Arm A) or matched placebo + CRT (Arm B) using dynamic allocation with complete randomization. Stratification factors are described in Section 6.3.
Analysis Sets	The following analysis sets will be used for planned analyses: Intent-to-treat, Safety, C [redacted] analysis set. Please refer to Section 10.3 for the description of the analysis sets.
Primary Endpoint/Hypothesis	Xevinapant prolongs EFS as assessed by the BIRC in previously untreated patients with LA-SCCHN suitable to receive CRT compared to matched placebo when administered in combination with platinum-based standard fractionation IMRT.
Statistical Methods for Key Efficacy Analyses	The hypothesis on EFS will be evaluated by comparing xevinapant to placebo in combination with CRT using a stratified log-rank test. The stratification factors are tumor size (T4 vs other) and lymph node involvement (N0-1 vs N2 vs N3). The hazard ratio will be estimated using a Cox-proportional hazard regression model adjusted for randomization stratification factors. Treatment effect on other time-to-event endpoints will be estimated using Cox regression model adjusted for randomization stratification factors. Estimation of the treatment effect on binary endpoints will be done using a logistic model adjusted for randomization stratification factors. Please refer to Section 10.4.2 and Section 10.4.3 for the detailed description of the efficacy analyses.
Statistical Methods for Key Safety Analysis	Only descriptive statistics will be provided for safety endpoints. Please refer to Section 10.4.4.
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Multiplicity	Hierarchical fixed sequence testing procedure is applied to control the type I error for the interim analyses and multiple hypotheses testing. The overall type I error is controlled at 0.025 one-sided). Please refer to Section 10.4.3 for the hierarchical fixed sequence procedure. An O'Brien & Fleming type α spending is used for the calculation of the significance levels and efficacy boundaries (p-value scale, see Section 10.4.7).
Sample Size and Power	With 429 EFS events, the clinical study has about 90% power to detect the expected hazard ratio benefit. Please refer to Section 10.2 for full description of the sample size determination.

Abbreviations: **BIRC:** Blinded Independent Review Committee; **CRT**: chemoradiotherapy; **EFS**: event-free survival; [redacted] **IDMC**, Independent Data Monitoring Committee; **IMRT**, intensity-modulated radiotherapy; **LA-SCCHN:** locally advanced squamous cell carcinoma of the head and neck; **OS**: overall survival; **PA**: primary analysis.

10.1. Statistical Hypotheses

10.1.1. Primary Hypothesis

Xevinapant prolongs EFS as assessed by the BIRC in previously untreated LA-SCCHN patients compared to matched placebo when administered in combination with platinum-based standard fractionation IMRT.

10.1.2. Secondary Efficacy Hypothesis

Secondary efficacy testing will be done with a hierarchical procedure for the following secondary endpoint. It is hypothesized that:

- Xevinapant + CRT prolongs OS compared to placebo + CRT.

Other efficacy endpoints will be analyzed without any type I error adjustment.

10.2. Sample Size Determination

Sample size calculation and evaluation of robustness was perform using R version 3.6.1 and R package ‘rpact’ version 2.0.4. as well as EAST 6.5.1.

10.2.1. Sample Size

The sample size was calculated considering the primary endpoint (blinded independent-assessed EFS) and interim analyses. CCI

It is anticipated that 700 participants will be randomized overall (~1000 participants screened).

Note: After global recruitment reaches the planned sample size for the ITT population (n=700), a Chinese extension cohort will be opened to reach randomization of approximately 106 Chinese participants from China Mainland (see Section 13.9 for further details).

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Justification of the assumptions:

Following the review of the literature (Table 10-2) and considering the variations in populations, treatment regimen-dose modulations, endpoint definitions and natural variation, it is expected that the Placebo + CRT group (Arm B) will experience a median time to EFS of about 17 months, leading to an exponential parameter λ of 0.041.

Table 10-2 Published studies used for the sample size assumptions

Reference	Population	Number of participants	Regimen	mPFS (months)
(Hitt et al. 2014)	Locally advanced inoperable	155	TPF-CCRT	14.6
		156	PF-CCRT	14.3
		128	CCRT	13.8
(Posner et al. 2007)	Nonmetastatic, histologically proven stage III or IV squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx	255	TPF CCRT	15
		246	PF CCRT	10
(Bonner et al. 2006)	LA-SCCHN, stage III or IV; including HPV positive OPC	211	Cetuximab-RT	17.1
		213	RT	12.5
(Geoffrois et al. 2018)	Patients with bulky nodal spread—N2b or N2c to N3	179	Carboplatin+5FU + RT	12.5
		151	TPF+cetuximab+RT	11.5
(Tao et al. 2018)	Patients with N0-2b, non-operated, stage III or IV (nonmetastatic) LA-SCCHN (including oral cavity, HPV-positive OPC)	204	CT-cetuximab-RT	37.9
		201	Cetuximab-RT	22.4

Abbreviations: 5FU: 5-fluorouracil; **CT**: chemotherapy; **HPV:** Human Papilloma Virus; **LA-SCCHN**: Locally Advanced Squamous Cell Carcinoma of the Head and Neck; **mPFS:** median progression-free survival; **OPC:** Oropharyngeal cancer; **PF-CCRT**: cisplatin and 5-fluorouracil -concurrent chemoradiation; **RT**: radiotherapy; **TPF-CCRT:** docetaxel (Taxotere), cisplatin and 5-fluorouracil - concurrent chemoradiation.

The Debio 1143-201 Part B Phase 2 study showed promising results (PFS improvement corresponding to a HR=0.37). These results together with a literature review were used to determine the EFS treatment effect assumptions. Thus, we expect that the addition of xevinapant to CRT will lead to a treatment effect CCI , corresponding to a difference of at least CCI in the prolongation of median EFS in the xevinapant + CRT group (Arm A) (median time estimate of CCI and exponential parameter CCI) as compared with Placebo + CRT group. This improvement in outcome is considered clinically relevant and is consistent with published data (Bonner et al. 2006); (Blanchard et al. 2011).

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10.2.2. Robustness of Sample Size

10.2.2.1. Robustness of Sample Size for Event-free Survival

Table 10-3 presents the expected power according to alternative hazard ratios while interim and primary analyses are triggered using assumptions from Section 10.2.1. In a situation where the hazard ratio is smaller than expected, the power at the first interim analysis provides good characteristics. In a situation where the hazard ratio is larger than expected, the power is at an appropriate level at primary analysis.

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10.2.2.2. Robustness of sample size for overall survival

Table 10-4 presents the number of events, expected timing of analyses and the power according to alternative hazard ratios (expected median OS in control at CCI [redacted] and annual lost to follow-up/dropout rate for OS at CCI [redacted]).

10.2.3. Sample Size for PK

PK blood samples will be collected from all randomized participants, ensuring sufficient collection of PK data to perform PK analyses and subsequent exposure/response analyses.

10.3. Analysis Populations

The following analysis sets will be used for the planned analysis of the global study population:

Intent-to-treat (ITT): The ITT set will include all randomized participants. Participants will be analyzed according to the randomized treatment assignment following the intention-to-treat principle. The ITT set will be the primary set for all efficacy and HRQL variables.

Safety (SAF): The SAF set will include all participants who received at least one dose of study medication. Participants will be analyzed according to the actual treatment received. The SAF will be used for all safety analyses.

Pharmacokinetics (PK): The PK set will include all the participants who have undergone at least one PK sample scheduled. The PK set will be used for all PK analyses.

10.4. Statistical Analyses

10.4.1. General Approach

Time-to-event data will be summarized based on Kaplan-Meier estimates, including but not limited to frequency and percentage at risk/censored, median, 1st and 3rd quartile, rate at predefined timepoints. Other continuous data will be described using descriptive statistics, including but not limited to the number of non-missing values (n), mean, standard deviation, median, minimum and maximum value. Categorical data will be described using the participant count and percentage in each category (including one for missing data).

Unless otherwise specified, all inferential tests will be one-sided. Type I error for primary objective null hypothesis is preserved at 0.025 one-sided using a group sequential design (O'Brien & Fleming type α spending).

Primary and selected secondary efficacy objectives will be evaluated in a hierarchical fixed sequence testing procedure (also called fixed sequence statistical strategy tests). Tests on the endpoints will be done in the predefined order specified in Section 10.1.2, all at the same significance level α, moving to the subsequent endpoint only after a success on the previous endpoint. Such a test procedure will preserve the overall type I error at 0.025 one-sided.

10.4.2. Analysis of the Primary Efficacy Endpoint

This section describes the statistical methods for the analysis of the primary endpoint.

The primary endpoint is EFS as assessed by the BIRC. Please refer to Section 3 for the definition of the primary endpoint and Section 11.2.4 for information on the BIRC. Supportive analysis will be done on EFS as assessed by Investigator.

Censoring rules for the primary and sensitivity analyses of EFS are described in Table 10-5. If a participant is meeting a multiple censoring situation, the earliest censoring criterion will be applied.

Primary treatment failure is defined as requirement of radical salvage surgery **before achieving a CR** that includes the primary tumor site, with documented viable tumor presenting anatomopathological findings even in the absence of formal RECIST v1.1 radiological progression, **occurring up to EOT visit.**

In the situation of a primary treatment failure, a participant will be considered to have an event (EFS) at the date of randomization (Michiels et al. 2009). This event can only occur during the treatment period. This rule aims to correct for potential bias in the follow-up schedules for tumor assessment during treatment (Michiels et al. 2009).

Table 10-5 Censoring rules for EFS

Situation	Primary	Sensitivity #1	Sensitivity #2
No evaluable baseline or post-baseline assessment*	Right censored at the date of randomization	Right censored at the date of randomization	Right censored at the date of randomization
Death, PD or any event entering in the definition of EFS after 2 or more	Right censored at last adequate assessment before the consecutive	Right censored at last adequate assessment before the consecutive	Not applicable

Situation	Primary	Sensitivity #1	Sensitivity #2
consecutive missing or inadequate tumor assessments	missing/inadequate assessments	missing/inadequate assessments	
Initiation of a new anticancer treatment for the disease under investigation before any event entering in the definition of EFS	Right censored at their last adequate assessment before the initiation of the new anticancer treatment	Not applicable	Not applicable
No death, PD, nor any event entering in the definition of EFS	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment

Abbreviations: EFS: Event-free survival; **PD**: Progressive disease

*An EFS event of any type is considered as a post-baseline assessment.

The Kaplan-Meier method will be used to estimate the EFS curve in each treatment group, see Section 10.4.1. Summary statistics, not limited to median, 1st and 3rd quartile, rate at 9, 12, 18, 24, 30 and 36 months after randomization, will be extracted from the Kaplan-Meier estimates.

The primary efficacy analysis will assess the difference in EFS between treatment arms using a one-sided stratified log-rank test at the α level of 0.025. The stratification factors are tumor size (T4 vs other) and lymph node involvement (N0-1 vs N2 vs N3). These factors were chosen among the randomization factors to avoid issues caused by very small sample stratum sizes. A Cox-proportional hazard regression model adjusted for the randomization factors will be used on the EFS with primary censoring rule to derive the hazard ratio and 95% CI between the 2 randomized regimens. Ties will be handled by replacing the proportional hazards model by the discrete logistic model. The stratification factors used for the randomization of participants will be inserted as covariates in the regression model. EFS with sensitivity censoring rules will be analyzed with the same approach.

10.4.3. Analysis of the Secondary Efficacy Endpoints

This section describes the statistical methods for the analysis of the secondary efficacy endpoints. Selected secondary efficacy endpoints will be evaluated in a hierarchical fixed sequence testing procedure (see Section 10.1.2 and Section 10.4.1).

10.4.3.1. Overall Survival

OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of analysis will be censored at the date of last known contact.

Kaplan-Meier method will be used to estimate the OS curve in each treatment group. Summary statistics, not limited to median, 1st and 3rd quartile, rate at 12, 24, 36, 48 and 60 months after randomization, will be extracted from the Kaplan-Meier estimates.

The treatment difference in OS will be assessed using a one-sided stratified log-rank test at the α level of 0.025 using tumor size (T4 and other) and lymph node involvement (N0-1 vs N2 vs N3). A Cox-proportional hazard regression model adjusted for the randomization stratification factors

will be used on the OS to derive the hazard ratio and 95% CI between the 2 randomized regimens. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

10.4.3.2. Progression-free Survival

Please refer to Section 3 for the definition of PFS as assessed by the BIRC. Supportive analysis will be done on PFS as assessed by Investigator.

Censoring rules for the primary and sensitivity analyses for PFS are described in Table 10-6.

Table 10-6 Censoring rules for progression-free survival

Situation	Primary	Sensitivity #1	Sensitivity #2
No evaluable baseline or post-baseline assessment*	Right censored at the date of randomization	Right censored at the date of randomization	Right censored at the date of randomization
Death, PD or any event entering in the definition of PFS after 2 or more consecutive missing or inadequate tumor assessments	Right censored at last adequate assessment before the consecutive missing/inadequate assessments	Right censored at last adequate assessment before the consecutive missing/inadequate assessments	Not applicable
Initiation of a new anticancer treatment for the disease under investigation before any event entering in the definition of PFS	Right censored at their last adequate assessment before the initiation of the new anticancer treatment	Not applicable	Not applicable
No death, PD, nor any event entering in the definition of PFS	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment

Abbreviations: PD: Progressive disease; **PFS**: Progression-free survival.
*Any PFS event is considered as a post-baseline assessment.'

Summary statistics and analysis of PFS will be performed using the same methods as for EFS, described in Section 10.4.2.

