Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Single Arm, Open label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants With Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy
Study Number:	MS202359_0025
Protocol Version:	27 November 2023/Version 2.0
Merck Compound:	Not applicable
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase 1b
Brief Title:	Phase 1b safety study of xevinapant, weekly cisplatin, and radiotherapy in participants with unresected LA SCCHN
Acronym:	HyperLynX
Coordinating or Principal Investigator:	Nabil F. Saba MD, FACP, Professor and Vice Chair, Hematology, and Medical Oncology The Lynne and Howard Halpern Chair in Head and Neck Cancer Research, Co-Director H&N CA Multidisciplinary Program Winship Cancer Institute Emory University

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Regulatory Agency Identifying Numbers:	IND:143330 EU trial number: 2023-505796-76-00
Keywords	Unresected, Combination with CRT, Stage III, Stage IVA, Stage IVB, oropharynx, hypopharynx, and larynx

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
2.0	Global Amendment	27 November 2023
1.0	Original Protocol	17 May 2023

Protocol Version 2.0 (27 November 2023)

Overall Rationale for the Amendment

The main rationale for this protocol amendment is to add inflammatory cutaneous adverse events as adverse event of special interest, to incorporate HA feedback on audiometric hearing tests during the treatment period and follow up period, on contraceptive period after cisplatin treatment, and to update the definitions of DLT-like events and add study stopping rules. Additionally, updates have been made to resolve identified discrepancies in the protocol.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities, Table 1, Table 2, and Table 3	Added weekly audiometry testing prior to weekly cisplatin dosing, if clinically indicated.	As per request from health authority

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criterion #9	To harmonize the period for contraceptive measures for chemotherapy across the protocol as per local guidelines and local product information.	As per request from health authority and IRB
5.2 Exclusion criterion #15	To change time period when a live attenuated vaccines can be used prior to start study intervention from 30 to 28 days.	To harmonize with Section 6.8.3.1Prohibited Medications with Xevinapant
6.5.2 Chemotherapy, and 6.8.1.1 Antiemetics	Update on proposed antiemetic regimens. Dexamethasone is proposed at 8 mg for Day 1 and 4 mg for Days 2 and 3 after cisplatin infusion; aprepitant is proposed to be taken only on Days 1 and 2 after cisplatin infusion.	Alternative dosage/schedule for anti-emetic regimens are proposed to mitigate DDI risks
8.2.5 Safety Monitoring Committee	To add that the SMC can decide to stop the study in case of unacceptable toxicities or treatment related deaths.	As per request from health authority
8.2.5.1 Definition of DLT-like events	Updated the definition of DLT-like events to include Hy's law cases and Grade ≥ 3 lab abnormalities, and exceptions to the