10.4.3.3. Locoregional Control

Please refer to Section 3 for the definition of LRC as assessed by Investigator. LRC will be investigated by BIRC as supportive analysis.

Censoring rules for the primary and sensitivity analyses for LRC are described in Table 10-7.

Table 10-7 Censoring rules for locoregional control

Situation	Primary	Sensitivity #1	Sensitivity #2
No evaluable baseline or post-baseline assessment	Right censored at the date of randomization	Right censored at the date of randomization	Right censored at the date of randomization
PD after 2 or more consecutive missing or inadequate tumor assessments	Right censored at last adequate assessment before the consecutive missing/inadequate assessments	Right censored at last adequate assessment before the consecutive missing/inadequate assessments	Not applicable
Initiation of a new anticancer treatment for the disease under investigation before any documented progressive disease	Right censored at their last adequate assessment before the initiation of the new anticancer treatment	Not applicable	Not applicable
No locoregional failure	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment	Right censored at the date of their last adequate assessment

Abbreviations: PD: Progressive disease

Summary statistics and analysis of LRC will be performed using the same methods as for EFS, described in Section 10.4.2.

10.4.3.4. Duration of Response

Please refer to Section 3 for the definition of DoR as assessed by the BIRC. Supportive analysis will be done on DoR as assessed by the Investigator. Participants with non-measurable disease only participants having best overall response at non-CR/non-PD will be imputed to non-responders.

Primary and sensitivity censoring rules for DoR following the same as those applied to PFS, described in Table 10-6.

Summary statistics and analysis of DoR will be performed using the same methods as for EFS, described in Section 10.4.2.

10.4.3.5. Complete Response Rate

For the computation of CRR, best overall response will be imputed to non-responder for participants without evaluable assessment.

Primary analysis for CRR will be based on the BIRC evaluation of response according to RECIST v1.1. Supportive analysis for CRR will be based on Investigator evaluation of response.

Summary statistics will be provided for CRR at 9 and 12-months post-randomization. CRR and CR status at 9 and 12-months post-randomization will be analyzed using a logistic regression. The same stratification factors used for the randomization will be applied to the analysis.

10.4.3.6. Overall Response Rate

For the computation of ORR, best overall response will be imputed to non-responders for:

- participants without evaluable assessment.
- non-measurable disease only participants with best overall response at non-CR/non-PD.

Primary analysis for ORR will be based on the BIRC evaluation of response according to RECIST v1.1. Supportive analysis for ORR will be based on Investigator evaluation of response.

Summary statistics will be provided for ORR status at 9 and 12-months post-randomization. ORR and objective response status at 9 and 12-months post-randomization will be analyzed using a logistic regression. The same stratification factors used for the randomization will be applied to the analysis.

10.4.3.7. Proportion of Participants with Radical Salvage Surgery

Participants experiencing END, without anatomopathological evidence of residual malignant cells will be imputed as not having experience a radical savage surgery for the computation of the proportion of participants with radical salvage surgery. If the number of events permits, time to radical salvage surgery will be analyzed using time-to-event techniques.

Summary statistics will be provided for the proportion of participants with radical salvage surgery experienced before 9, 12, 24, 36, 48 and 60-months post-randomization. In addition, the proportions will be analyzed using a logistic regression. The same stratification factors used for the randomization will be applied to the analysis.

10.4.3.8. Time to Subsequent Systemic Cancer Treatment

Time to subsequent systemic cancer treatment will be computed as the time from randomization to first subsequent systemic cancer treatment for SCCHN. Participant without documented subsequent systemic cancer treatment for this disease will be censored at the date of last known contact with evidence of no new systemic cancer treatment.

The Kaplan-Meier method will be used to estimate the time to subsequent systemic cancer treatment curve in each treatment group. Summary statistics, not limited to median, 1st and 3rd quartile, rate at 12, 18, 24, 36, 48 and 60 months after randomization, will be extracted from the Kaplan-Meier estimates.

The treatment difference in time to subsequent systemic cancer treatment will be assessed by using a one-sided stratified (T size and lymph node involvement) log-rank test at the α level of 0.025. A Cox-proportional hazard regression model adjusted for randomization stratification factors will be used to derive the hazard ratio and 95% confidence intervals between the 2 randomized regimens. Ties will be handled by replacing the proportional hazards model by the discrete logistic model

10.4.3.9. HRQL Assessment

For both EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires, data will be scored according to the algorithm described in the EORTC scoring manual (Fayers 2001).

[redacted]

Detailed descriptions of the analyses are reported in the statistical analysis plan.

10.4.4. Safety Analyses

Safety, tolerability, and extent of exposure will be assessed through summary information on AE, laboratory parameters, vital signs and dosing information.

10.4.4.1. Adverse Events

AE will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.1 or higher.

A treatment-emergent AE is any new sign or symptom, disease, other untoward medical event, or change of an existing condition in a participant that begins during or after the first study treatment (xevinapant, cisplatin or IMRT) and up to 30 days after treatment end date, whether or not considered to be drug-related. Further details will be provided in the statistical analysis plan.

Incidence (count and percentage) of TEAEs, TEAEs related to study treatments, dose-modifying TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to death, AESIs and SAEs will be tabulated and listed by grade group (overall and grade 3 or more) and arm, and by MedDRA system organ class and preferred term. Data will be presented overall, for AEs (up to EOT visit), SAEs (up to EOS), AESIs during treatment (up to EOT) and late onset AESIs (from EOT to EOS). Grade will be based on NCI-CTCAE v5.0. Incidence of participants with treatment interruptions, delays, and dose reductions will be tabulated, and treatment compliance will be presented as descriptive statistics by arm (overall and per cycle as appropriate). All on-study deaths and reasons will be listed.

10.4.4.2. Laboratory Parameters

Safety laboratory parameters worst grades as per NCI-CTCAE v5.0, during treatment until EOT, and corresponding changes from baseline will be presented as descriptive statistics by arm and by timepoint. Worst post-baseline shift tables will be presented by arm.

10.4.4.3. Vital Signs Parameters

Vital parameters, weight, and ECOG performance status and corresponding changes from baseline will be presented as descriptive statistics by arm and by timepoint.

10.4.4.4. Extent of Exposure

The exposure to xevinapant or matched placebo, chemotherapy and IMRT will be summarized by cycle and overall, up to EOT.

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10.4.6. Baseline Descriptive Statistics

Demographics and baseline characteristics will be assessed and summarized by arm in the ITT and safety sets using summary tables and figures. No statistical hypothesis will be performed on these baseline characteristics.

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10.4.8. Subgroup Analyses

Treatment effect and associated 95% CI for the primary endpoint and secondary efficacy endpoints (PFS, LRC, DoR, CRR, OS, etc.) will be estimated and plotted within each category of the following subgroups:

- Region: North America vs Western Europe vs Rest of the World.
- Primary tumor site: larynx vs other.
- Lymph node involvement: (N0-1 vs N2 vs N3).
- T size: T4 vs other.

Additional subgroup analysis will be specified in the statistical analysis plan.

11. ETHICAL, REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1. Ethics

11.1.1. Informed Consent Process

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each participant or their legally authorized representative before any study-specific activity is performed. The informed consent process must be documented (see below).

Each participant will be given oral and written information in an easily understandable language describing the nature and duration of the study.

If required by local regulations, an independent doctor who is not involved in conducting the study will be available for potential study participants to consult for information and advice.

The ICF will clearly state and inform the participants that there is a possibility that xevinapant in combination with chemoradiation is an experimental treatment which may not improve their condition. The potential side effects and risks, monitoring requirements will also be highlighted. The informed consent process must take place under conditions where the participant has adequate time to consider the risks associated with study participation.

The Investigator will retain the original of each participant's signed consent document. A copy of the signed ICF (or original of the ICF, if 2 originals are required to be signed as per local regulations) will be provided to the participant or the participant's legally authorized representative. The medical records of participant will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

Prior to initiation of the study at any site, the study, including the protocol and other study documents must be approved by an appropriate IEC or IRB and Regulatory Agencies. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented in the study. Amendments classified as "substantial" will also require prior approval by Regulatory Agencies before implementation.

The study must be approved before any participant is requested to sign the ICF. The ICF will be approved by an appropriate IEC/IRB and Regulatory Agencies, where required by local regulations, and any change to its content will require approval before implementation. In case of ICF amendment, a determination will be made regarding whether a new consent needs to be obtained from participants who initially provided consent based on a previous version of the ICF.

11.1.2. Independent Ethics Committees and Institutional Review Boards

The Clinical Study Protocol and Amendments to the protocol must be approved by the IRBs/IECs before implementation at the sites.

A letter documenting IEC/IRB approval (in which the protocol title and protocol number are specifically identified) and a list of IEC/IRB members (if available) and affiliations should be obtained by the Sponsor prior to initiation of the study.

Within 90 days of completion of the study (last participant, last visit) or 15 days of early termination of the study, the IEC/IRB will be informed of the end of the study by the Investigator, Sponsor or designee.

Every serious or unexpected AE that might affect participant safety must be brought to the IEC's or IRB's attention by the Investigator if required by relevant IEC/IRB regulations.

11.2. Study Governance and Study Committees

The study Sponsor are Affiliates of Merck KGaA, Darmstadt, Germany as listed on the title page.

IECs and IRBs are described in Section 11.1.2.

11.2.1. Independent Data Monitoring Committee / Firewall Team

An IDMC will be established before the randomization of the first participant to provide safety and efficacy oversight during the study. The review of safety and efficacy data will be performed according to an IDMC Charter that will be prepared before data collection start. All relevant data available from this study will be provided for these reviews.

The responsibilities of the IDMC include:

- To minimize the exposure of participants to an unsafe therapy or dose.
- To make recommendations for changes in study processes where appropriate.
- To advise on the need for dose adjustments because of safety issues.
- To endorse continuation of the study.

It will also be the responsibility of the IDMC to review the efficacy results at the interim analysis.

At any time during the study when the IDMC recommends major changes, these recommendations will be presented to the TSC (see Section 11.2.3).

Further details on the membership, responsibilities and working procedures of the IDMC are described in the IDMC Charter, provided as a separate document in the study file.

The Firewall Team will be comprised of relevant Sponsor senior experts (as described in a dedicated Firewall Charter), who are independent of the study team, to review the IDMC recommendation(s) following interim efficacy analyses with regards to the conduct of the study and according to the respective charters, preserving study integrity.

11.2.2. Quality Assurance Review Center

Two RT-QA Review Centers, one for the US sites and one for the rest of the world have been identified.

The responsibilities of the RT-QA Review Center include:

- To review and approve IMRT plan(s) before starting the first fraction administration to ensure IMRT requirements compliance.
- To approve the dosimetry planning before IMRT start.
- To confirm IMRT treatment delivery as per the approved planning and evaluate any critical/major deviations from the submitted plan.

A Radiation Therapy Quality Assurance Manual describing the IMRT plan and the roles and responsibilities of the RT-QA Review Center will be available prior to the initiation of the study.

11.2.3. Trial Steering Committee

The Trial Steering Committee (TSC) is a multidisciplinary group of Investigators that, collectively, have experience/expertise in the management of participants with condition(s) relevant to study and anticipated adverse effects, and in the conduct and monitoring of randomized clinical studies. The TSC will also include representatives of the Sponsor. The TSC will ensure transparent management of the study according to the protocol as initially written and through decisions made based on the IDMC recommendations. Details on the membership and responsibilities of the TSC are described in the TSC charter.

In particular, the TSC will be mainly responsible for:

- Periodic review of the progress of the study.
- Determining if amendments to the protocol or changes to study conduct are required.
- Monitoring the overall conduct of the study, ensuring that it follows the standards set out in the GCP guidelines.
- Reviewing the recommendations of the IDMC and/or other study committees and suggesting appropriate action to the Sponsor.
- Monitoring the progress of study and deciding on appropriate action in order to maximize the chances of completing it within the agreed timelines.

Additional responsibilities include but are not limited to:

- Approving proposed protocol amendments.

Details on the membership and responsibilities of the TSC are described in the TSC charter.

11.2.4. Blinded Independent Review Committee

The BIRC will perform a blinded central review of clinical and pathological assessments and radiological imaging of all participants, as per RECIST v1.1. It will be composed of blinded independent reviewers, including radiologists acting as primary reviewers and as adjudicators, and oncologists.

11.3. Data Collection and Quality Assurance

11.3.1. Clinical Monitoring

At mutually convenient times during the study and after study completion, the Investigator will let Sponsor representatives periodically review the eCRF and corresponding office, hospital, and laboratory records (source documents e.g., participant's medical chart, hospital, clinic, and laboratory records.) of each study participant. The eCRFs must be completed by the Investigator or authorized person on a regular basis and prior to each monitoring visit.

Monitoring visits allow the Sponsor to evaluate study progress, verify accuracy and completeness of eCRFs, resolve any inconsistencies in the study records, and ensure that all protocol requirements, applicable local laws, ICH guidelines, and Investigator obligations are fulfilled.

If eCRFs require support information, the Sponsor may request copies of participant records or other source documents. All necessary steps will then be taken to anonymize these documents and protect participant identity. Adherence to local and national laws governing protection of participant identity will be ensured.

Monitoring visits can be conducted on site or remotely. Centralized monitoring may be put in place when applicable. Details will be included in the study monitoring plan.

At timely intervals, and at the closing of the study, all investigational treatments will be accounted for and dispensing records made available to the Sponsor or its representative.

11.3.2. Future Use of Stored Specimens and Data

After completion of the analyses, the remaining blood and tissue samples may be stored for up to a maximum of 15 years after the end of the study. These samples may be used for a retrospective examination of safety laboratory tests, pharmacological effects of xevinapant, metabolic profiling, endogenous biomarkers, bioanalytical investigations or to further contribute to the understanding of molecular pathways involved in oncogenesis or the biology of cancer. For China, the use of remaining samples will be in accordance with local regulation.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research.

11.3.3. Quality Assurance and Quality Control

11.3.3.1. Sponsor Audits

During the study or after the study has been completed, the Investigator must allow Sponsor representatives or external auditors to conduct an audit of the study. The purpose of the audit is to evaluate compliance with GCP guidelines, applicable regulations, the study protocol and the Sponsor's procedures, and to assess accuracy of the study data.

Before the audit, the Investigator will be contacted by the monitor to arrange a convenient time for the visit. Investigator and staff are expected to be present, co-operate with the auditors, and allow direct access to all participant records supporting the eCRFs, and other study related documents.

11.3.3.2. Regulatory Agency Inspections

The Investigator must permit a Regulatory Agency/IEC/IRB inspection during the study or after the study has been completed. The purpose of such an inspection is to conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical study.

The Investigator and staff are expected to be available for the inspection and allow access to participant records supporting the eCRFs and other study related documents. If given advance notice of this inspection, the Investigator must contact the Sponsor immediately.

11.3.4. Data Handling and Record Keeping

11.3.4.1. Confidentiality and Privacy

The Investigator will ensure that participant reports and samples are identified only by an identifier to maintain participant confidentiality. All participant study records will be kept safely in an access-controlled area. Identification code lists linking the participant names to identifiers should preferably be stored separately from participant records. Clinical information will not be released without written permission from the participant, except for monitoring by Regulatory Authorities or the Sponsor.

11.3.4.2. Data Management and Validation

Data entry, verification and validation will be captured using an electronic data capture (EDC) system. EDC system is a web-based computerized system designed for the collection of clinical data in electronic format (eCRF); accessed via an Internet URL link. EDC system access (username and password) will be provided upon completion and confirmation of prerequisite training. Username and passwords are personal and confidential and must not be shared.

Validation of the eCRF data is performed by i) automatic EDC system checks and ii) other data review tools, such as data review listings. Data validation may result in the generation of queries. A query is a request for further information or clarification which may lead to data change. All queries (automatic and manual) will be generated and tracked within the EDC system until resolution. Manual queries can be raised directly into the EDC system by the clinical study team depending on the assigned EDC role throughout the duration of the study.

A clinical research associate will perform a source data verification on an ongoing basis to ensure completeness and consistency of data.

Data management reviews will be performed on an ongoing basis to ensure completeness and consistency of the eCRF data, taking also into account external data.

A medical review focused on completeness and consistency of clinical safety data will be conducted on an ongoing basis.

11.3.4.3. Data Reporting and Electronic Case Report Forms

The Investigator and/or designee will accurately, completely, and in a timely manner enter data resulting from execution of the protocol into eCRFs. One eCRF will be completed for each participant and must be electronically signed and dated by the Principal Investigator responsible for participant care during the study. The EDC system audit trail captures all eCRF data related activities such as: data entry, data modifications, data verification, data lock, e-signature etc. At the end of the study, each site will be given an electronic copy of all study data entered in the eCRF plus external data. eCRF data will be extracted from the EDC system into SAS® datasets on a periodic basis and at defined study timepoints for statistical analysis.

11.3.4.4. Study Records Retention

The Investigator will maintain adequate study records including the CD-ROM with electronically collected study data, medical records, laboratory reports, ICFs, drug disposition records, safety reports, information regarding participants who discontinued and other pertinent data, such as letters and administrative documents exchanged between the Sponsor and the center. Records can be in paper or electronic format.

All study records must be retained by the Investigator for the maximum period of time authorized by the hospital, institution or clinic but in no case for less than **15 years** after study completion.

To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records or if leaving the institution where the study was conducted. The Investigator will notify the Sponsor in the event of accidental loss or destruction of any study records.

11.4. Protocol Deviations

All protocol deviations should be documented.

11.5. Changes in the Conduct of the Study

See Section 13.9.

11.5.1. Public Health Emergencies

In case of a public health emergency, such as pandemics, study procedures might have to be adapted to enhance safety for participants and study personnel, as well as to accommodate WHO and/or local Health Agencies recommendations.

Such adaptations include, but are not limited to, more restrictive eligibility criteria to temporarily exclude participant sub-populations at higher health risk, alternative visit schedules for enrolled participants, study monitoring procedures, alternative supply chain to ensure delivery of medication to participant on treatment, etc.

Such changes will be implemented via separate communication to Investigators and captured in the trial master file.

Unless such changes are to be implemented on a permanent basis for the rest of the study, a protocol amendment will not be issued. Communication to the EC/IRBs and Regulatory Agencies on implementation of these time-limited changes will follow local requirements.

11.6. Publication and Data Sharing Policy

Results of this Phase 3 study will not be publicly disseminated or published until the study data are mature for the analysis of the primary study endpoint (as defined by the protocol). The publications must be conform to the CONSORT guidelines (Schulz et al. 2010).

However, for the purpose of submission of abstracts to congresses, a draft version of the analysis report may be generated if the Sponsor's Statistician determines prior to abstract submission that the inconsistencies remaining in the database will not affect the conclusions of the study, and that the database can be cleaned and locked in sufficient time to enable the preparation of the final statistical report by the time of presentation. In this case, the abstract should clearly stipulate that the results are not definitive.

The publication of the results of ancillary studies (e.g., translational research) is authorized at any time provided they do not mention the primary and secondary study endpoints.

All publications reporting results of this Phase 3 study must be reviewed and approved by the Sponsor's Statistician and Medical Monitor in charge of the study, the first author and the TSC. The first author is responsible for ensuring that all co-authors have seen and approved the final version of the publication prior to submission. A written agreement with the intent to submit a publication must be reached between the Sponsor, the first author and the TSC.

In accordance with the International Committee of Medical Journal Editors (Editors 2010), each author of the publication should have participated sufficiently in the work to take public responsibility for the content. All other contributors (clinicians, pathologists, etc.) who do not meet enough criteria for authorship will be acknowledged in the publication.

For the primary publication, the first author will be a TSC member who will be the primary person responsible for generating the first manuscript draft, followed by the other TSC members. In principle, the last author will be a TSC Chairman (if different from the first author). The Investigators who enrolled evaluable participants in the study will be included as co-authors up to the total number of co-authors allowed by the journal, according to their contribution to participant enrolment.

Coordinators of integrated translational research components of the study or pathologists responsible for the central pathology review that is part of the study also qualify as co-authors. Two Sponsor representatives will be co-authors. These 2 co-authors are usually the Statistician and the Medical Monitor who oversaw and contributed to the study.

All Investigators who enrolled evaluable participants into the study (i.e., clinicians) or contributed scientifically to the study (i.e., pathologists, collaborators from the same institutions, etc.) will be acknowledged in the publication. The acknowledgment list should include the name of all participating institutions and the name of the clinicians and other scientists involved with the study at that institution. Whenever a study participant has moved from one institution to another in the course of the study, that participant is listed with the institution to which he/she was affiliated at the time of starting his/her participation to the study, with the mention "(now at [*new affiliation*])".

Sponsor staff that made a substantial scientific contribution to the study but are not co-authors should be mentioned in the acknowledgment section (i.e., data managers, clinical scientists, clinical study managers).

The person who took the lead in conducting an ancillary study is the first author of the relevant publication. The Sponsor representatives who contributed to the design, conception, analysis and publication, if any, will also be co-authors. The list of co-authors must be approved by the TSC and Sponsor.

11.7. Insurance Policy

The Sponsor will subscribe a liability insurance covering his and the Investigator's responsibility as well as the responsibility of any person involved in the conduct of the study, provided there is proper adherence to the protocol. An insurance certificate will be provided by the Sponsor to the IEC/IRB if required.

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13. APPENDICES

13.1. ECOG Performance Status

Table 13-1 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: *Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group.* Am J Clin Oncol 5:649-655, 1982.

13.2. Cisplatin Administration

Please consult and follow the instructions provided in your local label.

Preparation

Do not use needles or intravenous sets containing aluminum parts that can come in contact with cisplatin for injection during preparation or administration. Aluminum reacts with cisplatin for injection, causing precipitate formation and a loss of potency.

Cisplatin for injection is a cytotoxic drug. Follow applicable special handling and disposable procedures.

Dilution

For preparation of the infusion solution, it is recommended that the solution be further diluted in 1 to 2 L of a compatible infusion solution with or without 37.5 g of mannitol. Refer to detailed references for specific infusion solution stability and compatibility information.

Administration

Administer cisplatin for injection by slow intravenous infusion.

Warnings and Precautions

Nephrotoxicity

Cisplatin for injection can cause dose-related nephrotoxicity, including acute renal failure that becomes more prolonged and severe with repeated courses of the drug. Renal toxicity typically begins during the second week after a dose of cisplatin for injection. Patients with baseline renal impairment, geriatric patients, patients who are taking other nephrotoxic drugs, or patients who are not well hydrated may be more susceptible to nephrotoxicity.

Ensure adequate hydration before, during, and after cisplatin for injection administration (see Appendix 13.3). Measure serum creatinine, blood urea nitrogen, creatinine clearance, and serum electrolytes including magnesium prior to initiating therapy, and as clinically indicated. Consider magnesium supplementation as clinically needed.

Creatinine, eGFR and electrolytes local measurement must take place 48 hours (±12 hours) after cisplatin administration to avoid or mitigate renal toxicities.

Peripheral Neuropathy

Cisplatin for injection can cause dose-related peripheral neuropathy that becomes more severe with repeated courses of the drug. Neurologic symptoms have been reported to occur after a single dose. Neuropathy can also have a delayed onset from 3 to 8 weeks after the last dose of cisplatin for injection. Manifestations include paresthesias in a stocking-glove distribution, areflexia, and loss of proprioception and vibratory sensation. The neuropathy may progress further even after stopping treatment. Peripheral neuropathy may be irreversible in some patients.

Consider permanent discontinuation of cisplatin for injection for patients who develop symptomatic peripheral neuropathy. Geriatric patients may be more susceptible to peripheral neuropathy.

Nausea and vomiting

Cisplatin for injection is a highly emetogenic antineoplastic agent. Premedicate with antiemetic agents. Without antiemetic therapy, marked nausea and vomiting occur in almost all patients treated with cisplatin for injection and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 72 hours. Maximal intensity occurs 48 to 72 hours after administration. Various degrees of vomiting, nausea, and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin for injection therapy. Consider the use of additional antiemetics following infusion.

Myelosuppression

Myelosuppression suppression occurs in 25% to 30% of patients treated with cisplatin for injection. Fever and infection have been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Geriatric patients may be more susceptible to myelosuppression.

Perform standard hematologic tests before initiating cisplatin for injection, before each subsequent course, and as clinically indicated. Closely monitor participants for the development of signs and symptoms of infection during and after treatment with cisplatin for injection. For participants who

develop severe myelosuppression during treatment with cisplatin for injection, consider dose modifications and manage according to clinical treatment guidelines.

Hypersensitivity reactions

Cisplatin for injection can cause severe hypersensitivity reactions, including anaphylaxis and death. Manifestations have included facial edema, wheezing, tachycardia, and hypotension. Hypersensitivity reactions have occurred within minutes of administration to patients with prior exposure to cisplatin for injection.

Monitor participants receiving cisplatin for injection for possible hypersensitivity reactions. Ensure supportive equipment and medications are available to treat severe hypersensitivity reactions. Severe hypersensitivity reactions require immediate discontinuation of cisplatin for injection and aggressive therapy. Participants with a history of severe hypersensitivity reactions should not be rechallenged with cisplatin for injection. Cross-reactivity between platinum-based antineoplastic agents has been reported. Cases of severe hypersensitivity reactions have recurred after rechallenging patients with a different platinum agent.

Ototoxicity

Cisplatin for injection can cause ototoxicity, which is cumulative and may be severe. Consider audiometric and vestibular function monitoring.

Ototoxicity is manifested by tinnitus, hearing loss in the high-frequency range (4,000 to 8,000 Hz) and/or decreased ability to hear normal conversational tones. Ototoxicity can occur during or after treatment and can be unilateral or bilateral. Deafness after the initial dose of cisplatin for injection has been reported. Vestibular toxicity has also been reported.

Ototoxic effects can be more severe and detrimental in pediatric patients, particularly in patients less than 5 years of age. The prevalence of hearing loss in pediatric patients is estimated to be 40-60%. Additional risk factors for ototoxicity include simultaneous cranial irradiation, treatment with other ototoxic drugs and renal impairment. Consider audiometric and vestibular testing in all pediatric patients receiving cisplatin.

Genetic factors (e.g., variants in the thiopurine S-methyltransferase [TPMT] gene) may also contribute to the cisplatin-induced ototoxicity; although this association has not been consistent across populations and study designs.

Ocular toxicity

Optic neuritis, papilledema, and cortical blindness have been reported in patients receiving standard recommended doses of cisplatin for injection. Blurred vision and altered color perception have been reported after the use of regimens with higher doses and dose frequencies of cisplatin for injection. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis and irregular retinal pigmentation of the macular area on fundoscopic exam. Improvement and/or total recovery usually occurs after discontinuing cisplatin for injection but can be delayed.

Secondary malignancies

The development of acute leukemia secondary to the use of cisplatin for injection has been reported. In these reports, cisplatin for injection was generally given in combination with other leukemogenic agents.

Embryo-fetal toxicity

Based on human data, cisplatin for injection can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 14 months after the last dose of cisplatin for injection. Advise male participants with female partners of reproductive potential to use effective contraception during treatment and for 11 months after the last dose of cisplatin for injection.

Injection site reactions

Injection site reactions can occur during the administration of cisplatin for injection. Local soft tissue toxicity has been reported following extravasation of cisplatin for injection. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin for injection solution. Infusion of solutions with a cisplatin for injection concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

Because of the possibility of extravasation, closely monitor the infusion site during drug administration.

13.3. Cisplatin Hydration Guidelines

Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin (SmPC TEVA v6.0 2019).

Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realized by intravenous infusion of one of the following solutions:

- Sodium chloride solution 0.9%
- Mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1).

Hydration prior to treatment with cisplatin:

- Intravenous infusion of 100 to 200 ml/hour for a period of 6 to 12 hours, with a total amount of at least 1 L.

Hydration after termination of the administration of cisplatin:

- Intravenous infusion of another 2 liters at a rate of 100 to 200 ml per hour for a period of 6 to 12 hours.

Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be realized by intravenously administering 37.5 g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of a diuretic if the kidney functions are normal. The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60 mg/m^2 of body surface.

It is necessary that the participant drinks large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved, and renal function remains adequate.

Consider a more extensive hydration regimen under certain circumstances:

Additional pre hydration with normal saline iv or orally at minimum in the 48 hours preceding cisplatin infusion and a more extensive post-hydration regimen is requested whenever possible in those patients with risk factors for renal toxicity, e.g., proteinuria, diabetes, and hypertension.

The patient's hydration status is requested to be reviewed whenever a patient's renal lab is worsening during the study, with a mandatory review on Day 4. Attention should also be paid to any signs of dehydration (insufficient urine outputs) or conditions leading to a potential dehydration like diarrhea, vomiting, undernutrition, infection/fever.

In case of inadequate hydration status and worsening renal lab, additional iv hydration is requested whenever possible until renal lab improves.

13.4. HRQL Questionnaires

13.4.1. EORTC QLQ-HN35

The EORTC QLQ-HN35 is a disease-specific module capturing HRQL dimensions that affect patients with head and neck cancer. It is composed of 7 symptom scales (pain, swallowing, senses, speech, social eating, social contact, sexuality), 6 symptom items (problems with teeth, trismus, xerostomia, sticky saliva, coughing, feeling ill), and 5 dummy (yes/no) items (use of painkillers, use of nutritional supplements, use of feeding tube, weight decrease, weight increase), for a total of 35 items. Participants' answers are collected with a one-week recall period. Symptom scales and items are presented in 4-point Likert scales.

Large international samples (N=662) exhibited a high internal reliability (Cronbach's $\alpha > 0.70$), construct validity (multi-trait scaling analysis $\rho \geq 0.40$) and criterion validity (as assessed by group comparison method) of the instrument (Bjordal et al. 2000; Sherman et al. 2000).

The EORTC QLQ-HN35 module has been validated for the different anatomical subsites, multiple disease stages, different treatment modalities (i.e., RT, chemotherapy, CRT and surgery) and across multiple countries (Bjordal et al. 1999; Bjordal et al. 2000; Singer et al. 2009). Validated translations of the EORTC QLQ-HN35 are available in 65 languages, including languages from European, Asian and Latin American countries covering target study sites. The instrument is meant to be used in conjunction with the EORTC core cancer module (EORTC QLQ-C30).

A specimen of the questionnaire (UK English) is available at https://qol.eortc.org/questionnaire/qlq-hn35/.

13.4.2. EORTC QLQ-C30

The EORTC QLQ-C30 version 3.0 questionnaire captures HRQL dimensions that are common to patients with cancer independently of the cancer type by which they are affected. It is composed of 5 functional scales (emotional, physical, cognitive, social and role), 3 multi-item scales (fatigue, pain, nausea/vomiting) and 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and one global health scale, for a total of 30 items (Aaronson et al. 1993).

Participants' answers are collected with a one-week recall period and questionnaire items are presented in Likert scales (7-point scale for global health status, 4-point scale for all other items).

The internal reliability and construct validity of the instrument have been tested in large international samples of heterogeneous head and neck patients; validated translations of the EORTC QLQ-C30 are available for more than one hundred languages (Bjordal et al. 2000).

For both selected EORTC questionnaires, a score variation of at least 10 points for each item is considered clinically meaningful (King 1996; Osoba et al. 1998; Bjordal et al. 2000; Hammerlid et al. 2001; Cocks et al. 2011; Cocks et al. 2012). The 10-point threshold of clinical significance has been defined across different cancer indications and could be lower in specific cancer types (Cocks et al. 2011; Cocks et al. 2012).

A specimen of the questionnaire (US English) is available at https://qol.eortc.org/questionnaire/eortc-qlq-c30/.

13.5. Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 Applied to this Study in Locally Advanced SCCHN

The text below was derived from Eisenhauer et al. 2009 and Schwartz et al. 2016. Guidance, adjustments and clarification specific to this study in locally advanced SCCHN, and not necessarily in the original articles, has been added.

Background and definitions

Response and progression will be evaluated in this study based on the international criteria proposed by the RECIST Working Group (Version 1.1). Unidimensional measurements of tumor lesions are used in the RECIST criteria. Individual lesions are either measurable or non-measurable using the criteria provided below.

Study-permitted imaging modalities and associated procedures

- *CT, MRI*

CT is the best and most reproducible method currently available to measure lesions selected for response assessment. If CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in this study, except for chest imaging, where CT is mandatory.

- *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Needle localization images for biopsy site may however be useful.

- *Endoscopy, laparoscopy*

The utilization of these techniques alone for objective tumor evaluation is not permitted in this study. In this study, biopsy (endoscopic or otherwise) of a suspected new lesion to confirm or exclude malignant nature and provide relevant histological information is strongly encouraged when clinically feasible. Unbiopsied apparent recurrences visible only on endoscopy are not considered sufficient evidence alone to be markers of progression.

- *Tumor markers*

Tumor markers for progression are not used in this study.

- *Cytology, histology*

In this study, biopsy of a suspected new lesion or residual/recurrent mass to confirm or exclude malignant nature and provide histological information relevant to the endpoint is strongly encouraged when clinically feasible.

- *^{18}F-FDG -PET + CT*

This study incorporates 18F-FDG -PET scanning to complement CT/MRI scans in assessment of progression (particularly possible ‘new’ disease.) However, the use of 18F-FDG-PET to upgrade response to CR unsupported by biopsy is not applied to this study.

Assessment methodology

- *Assessment methodology of measurable lesions selected for measurement*

Non–nodal tumor lesions must be accurately measured in one dimension, the longest diameter in the plane of measurement, with a minimum size of 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm.) Clinical observations, clinical caliper measurements, photographic assessments, and plain radiographs are not permitted in this study. All measurements should be recorded in metric notation.

The short axis of a lymph node, or conjoined mass of nodes, is the longest perpendicular to the longest diameter in the axial plane. To be considered pathologically enlarged and measurable at baseline, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (Scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis of nodes will be measured and followed.

- *Assessment methodology of non-measurable disease*

All other lesions (or sites of disease), including small lesions (< 10 mm using spiral CT or MRI scan), as well as measurable lesions that are not selected as target lesions, are considered non-measurable disease. RECIST criteria define many baseline types of lesion that are always non-measurable, but all of these are excluded from this study. Participants with only non-measurable disease at baseline but whose overall disease burden is still assessable by imaging are considered to have evaluable (non-measurable) disease.

- *Assessment of special lesion types*

a) *Bone lesions*. There will be no malignant bone lesions at baseline in this study due to inclusion/exclusion criteria, hence discussion of measurability of bone lesions at baseline and of lesions seen at baseline on bone scans is unnecessary.
b) *Cystic lesions.* Radiographically defined simple cysts should not be considered as malignant lesions. Complex malignant cystic lesions will not occur at baseline in this study due to inclusion/exclusion criteria and hence need not be considered further
c) *Lesions with local irradiation:* In this study, all lesions seen at baseline will receive irradiation as part of the study treatment, and therefore it is impossible to avoid radiation impact on assessments. As a result, the processes of selection and following of target lesions should not be influenced by past or current irradiation.

Process for evaluation of disease at baseline

All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- *Target Lesions*

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but also should be those suitable for reproducible repeated measurements.

Lymph nodes: Pathological nodes which are defined as measurable and may be identified as target lesions at baseline must have a short axis of ≥ 15 mm by CT or MRI scan. Only the short axis of these nodes will contribute to the baseline sum of diameters. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm at baseline are considered non-pathological and should not be recorded or followed.

A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and recorded as the **baseline sum of diameters**. The baseline sum of diameters will be used as reference to further characterize any later objective tumor changes in the measurable dimension of the disease.

- *Non-target Lesions*

All other lesions (or sites of disease) including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, except short axis of nodes and then only to confirm or exclude pathological enlargement: these lesions should be followed as 'present', 'absent', or reported overall as 'unequivocal progression'. Multiple non-target lesions involving the same organ can be a single item on the case record form (e.g., 'multiple liver metastases').

Process for assessment of disease at each timepoint after baseline

- *Evaluation of Target Lesions*

A new sum of diameters for all target lesions will be calculated and recorded as the **sum of diameters** for that timepoint. This timepoint sum of diameters will be used for comparison with that at baseline and at the timepoint when the sum of diameters is least (the nadir): the details of the outcome of each comparison are shown in Table 1 below.

Table 1 Response Status Definition for Target Lesions at each Timepoint

Observed disease	Response	Abbreviation
Disappearance of all target lesions except pathological lymph nodes. Any pathological nodes (target or non-target) must have reduction in short axis to < 10 mm.	Complete Response	CR
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.	Partial Response	PR
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or at baseline (the nadir.) In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.	Progressive Disease	PD
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters at baseline or on study.	Stable Disease	SD
One or more target lesions have not been assessed or assessed using a different modality from baseline or nadir, so adequate comparison of the images is impossible.	Not Evaluable	NE

- *Special points*

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. This means that, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if CR criteria are met. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes also is to be included in the sum of diameters of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes the radiologist may not feel able to assign an exact measure and may consider them 'too small to measure'. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Target lesions that are biopsied or excised: On occasion, target lesions may be biopsied or excised. Measurements of such lesions may no longer be suitable for accurate assessment of response and/or progression. In this situation a sum of diameters including any residual lesion should still be calculated, and if the sum of diameters is still increased by 20% over nadir, disease progression is diagnosed. If doubt remains, the entire disease burden of the participant should be considered and compared with that at baseline as though there was only evaluable, non-measurable disease at baseline. In such a situation, non-CR/non-PD becomes a possible timepoint assessment and even best overall response even though there was measurable disease at baseline. To minimize the risk of this eventuality, study imaging before biopsy is advised.

- *Evaluation of Non-target Lesions*

While some non-target lesions may actually be measurable, they need not be measured (except lymph nodes when pathological nature is uncertain) and instead should be assessed only qualitatively, according to the timepoint assessment criteria shown in Table 2 below:

Table 2 Response Status Definition for Non-target Lesions at each Timepoint

Observed disease	Response	Abbreviation
Disappearance of all non-target lesions except for lymph nodes. All lymph nodes must be non-pathological in size (< 10 mm short axis).	Complete Response	CR
Persistence of one or more non-target Lesions.	Neither complete response nor progressive disease	Non-CR/non-PD
Unequivocal progression of existing non-target lesions	Progressive disease	PD

Observed disease	Response	Abbreviation
No non-target lesions seen at baseline	No non-target lesions	NA
Assessment not possible due to inadequate or missing images.	Not Evaluable	NE

- *Special points*

When the participant has both target and non-target lesions. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit new therapy. A modest 'increase' in the size of 1 or more non-target lesions is insufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-target lesions. In this study, it is not a requirement for study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there will be no measured disease assessment to balance the interpretation of an increase in non-measurable disease burden. The test that should be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is at least comparable in magnitude to the increase that would be required to declare PD for measurable disease.

- *Evaluation of New Lesions*

The appearance of new malignant lesions denotes disease progression by RECIST v1.1. The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. Exceptionally, since the endpoints of this study differentiate between locoregional progression and distant metastasis, it is necessary to differentiate between locoregional lesions and metastases elsewhere. Therefore, data on new lesions in each of these *locations* will be required if available. If the first manifestation of disease progression is distant metastasis, then assessments for locoregional control should continue if possible, and vice versa. Note: As this study is in locally advanced disease, all target and non-target lesions at baseline will lie within the locoregional volume and therefore no similar differentiation at baseline is possible or required.

If a new lesion is equivocal, either continued therapy and follow-up evaluation or biopsy and histological examination will clarify if it represents truly new disease. If repeat scans or biopsy confirm a new lesion, then PD should be declared using the date of the initial scan.

In case histopathological results of a new lesion unequivocally reveal a non-squamous histology of the new malignant lesion, this will not be counted as disease progression within the primary or secondary endpoints of this study.

Evaluation of disease status at each post-baseline timepoint

For participants with measurable disease, the assessment of response status at each timepoint will be an *amalgamation* of the individual response statuses of target lesions, non-target lesions and new lesions, and is shown in Table 3 below.

Table 3 Timepoint Assessment of Disease Status by Imaging for Participants with Measurable Disease at Baseline.

Timepoint response in:			Overall Timepoint Response
Target Lesions	Non-Target Lesions	New Lesions	
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Any, except PD or NE	No	PR
SD	Any, except PD or NE	No	SD
Not all measured	Any, except PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response, NE=not evaluable, PD=progressive disease, PR=partial response, SD=stable disease.

The RECIST papers referenced in this document provide no similar assessment paradigm for response status at timepoint for participants with evaluable but non-measurable disease at baseline, but one can be derived from the information above, and it is provided in Table 4 below.

Table 4 Timepoint Assessment of Disease Status by Imaging for Participants with Non-measurable Disease at Baseline, or due to Biopsy or Excision

Timepoint response		Overall Timepoint Response
Non-Target Lesions	New lesions	
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
NE	No	NE
PD	Yes or no	PD
Any	Yes	PD

CR=complete response, NE=not evaluable, PD=progressive disease.

- *Special points*

Impact of biopsy and excision. Due to biopsy or excision of target lesions, some participants with measurable *disease* at baseline may have a timepoint response or best overall response of Non-CR/Non-PD

Symptomatic progression. Symptomatic progression alone is not a determinant of disease progression in this *study.*

Handling equivocal findings of progression. For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), in the absence of histological *verification* of new malignant lesions, treatment may continue at the investigator's discretion until the next scheduled assessment. If, at the next scheduled assessment, progression is definite, the date of progression should be the earlier date when progression was first suspected

Further information

Further information on the assessment of disease by imaging in this study is available in the training materials, including slide presentations and videos.

13.6. Audiometry Assessment (Specific for investigational sites in France)

As requested by the French ANSM, an audiometry must be performed at screening, C2D1 and C3D1 within 5 days before platinum-based chemotherapy and at any time if clinically indicated as per institutional or national guidelines. During the follow-up period, an audiometry is to be performed only if clinically indicated, as per institutional or national guidelines.

13.7. Conduct of The Study during the COVID-19 Pandemic (Specific for Investigational Sites in Germany)

Benefit/risk assessment of the conduct of the study during the COVID-19 Pandemic

Efficacy results from the 36-month analysis of Debio 1143-201B in LA-SCCHN patients have shown antitumor activity of xevinapant. Estimate of LRC at 36 months was 78% (95% CI: 61–88) in the xevinapant arm versus 56% (95% CI: 34–73) in the placebo arm, leading to a reduction of LRC failure risk of 53% in the xevinapant group compared to the placebo group (Hazard Ratio: 0.47; 95% CI: 0.19–1·14; P=0.095).

Xevinapant+CRT treatments also demonstrated a statistically significant and clinically meaningful improvement in PFS versus the control group. Estimate of PFS at 36 months was 72% (95% CI: 56–84) in the xevinapant arm versus 36% (95% CI: 20–51) in the placebo arm, reflecting a significant reduction of 66% in the risk of disease progression or death in the xevinapant group compared to the placebo group (Hazard Ratio:0.34, [95%CI: 0.17-0.68], P=0.0023).

Xevinapant combined with CRT also showed a clinically significant improvement in overall survival vs the control group. Estimate of overall survival at 36 months was 66% (95% CI: 49–78) in the xevinapant arm versus 51% (95% CI: 34–65) in the placebo arm, reflecting a 51% reduction in the risk of mortality of any cause in the xevinapant group compared to the placebo group (Hazard Ratio:0.49, [95%CI: 0.26-0.92], P=0.0261).

To date, the observed safety profile associated with xevinapant given alone or in combination with chemotherapy, CRT or immunotherapy suggests an acceptable and predictable safety profile of the compound. The observed toxicities were in line with those expected in patients with advanced solid tumors, and/or with those observed in patients treated with a similar combination chemotherapy or CRT regimen. In general, the predominant toxicities were mild and/or mostly reversible, could be monitored by routine clinical examinations and were manageable by dose delay, dose reduction and/or supportive care.

Based upon the safety data observed thus far, xevinapant doses of up to 200 mg/day were safely combined with either chemotherapy, RT or both. In study -201B, xevinapant was administered to patients with LA-SCCHN in combination with cisplatin and standard radiation therapy. An increased risk of nausea, mucosal inflammation, dysphagia, weight decrease, radiation skin injury, tinnitus, hyperlipasemia, elevation of transaminase and grade 3 anemia were observed versus placebo. Nevertheless, the safety profile of xevinapant used in combination with CRT remained acceptable and manageable.

Overall, results from study -201B provide solid preliminary evidence that xevinapant can be safely administered in combination with high-dose cisplatin and RT and has the potential to offer substantially improved efficacy over the standard of care in high-risk LA-SCCHN. Therefore, the benefit/risk is favorable and justifies the clinical investigation proposed to be conducted in the study.

The COVID-19 pandemic affected globally our society in many aspects, including the conduct of clinical studies. While patients with cancer are one of the sub-populations at increased risk during the pandemic, they are also a patient population in urgent need of receiving treatment for their disease. Receiving treatment might make a difference between life and death. Therefore, during the COVID-19 pandemic, the decision to start cancer treatment is very individual and relies more

than ever on a thorough benefit/risk analysis by the patient in discussion with her/his treating physician.

Recommendations for mitigation Measures during a COVID-19 crisis

Considerations for participants' eligibility:

The safety of the clinical study participants is of primary importance. The individual risk-benefit ratio should be carefully evaluated for each of the potentially eligible participants, since participants with cancer are at higher risk of severe complications caused by COVID-19 infection. Furthermore, special attention should be paid to those participants with additional risk factors for more serious COVID-19 infections.

Recommendations for the initiation of study treatment:

In the context of the study protocol exclusion criteria #8 "Other infections (viral and/or bacterial and/or mycotic) requiring systemic treatment", a COVID-19 diagnostic test is recommended during screening. If the test is performed, the result should be available before randomization.

Should the test be positive, irrespective of the absence or presence of symptoms, the initiation of the study treatment should be postponed.

If initiation of treatment is postponed, study treatment should not be started before a negative COVID-19 test result. Additionally, in case of symptoms study treatment initiation should be postponed until resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath).

Once the informed consent has been signed, all the confirmed COVID-19 infections should be reported as an AE even if they are asymptomatic.

Recommended study procedures in case of COVID-19 crisis in your area:

The points mentioned below are intended to provide the Investigator with recommendations for the management of the participants enrolled in the study during a COVID-19 crisis. There might be specific national legislation and guidance in place, which can be considered to complement these recommendations, or, with respect to particular matters, take priority over these recommendations.

In the case the hospital facility cannot ensure the safety of the study participants during the visits despite of all efforts made, the following procedures may be considered:

- Certain study assessments, especially those related to safety, such as electrocardiograms and blood monitoring (see Section 8.3 of the protocol) can be exceptionally performed in institutions other than the study site. More specifically, these assessments can exceptionally be performed at local laboratories or relevant clinical facilities authorized/certified (as legally required nationally) to perform such tests routinely, if this can be done within local restrictions on social distancing. Nevertheless, all procedures related to primary endpoint (clinical and radiological evaluations as listed in Section 8.2 of the protocol) should be performed at the study site.

This decision will be at Investigator's discretion, based on an assessment of potential COVID-19 infection risk between a visit to the study site versus a visit to another institution.

Additionally, this exception should also be considered in case of operational limitations at the site e.g., overburden of the site laboratories due to management of participants with COVID-19.

Assessments done in other institutions will be accepted for study purposes if the data generated by those institutions are included in your medical records to allow for study data entry and monitoring.

- To minimize the likelihood that the participant might run out of Investigational Medical Product in case she/he has to skip visits due to the COVID-19 risks, the IMP may be shipped from sites to the participant's residence according to the site internal procedures, local laws/regulations for privacy data protection and according to the product specifications.

In any case, the sites should inform immediately the CRO and the Sponsor about the implementation of such adaptations or measures.

In case a participant becomes infected with SARS-CoV-2 during the treatment period, consider any study treatment modification in the best interest of the participant and in accordance with the protocol Section 6.1.2 (Table 6-1). This includes an evaluation of potential drug-drug-interactions if the use of concomitant medications is necessary to manage the COVID-19 infection (see Section 6.5 of the protocol). Any modification to study treatment or use of concomitant medication must be clearly documented in the participant's medical records and reported in the study CRF.

Please note that in case of study treatment discontinuation, it is very important that the participant remains in the follow-up of the study to not jeopardize the primary and secondary endpoints data collection.

Recommendations for the implementation of Remote Source Data Verification (rSDV):

In justified exceptional cases and only to the extent strictly necessary, rSDV can take place. In case of rSDV implementation at some point, the *supplementary recommendations of BfArM and PEI to the European Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic* will be followed.

Conclusions:

These measures are considered adequate to further minimize the risks to participants during the COVID-19 pandemic. Thus, the benefit/risk for the study during the COVID-19 pandemic is considered to remain favorable.

Any activity related to implementation of these temporary measures will be captured in the Trial Master File for the study and will be described in the Clinical Study Report.

13.8. Country-Specific Amendment for Japan

With the following additions and exceptions, all country-specific protocol requirements are outlined within the protocol.

Japan

5.1 Inclusion Criteria, Item 11, Breastfeeding

Participants should refrain from breastfeeding during and until at least 3 days (e.g., 5 terminal half-lives) after the end of the xevinapant/placebo treatment.

5.1 Clarification to Inclusion Criteria, Item 11, Women of childbearing potential

Participants suspected to be pregnant by the investigator even if a serum pregnancy test is negative will not be eligible.

5.2 Exclusion Criteria, Item 7, HBV

HBsAb will be tested for the participants enrolled in Japan. If HBsAb is positive, quantitate HBV-DNA will be tested. If HBV-DNA is ≥20 IU/ml along with HBsAb being positive, the participant will be excluded from the study.

Note on measures to be taken to ensure the safety of participants: Investigators will continue to monitor HBV reactivation during the study treatment based on the Japanese HBV guidelines for immuno- and chemotherapy.

8.1.3 Contraception

Contraceptive measures which are considered highly effective comprise combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal*, transdermal*), progestogen-only hormonal contraception associated with inhibition of ovulation (oral*, injectable*, implantable*), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner and sexual abstinence. *Not approved in Japan.

Tolerability assessment

The safety and tolerability of Japanese participants will be assessed in the initial 9 participants to be recruited in Japan using the DLT-like criteria shown below. The safety and tolerability will be assessed during the initial 5 weeks for each participant (= DLT-like assessment period).

The IDMC will review the safety data in an unblinded manner and make a recommendation on the acceptability of continuation of recruitment of Japanese participants.

1. If the incidence of DLT-like adverse events is <40% in the xevinapant arm, treatment will be determined to be tolerable.
2. If the incidence of DLT-like adverse events is ≥40% in the xevinapant arm, tolerability will be assessed by the IDMC after referring to the safety in non-Japanese and Japanese participants for both the xevinapant and placebo arm, as well as other existing clinical information, and also taking the limitation of small sample size into consideration. The IDMC will make a recommendation on the enrollment of additional participants for further safety and tolerability assessment, withholding further recruitment in Japan, or continuing recruitment.

3. If there are ≤2 Japanese participants amongst the first 9 participants randomized to the xevinapant/CRT arm, enrollment will be continued up to a total of 12 participants.
4. If amongst the participants enrolled into the xevinapant/CRT arm, it is still difficult to determine tolerability, additional participants from Japan will be enrolled until there are an additional three participants in the xevinapant/CRT arm. Assessment of tolerability will thereafter be repeated.

DLT-like criteria were defined as any of the following laboratory abnormalities or treatment-related AEs occurring during the DLT-like assessment period that are assessed as related to investigational treatment:

1. Asymptomatic CTCAE Grade 4 neutropenia that persists > 7 days
2. CTCAE Grade ≥ 3 febrile neutropenia
3. Grade 4 Thrombocytopenia without bleeding lasting ≥ 5 days or Grade ≥ 3 thrombocytopenia with bleeding or requiring platelet transfusion.
4. CTCAE Grade ≥ 3 non-hematologic toxicity, including but not limited to (also see exceptions below)
    - Renal function based on eGFR
5. CTCAE Grade 4 skin or mucosal reactions
6. A dose of less than 60% of the planned dose of xevinapant per cycle due to treatment-related AE occurring during the DLT period
7. CDDP treatment delay > 2 weeks due to a treatment-related AE occurring during the DLT period
8. CTCAE Grade 2 or higher ototoxicity worsening by 2 grades or more from baseline
9. Any other life-threatening toxicity
10. Grade 5 toxicity

Exceptions,

I. Grade 3/4 nausea, vomiting, and diarrhea will be considered DLTs if they persist > 3 days despite optimal therapy. Grade ≥ 3 alopecia, fatigue and anorexia will not be considered DLTs
II. Common CRT related grade 3 toxicities including laryngeal inflammation, skin reaction, dysphagia, oral dysesthesia, mucositis, mucosal infection, skin infection, oropharyngeal pain, laryngitis, pharyngitis, decreased appetite, salivary duct inflammation, radiation recall reaction, and xerostomia will not be considered DLTs
III. CTCAE Grade ≥ 3 lab abnormalities that are not clinically significant will not be considered DLTs
IV. Amylase increases originating from the salivary gland will also not be considered DLT

13.9. Country-Specific Amendment for China

With the following additions and exceptions, all country-specific protocol requirements are outlined within this protocol.

The intention of the China-specific extension cohort is to allow for the collection and analysis of data from approximately 106 China Mainland participants to adequately represent the Chinese population. A separate analysis evaluating the Chinese population randomized in the global study and in the China-specific extension cohort will be conducted. This analysis will be referred to as the "overall Chinese population analysis" throughout this document.

The extension cohort will be opened for enrollment once the necessary approvals to implement the extension cohort have been obtained and the randomization of participants to the global ITT population has been completed.

As an exception to Section 6.3, although anticipated to be distributed to CRO and Sponsor team at the Primary Analysis of the global study, the randomization codes for China Mainland participants included in the global ITT population will be maintained blinded to the study participants and Investigators/site personnel until the overall Chinese population analysis. In addition, randomization codes for all participants randomized in the China-specific extension cohort will be kept confidential and maintained blinded to the study participants, Investigators/site personnel, CRO and Sponsor team until the overall Chinese population analysis. However, randomization codes will be disclosed to the third party laboratory in charge of bioanalytical assays C [redacted] to prevent analyses of placebo participants' samples while allowing C [redacted] sample analysis within the sample stability period.

Overall Chinese population analysis

Participants from China Mainland enrolled prior to global enrolment completion (n=700) will be included in the global ITT population for Primary Analysis.

A separate analysis referred to as the "overall Chinese population analysis" will be performed. The sample size for this analysis will comprise approximately 106 China Mainland participants, as follows:

- China Mainland participants randomized into the global study, who will also be included in the Primary Analysis based on the global ITT population (approximately 700 participants).
- Additional China Mainland participants randomized into the China-specific extension cohort. These participants will not be part of the global ITT population.

Therefore, the sample size of the overall Chinese population analysis will correspond to approximately 15% of the global ITT population, based on a sample size of 700 participants.

As outlined in Section 10.3, the overall Chinese population will follow the same ITT principle, and accordingly the China-specific Safety C [redacted] analysis sets will be defined and used for the planned analysis of data from the approximately 106 China Mainland participants.

The statistical considerations described in Section 10.4 are applicable for the overall Chinese population analysis with the following exceptions:

- General approach: no inferential test will be performed. The primary and secondary efficacy objectives will be summarized in the predefined order specified in Section 10.1 but the hierarchical testing procedure is not applicable. The objective of the overall Chinese

population analysis is to evaluate the HR from the analysis of EFS as assessed by the BIRC, and the analyses for other endpoints are considered as supportive.

- Analysis of the Primary Efficacy Endpoint: the log-rank test is not applicable.
- Analysis of the Secondary Efficacy Endpoints: as specified in the general approach, the testing procedure is not applicable.
- Safety analyses: In addition to the analyses in Section 10.4.4, safety analyses for the overall Chinese population as well as for the pooled population (global safety analysis set combined with the China-specific extension cohort) will be performed at the same cut-off date.
- Planned analyses: the overall Chinese population analysis will be triggered once 65 EFS events are observed in China Mainland participants, and it is anticipated to occur 1 year after the Primary Analysis based on the global ITT population. The consistency of the results in EFS between the global ITT population and the overall Chinese population is demonstrated if the observed risk reduction for EFS events in the Chinese population is at least 50% of the observed risk reduction in Primary Analysis of the global ITT population. Assuming the same HR of 0.73 for the benefit in EFS, an overall number of approximately 106 China Mainland participants with 65 EFS events provides at least 75% probability of achieving consistent results in EFS between the global ITT population and the overall Chinese population.
- Subgroup analyses: the subgroup analysis by region will not be performed for the overall Chinese population analysis. Other subgroup analyses according to Section 10.4.8 will be considered as exploratory.

Further details on the analyses specific to the Chinese extension cohort are provided in the statistical analysis plan.

Prohibited or concomitant use of traditional Chinese medicines

Any traditional Chinese medication with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted during study treatment. Traditional Chinese medicines for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator. Any traditional Chinese medicines or herbal supplement, if known to be strong inhibitors/inducers of CYP 3A4 or inhibitors of P-gp, will not be permitted. Use of traditional Chinese medicines as part of next line of anticancer treatment should be documented as such.

13.10. Protocol Amendment History

The information for the current amendment is on the title page.

Section # and Name	Description of Change	Brief Rationale	Version Implemented
[redacted]			

Section # and Name	Description of Change	Brief Rationale	Version Implemented
[redacted]			
Appendix 13.3	Addition of further wording in the cisplatin hydration guideline to consider a more extensive hydration regimen under certain circumstances.	Further mitigation and management of renal toxicities guidance added to prevent nephrotoxicity in high risk patients	10.0
1.1 Synopsis 3 Objectives and Endpoints	Time to locoregional control and distant metastasis changed from assessment by BIRC to assessment by Investigator.	After an initial EFS event has occurred, the participant will enter the OS follow-up and no further imaging for tumor assessment will be collected according to the protocol. Therefore, BIRC will not be able to assess distant metastasis in case the first event was local recurrence or vice versa. In contrast, the Investigator will still have information on subsequent events and can provide them. Hence, assessment of these endpoints has been changed from BIRC to Investigator assessment.	9.0
1.1 Synopsis 5 Study Population 5.5 Strategies for Recruitment and Retention	Number of study sites changed from approximately 200 to 280.	Additional sites are opened to support study recruitment.	9.0
1.1 Synopsis 5.1 Inclusion Criteria 8.1.2 HPV Status in Participants with OPC	Addition of p16 cutoff definition for determination of HPV status for OPC participants.	To ensure consistency and alignment between local sites and central laboratory on HPV status determination for OPC participants.	9.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
1.1 Synopsis 1.3 Schedule of Assessments 3 Objectives and Endpoints 6.1.2.1 Xevinapant or Matched Placebo 8.3.8 Participant Diary C [redacted]	C [redacted]	[redacted]	[redacted]
1.1 Synopsis 4.1 Study Design and Overview 10 Statistical Considerations	Figure 3, Figure 4-1 and Table 10 updated to reflect the change from follow-up analysis to final analysis	A final analysis was added which is OS event driven and replaces the follow-up analysis.	9.0
1.1 Synopsis 5.2 Exclusion Criteria	#18 - History of other malignancies: T1a squamous esophageal carcinomas added as an exception. #19: Contraindication changed to include both MRI **and** CT scans	SCCHN patients with early squamous cell carcinoma of the esophagus (ESCN) are similar in prognosis as patients without ESCN and therefore can be considered eligible for clinical studies as the natural history and treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational drug. Participants able to undergo either enhanced MRI or enhanced CT can enter the study.	9.0
1.1 Synopsis 5 Study Population 5.5 Strategies for Recruitment and Retention 10.2.1 Sample Size	Assumed screening failure rate changed to 30% with approximately 1000 participants being screened.	Based on the currently observed screening failure rate the numbers have been adjusted.	9.0
1.3 Schedule of Assessments Section 8.3.6 Electrocardiograms	Remove ECG assessment at C4.	Available data do not suggest xevinapant has long-term effects on ECG.	9.0
1.3 Schedule of Assessments 8.3.7 Laboratory Tests 13.2 Cisplatin Administration	Additional renal function monitoring to take place 48 hours (±12 hours) after cisplatin infusion.	Monitoring included to avoid or mitigate renal toxicities.	9.0
4.1 Study Design and Overview 6.3 Measures to Minimize Bias CCI [redacted]	Introduction of a Firewall Team as an additional oversight committee.	Added to keep the study team blinded at Interim Analysis until a decision is made if the results are sufficient for a regulatory filing.	9.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
11.2.1 Independent Data Monitoring Committee			
6.1.2.3.1 Treatment Interruption	Compensation of missed RT fractions can be administrated at the end of treatment or during treatment at least 6 hours apart.	To facilitate treatment delivery as per local policies and reduce participant and site burden.	9.0
6.5.2 Medications to be Used with Caution 6.5.3.1.3 CYP3A4 low therapeutic index drugs or sensitive substrates	Midazolam and alfentanil added to Table 6-8. Alfentanil removed from Table 6-5. Apixaban removed from Table 6-6 (kept in Table 6-8)	Since xevinapant has the potential to strongly inhibit CYP3A4/5, the CYP3A4 sensitive substrates midazolam, apixaban, alfentanil, which may be used for the study population, are now added to the prohibited medication list (Table 6-8).	9.0
6.5.3.3 Prohibited or concomitant use of traditional Chinese medicines	New section on prohibited or concomitant use of traditional Chinese medicines added	Traditional Chinese medicine is employed to treat or prevent health problems. Use of traditional Chinese medicine may have an effect on efficacy and outcome of the study objectives.	9.0
6.5.3.5 6 Use of Other Investigational Agents and Devices 6.5.3.6 Use of Anticancer Treatments	Prohibition of treatment with an investigational agent other than xevinapant/placebo, use of other anticancer treatment or use of an investigational device added	To avoid overlapping efficacy or toxicity effects in the study disease that would impact the safety of the patient or the outcome of the study	9.0
Section 7.2 End of study	Definition of EOS updated to include the event-driven final OS analysis.	The event driven final OS analysis is added that specifies the OS testing strategy regarding effect size, control of the type I error, power, and number of events.	9.0
7.3 Premature Study Withdrawal	Addition of details on the reasons for withdrawal of participants from study by Investigator.	Provide clarity for Investigator of when a participant may be withdrawn from the study at his discretion.	9.0
7.3 Premature Study Withdrawal 9.4.2 Pregnancy	Removal of pregnancy as a trigger for premature withdrawal from study. Note: Pregnancy will remain a reason for discontinuation from study treatment.	There are no procedures during the OS follow up period that could interfere with pregnancy. Therefore, pregnancy is not a reason to be discontinued from the study, and these participants should be followed up for OS.	9.0
8.2.2 Clinical Assessment	Decision tree for the determination of tumor status added (Figure 8-1).	To help investigators with clinical assessment when histopathology results or other clinical data are not consistent with the radiology report.	9.0
10.1.2 Secondary Efficacy Hypothesis	Update of the secondary endpoints to be used for the hierarchical testing procedure.	To focus on OS only, as OS is the most reliable endpoint regarding clinical benefit and	9.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
		complements the primary endpoint EFS. .	
10.2.1 Sample Size Determination 10.2.2 Robustness of Sample Size 10.4.7 Planned Analysis	Non-binding futility analysis for the primary endpoint EFS added. Testing strategy for the secondary endpoint OS was specified.	To provide guidance for the IDMC via a futility boundary for the primary endpoint EFS at the interim analysis. To specify the OS testing strategy regarding effect size, control of the type I error, power, number of events.	9.0
10.4. Statistical Analyses	Cox Model: Method how to handle ties was updated.	In case of a high number of ties, which is the case in the situation of predefined scan intervals, a more appropriate method how to handle ties is replacing the proportional hazards model by the discrete logistic model.	9.0
10.4.4.1 Adverse Events	Definition of TEAE.	Time period was specified for clarity.	9.0
13.5 Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 applied to this study in locally advanced SCCHN	RECIST v1.1 revised by adding guidance on assessment for LA SCCHN.	Revised for clarity.	9.0
13.9 Country-specific Amendment for China	Country-specific Amendment for China added (v8.1 CHN)	To allow for the collection and analysis of data from approximately 106 China Mainland participants to adequately represent the Chinese population.	9.0
Throughout document	Minor editorial and document formatting changes.	Minor, therefore changes have not been summarized.	9.0
Synopsis: Study Population and Sample Size Section 4.1: Study Design and Overview Section 5: Study Population Section 5.5: Strategies for Recruitment and Retention. Section 10.2.1: Sample Size	Added wording on the addition of a China-specific extension cohort.	An additional China-specific extension cohort is added to increase the sample size of the overall Chinese population to approximately 15% (106 subjects) of the global ITT population, to adequately represent the Chinese population.	8.1
Section 10.3: Analysis Populations	Added wording on global study population.	Clarify that the analyses sets in this section are described for the global study population.	8.1
Section 11.3.2: Future Use of Stored Specimens and Data	Explanation added that for China, the use of remaining samples will	Clarify the future use of specimen in China.	8.1

Section # and Name	Description of Change	Brief Rationale	Version Implemented
	be in accordance with local regulation.		
Section 13.9: Country-specific Amendment for China	New country-specific section added to include information on the inclusion of a China-specific extension cohort. The analysis of the overall Chinese population is described.	An additional China-specific extension cohort is added to increase the sample size of the overall Chinese population to approximately 15% (106 subjects) of the global ITT population, in order to adequately represent the Chinese population.	8.1
	Wording added to prohibit traditional Chinese medicine for anticancer treatment and if they are known to be strong inhibitors/inducers of CYP 3A4 or inhibitors of P-gp.	Traditional Chinese medicine is employed to treat or prevent health problems. Use of traditional Chinese medicine may have an effect on efficacy and outcome of the study objectives.	8.1
Section 13.10: Protocol Amendment History	Addition of the last amendment (V8.0).	Changes made in V8.0 have now become part of the amendment history.	8.1
Throughout Document	Minor editorial and document formatting changes.	Minor, therefore changes have not been summarized.	8.1
Entire document	**Merck KGaA, Darmstadt, Germany** replaces ~~Debiopharm~~ **Changed "Debio 1143" to "xevinapant" as applicable**	Updated due to change in sponsors	8.0
Updates to Title Page section	Added protocol amendment history **Added Merck KGaA, Darmstadt, Germany protocol number** MS202359 _0006	To align with sponsor standards	8.0
Section 1.1	MS202359 _0006	Added new study number	8.0
Table 1-1, Footnote 12	**For subjects switching to carboplatin on C2D2 and/or~~C2D3~~** C3D2**, 1 additional** C [redacted] **sample should be collected at the end of the carboplatin infusion.**	To align with Section 8.4.1	8.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
Section 4.3	**Tumor penetration and target engagement (IAP1 degradation) in the tumor was shown in Phase 2 studies Debio 1143-201 and Debio 1143-SCCHN-202. In the blood,** ~~T~~target engagement ~~**In the study Debio 1143-HCCHN-202, intratumoral pharmacokinetic (PK) measurements identified high Debio 1143 tumor penetration and distribution, largely exceeding the IC50 of IAPs, which are the targets of Debio 1143, by 100 to 1000-fold at the dose level of 200 mg.**~~	Clarified PK outcomes	8.0
Section 6.1.2.1.2, Table 6-1	In Hearing Impaired row, 1st occurrence: **For subjects on carboplatin** ~~**or switching to carboplatin**~~**: resume treatment at AUC=4.**	Subjects do not switch to carboplatin from carboplatin	8.0
Section 6.1.2.3.	~~**An elective intermediate 63 Gy volume at the periphery of the PTV (1.8 Gy/fraction per week [5/7 days]) is not recommended but if it is used will not be considered as a deviation (Hodapp 2012; Garden et al. 2013; Daly et al. 2010).**~~	Deleted to align with Intensity Modulated Radiation Therapy manual and international guidelines	8.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
[redacted]			
Sections 9.3 and 9.4.2	Updated SAE reporting information: If for any reason the eCRF is not available, as a backup option, the SAE can be declared by email at **SafetyReporting@SyneosHealth.com** ~~Safety-Debio-1143-301@debiopharm.com~~ using the ~~Debiopharm International (DPI)~~ paper "SAE report form" 1-877-464-7787 ~~**41 21 321 06 97**~~	Updated due to change in sponsors	8.0
Section 13.8	**Country-specific Amendment for Japan added**	To incorporate changes requested by the local health authority	8.0
Section 13.10	**Moved and updated Protocol Amendment History (formerly Section 11.4.1.2.1.1.1.1 and currently Section 11.5) to Section 13.9**	To align with sponsor standards	8.0

Section # and Name	Description of Change	Brief Rationale	Version Implemented
Section 13.11	**Updated and moved Sponsor Signature Page**	To align with sponsor standards	8.0
Section 13.12	**Updated and moved Coordinating Investigator Page**	To align with sponsor standards	8.0
Section 13.13	**Updated and moved Principal Investigator Page**	To align with sponsor standards	8.0
Section 6.1.2.1.2, Table 6-1	In Hearing Impaired row, 1st occurrence: For subjects on carboplatin ~~or switching to carboplatin~~: resume treatment at AUC=4.	Subjects do not switch to carboplatin from carboplatin	7.2
Section 13.8	**5.1 Clarification for Inclusion Criteria, Item 11, Women of childbearing potential** **Participants suspected to be pregnant by the investigator will not be eligible even if a serum pregnancy test is negative.**	Per health authority requirements	7.2
Section 13.8	**Note on measures to be taken to ensure the safety of participants: Investigators will continue to monitor HBV reactivation during the study treatment based on the Japanese HBV guidelines for immuno- and chemotherapy.**	Per health authority requirements	7.2
Section 13.8	4. CTCAE Grade ≥ 3 non-hematologic toxicity, including but not limited to (also see exceptions below) • ~~CTCAE Grade 3 or higher worsening of renal~~ **Renal function based on GFR**	Per health authority requirements	7.2
Section 13.8	6. ~~CDDP and/or xevinapant~~ **A dose of less than 60% of the planned dose of xevinapant per cycle due to treatment-related AE occurring during the DLT period**	Per health authority requirements	7.2
Section 13.8	7. CDDP ~~and/or xevinapant~~ treatment delay > 2 weeks due to a treatment-related AE occurring during the DLT period	Per health authority requirements	7.2
Entire document	**Merck KGaA, Darmstadt, Germany** replaces ~~Debiopharm~~	Updated due to change in sponsors	7.1
Updates to Title Page section	Added protocol amendment history	To align with sponsor standards	7.1

Section # and Name	Description of Change	Brief Rationale	Version Implemented
Table 1-1, Footnote 12	For subjects switching to carboplatin on C2D2 and/or~~C2D3~~ **C3D2**, 1 additional [redacted] sample should be collected at the end of the carboplatin infusion.	To align with Section 8.4.1	7.1
Section 4.3	**Tumor penetration and target engagement (IAP1 degradation) in the tumor was shown in Phase 2 studies Debio 1143-201 and Debio 1143-202. In the blood,** ~~T~~target engagement ~~In the study Debio 1143-HCCHN-202, intratumoral pharmacokinetic (PK) measurements identified high Debio 1143 tumor penetration and distribution, largely exceeding the IC50 of IAPs, which are the targets of Debio 1143, by 100 to 1000-fold at the dose level of 200 mg.~~	Clarified PK outcomes	7.1
Section 6.1.2.3.	~~An elective intermediate 63 Gy volume at the periphery of the PTV (1.8 Gy/fraction per week [5/7 days]) is not recommended but if it is used will not be considered as a deviation (Hodapp 2012; Garden et al. 2013; Daly et al. 2010).~~	Deleted to align with Intensity Modulated Radiation Therapy manual	7.1
Sections 9.3 and 9.4.2	Updated SAE reporting information: If for any reason the eCRF is not available, as a backup option, the SAE can be declared by email at **SafetyReporting@SyneosHealth.com** ~~Safety-Debio-1143-301@debiopharm.com~~ using the ~~Debiopharm International (DPI)~~ paper "SAE report form" **1-877-464-7787**~~41 21 321 06 97~~	Updated due to change in sponsors	7.1
Section 13.8	Country-specific Amendment for Japan added	To incorporate changes requested by the local health authority	7.1
Section 13.9	Moved and updated Protocol Amendment History (formerly Section 11.4.1.2.1.1.1.1) to Section 13.9	To align with sponsor standards	7.1
Section 13.10	Updated and moved Sponsor Signature Page	To align with sponsor standards	7.1
Section 13.11	Updated and moved Coordinating Investigator Page	To align with sponsor standards	7.1
Section 13.12	Updated and moved Principal Investigator Page	To align with sponsor standards	7.1

13.10.1. Protocol Amendments 1 through 6

The amendment must be approved by the Sponsor and, if substantial as defined in directive 2001/20/EC or other local applicable regulations, submitted for approval to the Health Authorities and IEC/IRB prior to being implemented. If the change implies a modification of treatment or of subject evaluation tests, a new version of the ICF must be prepared and submitted for approval to Health Authorities and the IEC/IRB. The Sponsor will assume any responsibility or liability resulting from a change in the protocol, only if the change has been approved in writing by himself, the Health Authorities, and the IEC/IRB.

13.10.1.1. Protocol Amendment History Prior to Merck KGaA Sponsorship

13.10.1.1.1. Amendment 1 - 12 May 2020

The original protocol (*V1.0 dated 02 April 2020)* was amended on 12 May 2020 (*V2.0 dated 12 May 2020)* to correct a typo in the gender specific QTcF values mentioned in the exclusion criterion 16. The standard QTcF values for male and female patients were unintentionally reversed in the original protocol.

13.10.1.1.2. Amendment 2 - 2 July 2020

The protocol V2.0 dated 12 May 2020 was amended on 2 July 2020 (*V3.0 dated 2 July 2020)* further to modification requests from Regulatory Authorities. These requests included:

- The addition of a recommendation on cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with cisplatin, carboplatin or Debio 1143.
- The addition of an ECG examination before starting Cycle 4 with Debio 1143 monotherapy.
- The addition in the prohibited medication list of live-attenuated vaccinations during the treatment with Debio 1143/matched placebo and up to 90 days after the end of treatment.
- CCI [redacted]
- A clarification of the assumptions used for the sample size calculation.
- A clarification of dynamic allocation.

In addition, the following changes were made:

- Correction regarding laboratory assessments: all laboratory parameters included in the full hematology and full chemistry panels will be performed centrally even if they are performed locally. Estimated volume of blood collected during the study remains identical.
- Throughout the protocol, minor edits, clarifications, correction of typographical errors and formatting were made to improve readability.

13.10.1.1.3. Amendment 3 - 23 July 2020

Protocol V3.0 dated 2 July 2020 was amended on 23 July 2020 (*V4.0 dated 23 July 2020)* to clarify the randomization procedure as requested by Regulatory Authorities.

13.10.1.1.4. Amendment 4 - 6 December 2020

Protocol V4.0 dated 23 July 2020 was amended on 6 December 2020 (*V5.0 dated 6 December 2020)* further to modification requests from the French Regulatory Authority Agence Nationale de Sécurité du Medicament et des produits de Santé (ANSM).

To answer those requests the following modifications were made to the protocol:

- Exclusion of patients with hypersensitivity to the active substances or other compounds containing platinum.
- Additional information on the management and dose modification of the Investigational Medicinal Products in case of hemolytic uremic syndrome.
- Additional information on the management and dose modification of the Investigational Medicinal Products in case of allergic reactions.
- Addition of an optional audiogram before each new cycle of cisplatin throughout the study, as required per the cisplatin prescribing information.
- Additional information on the prohibited medications and medications to be used with caution in combination with cisplatin and carboplatin, following the prescribing information of these products.
- Clarifications on the timing of study procedure:
    - The wording of the inclusion criteria number 8 was modified to clarify that an audiogram must be performed at screening, in alignment with the initial instructions provided in the *Section 8.3.5 Audiogram*.
    - The Section *8.1.1 Baseline Disease Characteristics and Assessments* was updated accordingly.
- Other modifications:
    - The new International Nonproprietary Name of Debio 1143 (xevinapant) was introduced in the protocol.
    - Throughout the protocol, a few minor edits were made.

13.10.1.1.5. Amendment 5 - 7 December 2020

Protocol V5.0 dated 6 December 2020 was amended on 7 December 2020 (*V6.0 dated 7 December 2020)* to include the following modifications:

<u>Clarifications on the primary endpoint:</u>

- The time window for primary treatment failure, which is one of the EFS components, was clarified as follows: only events occurring during the treatment period, and up to the EOT visit,

are considered as primary treatment failures. This rule aims to correct for potential bias in the follow-up schedules for tumor assessment.

Clarifications on statistical analyses:

- The stratification factors to be used for the statistical test of the EFS, PFS, OS and all time-to-event analyses were clarified. The list of stratification factors is now limited to tumor size and lymph node involvement, but the type of test remains the same (stratified log-rank test). The 4 randomization factors originally proposed would result in 36 strata, which could lead to sparse sample size in some strata. The stratification factors retained are considered the most relevant while assuring sufficient sample size.
- Correction of a typo in the Table 10 4 Robustness of sample size for OS: the title of the column mentioning Expected Number of Death Events and Expected Power provided should read **Primary Analysis** instead of *Follow up analysis*.

Extension of safety data collection:

- The time window for collection of SAEs and late onset AESIs unrelated to study treatments was extended during the follow-up period as follows:
    - SAEs will be collected until the EOS visit regardless of their relationship with study treatments. Previously only SAEs considered related to study treatments were to be collected during the follow-up period.
    - Late onset AESIs will be collected from the EOT until the EOS visit regardless of their relationship with study treatments. Previously, only late onset AESIs related to study treatments were to be collected from Month 7 until the EOS visit.
- Clarifications on the reporting of death when related to disease progression: only death attributed by the Investigator as **solely** due to disease progression are not considered as SAEs.
- Clarification that AE, SAE and AESI data will be collected for all study treatments, including IMRT.

Clarifications on data collection:

- The EFS data collection starting date was added in the Study Diagram.
- The row “EFS data collection” was added to the Tables of assessment 1-1 as a reminder to collect EFS data status throughout the study.
- The row “Progression status (until potential EFS event)” was renamed “EFS data collection” for clarity. The parentheses around the arrow which indicated that the EFS data collection follow-up was to be performed until an EFS event was removed for consistency with the lack of parenthesis for the row “Survival status”.
- Pregnancy was added as a reason for premature study withdrawal in Section 7.3, for consistency with the safety Section 9.4.2.

- The study flow chart was modified to clarify that the EOT will occur 15 days after last **study treatment administration** (Debio 1143, placebo, chemotherapy or IMRT) not only *Debio 1143/placebo treatment*, in alignment with the Study assessment table.
- Removal of an instruction regarding data collection in case of rescreening to avoid redundancy within the same section and given that all data are collected in the same database (Section 5.4 Screen failure).

Modifications on the timing of study procedures:

- The timing of approval of the IMRT plan by RT-QA Review Center was modified as follows: the IMRT plan should be approved **before the start of radiotherapy** instead of *before randomization*. This change does not impact the eligibility of a patient for the study. In addition, a mention to the approval of the IMRT plan by the RT-QA Review Center prior to the start of the IMRT was added in the Section 1.3 Schedule of Assessment for consistency.
- Alignment with the ITT analysis principles: if several i.v. contrast-enhanced CT scans/MRI of the head and neck and CT scans of the chest are available before treatment start, the closest imaging **to randomization,** instead of *Cycle 1 Day 1*, will be used as baseline.
- Physical examination abnormalities are to be recorded as an AE if started on or after **ICF signature** instead *after randomization*.

Clarifications regarding chemotherapy administration:

- A cross reference to Section 6.1.2.1.2 was added in the synopsis and included the dose of carboplatin to be used in case of toxicity after the first cisplatin dosing.
- A reminder to consult and follow cisplatin administration instructions provided in the local label was repeated in Section 6.1.2.2.
- The description of the reconstitution of cisplatin in Section 13.2 was removed given that the cisplatin formulation provided to sites does not need to be reconstituted.

Other modifications:

- Additional information on the RT-QA Review Centers selected for the study was added.

13.10.1.1.6. Amendment 6 – 28 June 2021

The protocol for study Debio 1143-SCCHN-301 version 7.0 dated 28 June 2021 has been amended to reflect the following changes:

Modification of inclusion criterion number 8

Most adults with clinically normal hearing demonstrate some evidence of mild hearing loss at certain frequencies by pure tone audiometry test. The current inclusion criterion number 8 stating *"No hearing loss by clinical assessment and audiogram*", appears to exclude these patients, even though clinically the Investigators would proceed with cisplatin-radiation therapy as the gold standard curative-intent treatment. The inclusion criterion number 8 has been modified as follows: *No hearing loss by clinical assessment or ≤ grade 2 hearing impairment (according to NCI-CTCAE v.5).*

Granulocyte-Colony Stimulating Factors (G-CSF) use

The study IDMC requested to exclude prophylactic use of G-CSF and provide further guidance on its use in the protocol. The following explanation has been included in Section 6.5.4:

Granulocyte-Colony Stimulating Factors (G-CSF) are not allowed throughout the screening period and for prophylaxis. Nevertheless, for subjects presenting with febrile neutropenia who have risk factors for infection-related complications or poor clinical outcome, therapeutic G-CSF including secondary prophylaxis should be considered (Becker et al. 2020). Features associated with poor outcome include age >65 years, sepsis syndrome, ANC <100 neutrophils/m^3, anticipated prolonged (>10 days) neutropenia, pneumonia or other clinically documented infection, invasive fungal infections, and hospitalization at the time of fever.

In Table 6-1 (neutrophil count decrease row), the note stating that "the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis is recommended if chemotherapy is continued" has been removed to be consistent with the IDMC request.

Abnormal QTcF prolongation definition and triplicate ECG recordings

An inconsistency in the current protocol version 6.0 concerning the definition of abnormal QTcF prolongation requiring a triplicate ECG recording has been detected between Section 9.1.3 and Section 8.3.6.

In Section 9.1.3, abnormal QTcF prolongation is defined when at least 2 consecutive ECG readings show an increase of more than 30 ms compared to the baseline value.

In Section 8.3.6, a triplicate ECGs is requested when a significant prolongation of >500 ms or change from baseline of >60 ms is observed.

The definition of abnormal QTcF prolongation requiring a triplicate ECG recording has been modified in Section 8.3.6 as follows: *"In case of **abnormal** ECG findings (e.g., QTcF prolongation >30 ms compared to baseline, or QTcF interval >500 milliseconds), ……, triplicate ECG readings will be performed".*

Audiometry assessment

Audiometry is mandatory only at screening. Considering the current COVID-19 pandemic, the safety of the study participants is of primary importance since patients with cancer are at higher risk of severe complications caused by COVID-19 infection. Therefore, special attention should be paid in reducing the unnecessary patients' visits to the investigational sites, mainly due to the execution of complimentary clinical assessments.

The current protocol version 6.0 includes several sequential audiometry tests. Since audiometry at screening is mandatory to evaluate the eligibility of the subject, further audiometry tests may be performed only if clinically indicated as per institutional or national guidelines.

In Section 8.3.5 and in Table 1-1 (footnote 10), the text has been modified as follows: *"An audiometry must be performed at screening. In addition, hearing clinical evaluation and audiometry should be performed at C2D1 and C3D1 if clinically indicated (except for France, see Appendix 13.6 and at any time if clinically indicated as per institutional or national guidelines. During the follow-up period, an audiometry is to be performed only if clinically indicated, as per institutional or national guidelines."*

The Appendix 13.6 Audiometry assessments has been added to provide the following information to investigational sites in France: *"*As requested by the French ANSM, an audiometry must be performed at screening, C2D1 and C3D1 within 5 days before platinum-based chemotherapy and at any time if clinically indicated as per institutional or national guidelines. During the follow-up period, an audiometry is to be performed only if clinically indicated, as per institutional or national guidelines*".*

Frequency of follow-up contacts for survival status

To mitigate the potential risk of subjects lost to follow-up during the survival follow-up period, the frequency of survival follow-up contacts has been reduced from 6 to 3 months.

Discontinuation of IMRT and subject admission to monotherapy period

In line with the rationale to include xevinapant monotherapy to increase the subject outcome benefit and considering that an ITT analysis will be performed, the inclusion of all the enrolled subjects in the monotherapy period is now allowed, even if they received a total radiotherapy dose less than 50 Gy.

In Section 6.1.2.3.1, the text has been accordingly modified as follows: *"If IMRT is permanently discontinued due to severe and intolerable toxicities as per Investigator's judgment, then Debio 1143/matched placebo monotherapy administration should be maintained*."

Collection of efficacy assessments and Patient-Reported Outcomes (PROs)

In Section 8.2 the following instructions were added: *Tumor assessment and HRQL questionnaires or assessments should be continued until disease progression (as per RECIST v1.1) occurs or Month 60 post-randomization, whichever occurs first.*

The resulting data will be used in a sensitivity analysis of the secondary efficacy endpoints.

Even in case of premature discontinuation of treatment in subjects without disease progression according to RECIST v1.1 (e.g., unacceptable toxicity), efficacy assessments will continue to be performed until disease progression (as per RECIST v1.1) to correctly evaluate all the secondary efficacy endpoints or Month 60 post-randomization, whichever occurs first.

Radiological tumor assessments at screening

Section 1.3, Table 1-1(footnote 4) and Section 5.4 have been modified to clarify that ^{18}F-FDG-PET, i.v. contrast-enhanced CT-scan or MRI of head and neck, and CT-scan of chest are only accepted if they are performed within 4 weeks before randomization. This will minimize the risk of distant metastasis or tumor growth before randomization and the beginning of treatment.

Pharmacokinetics (PK) subgroup expansion and extra PK sampling

To ensure sufficient collection of PK data to characterize PK disposition, the timepoints and the exploratory endpoints of the Debio 1143/placebo PK blood sampling have been modified. The new timepoints are C3D8, C3D15 and C4D1. PK blood samples will be drawn predose on C1D1, C1D2, C1D8, C2D2, C3D1, C3D2. On C3D8, C3D15, C4D1, the PK blood sample will be drawn at the time of hematology/biochemistry blood sampling. An optional pharmacogenetic blood sample will be drawn predose on C1D1 (except for China).

The PK sample size has been expanded to include all the enrolled subjects.

This was modified across the protocol in all the relevant sections.

CCI [redacted]

Recommendation for the SARS-CoV-2 vaccination during study treatment

Considering the pandemic situation, recommendations for the SARS-CoV-2 vaccination during study treatment were included in Section 6.5.1.2.

Conducing the study during the COVID-19 pandemic

German BfArM requested to perform a benefit/risk assessment of the conduct of the study during the COVID-19 pandemic. This has been included in Appendix 13.7 and is specific for the investigational sites in Germany.

CCI [redacted]

Cisplatin hydration guidelines

TEVA cisplatin 1mg/ml or other registered cisplatin brands are provided for the study. Recommended hydration guidelines (per TEVA SmPC v6.0) are provided in Section 13.3.

Archival tumor sample and pharmacogenetics blood sample for exploratory analysis

As the exploratory biomarkers will be analyzed centrally outside China and the Chinese regulations do not allow the exportation of samples outside the country, the collection of both archival tumor samples and pharmacogenetic blood samples for exploratory analysis are not applicable in China.

This was modified across the protocol in all the relevant sections.

ECG collection plan at C4D1

A postdose will be collected at C4D1 prior to the pharmacokinetic sampling and the blood sampling to enable calculation of AESI (change from baseline of > 30 ms) at both timepoints (pre-dose and post-dose).

Clarifications:

- Carboplatin administration should follow the local label instructions.

In Section 6.1.2.2, the text has been modified as follows: "*The subject can switch to carboplatin in C2 and/or C3 as per the dose modifications outlined in Table 6-1. Please consult and follow carboplatin administration instructions provided in your local label.*"

- Use of albumin transfusions.

Albumin transfusions are not allowed within 2 weeks before randomization. The text of exclusion criterion number 12 has been modified as follows: "*Documented weight loss of >10% during the last 4 weeks prior to randomization (unless adequate measures are undertaken for nutritional support), OR plasmatic albumin < 3.0 g/dL. No albumin transfusions are allowed within 2 weeks before randomization.*"

- Exclusion of subjects suffering from autoimmune diseases requiring treatment with anti treatment with antitumor necrosis factors (TNF) medication.

Subjects suffering from autoimmune disease requiring TNF medication are ineligible. The exclusion criterion number 14 has been modified as follows: "*Active uncontrolled inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis, and other autoimmune diseases) requiring ongoing treatment with anti-TNF medication*."

- Rules for subject's rescreening

It has been clarified that the subject's rescreening is allowed in case a reversible cause of screening failure is adequately treated and/or resolved. The text in Section 5.4 has been modified as follows: *"Reversible causes of screening failure that were adequately treated and/or resolved."*

- Premature discontinuation from all treatments and follow-up

In Section 6.1.2.1.2, new text has been added as follows: "*Subjects who prematurely discontinue from all treatments, i.e., chemotherapy, IMRT and Debio 1143/matched placebo, in the absence of an EFS event, will undergo the EOT visit and then enter the EFS follow-up period according to schedule."*

This new text has been added to be consistent with Table 1-2.

- End of treatment visit (EOT)

In Section 1.3, new text has been added to specify that EOT visit should be performed prior to the start of any subsequent anticancer therapy.

Radiotherapy Quality Assurance

To avoid confusion and misunderstanding with the company name of one of the vendors (QARC), the wording in Section 6.1.2.3 has been modified as follows: *"The RadioTherapy Quality Assurance (RT-QA) Review Center (Section 11.2.2) will centrally review the IMRT treatment plan(s) to ensure compliance with protocol guidelines and provide feedback to the site.*"

The abbreviation QARC has been replaced with RT-QA across all the protocol.

- Head and neck CT-scan

To avoid misleading interpretation, it has been clarified in Section 8.2.1 that i.v. contrast-enhanced CT-scan or MRI of head and neck should cover the orbits and ^{18}F-FDG-PET scan should be from the skull base to proximal upper legs.

- Radiation therapy scheme

After discussion with several radiation oncologists, the Table 6-3 has been modified replacing the technical terminologies "Gross Target Volume (GTV)" and "Clinical Target Volume (CTV)" with the most appropriate one "Planning Target Volume (PTV)".

- Central and local laboratory assessments at screening

To avoid misleading interpretation, the following sentence has been added in Section 8.1 *"The central laboratory assessments needed for subject eligibility are specified in* Table 8-2*. Local laboratory results only for HBV/HCV/HIV tests and HPV status obtained within 2 weeks before ICF signature may be accepted"*.

- IMRT dosage across the protocol

After discussion with several radiation oncologists, the GTV was replaced by the PTV and consequently, the wording of the IMRT has been modified as follows: *"IMRT (70 Gy in 35 fractions over 7 weeks, 2.0 Gy/fraction, 5 days/7)*".

- Blood transfusions

To avoid misinterpretation, transfusions mentioned in inclusion criterion number 10 were clarified as *blood transfusions*.

- Definition of eligibility to receive the study treatments

To avoid misinterpretation between the terms “enrolled” and “eligible”, the text in Section 1.3 has been modified as follows: *“A subject will be considered eligible to receive the study treatments after he/she has signed the ICF, all eligibility criteria have been met and the IMRT plan has been sent to the Radiotherapy Quality Assurance (RT-QA) Review Center (see Section 11.2.2). Randomization can be performed once the subject is considered eligible”.*

Other minor modifications:

- Section 1.3: Study treatment (C1D1) should begin within 7 days after randomization.
- Table 1-3: The visit window of ± 3 days on C2D2 and C3D2 were removed since these visits must be done the day after C2D1 and C3D1.
- Throughout the protocol, minor edits, abbreviations, correction of typographical errors and formatting were made to improve readability.

13.11. Sponsor Signature Page

Study Title:	A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2020-000377-25
Clinical Study Protocol Version:	V13.0, 18 March 2024, including amendments 1-12.0

[redacted]

Name, academic degree:	[redacted]
Function/Title:	[redacted]
Institution:	Merck, S.L.
Address:	María de Molina, 40 28006 Madrid, Spain
General Merck Phone Number:	0034 659797632
General Merck Fax Number:	Not Applicable

13.12. Coordinating Investigator Signature Page

Study Title:	A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2020-000377-25
Clinical Study Protocol Version:	V13.0, 18 March 2024, including amendments 1-12.0

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national

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21.03.2024

Date of Signature

Name, academic degree:	Þ
Function/Title:	Þ
Institution:	Þ
Address:	Þ
Telephone number:	Þ
Fax number:	Þ
E-mail address:	Þ

13.13. Principal Investigator Signature Page

Study Title:	A randomized, double-blind placebo-controlled, Phase 3 study of Debio 1143 in combination with platinum-based chemotherapy and standard fractionation intensity-modulated radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy (TrilynX)
Regulatory Agency Identifying Numbers:	EudraCT Number: 2020-000377-25
Clinical Study Protocol Version:	V13.0, 18 March 2024, including amendments 1-12.0
Site Number:	_____

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:	_____
Function/Title:	_____
Institution:	_____
Address:	_____
Telephone number:	_____
Fax number:	_____
E-mail address:	_____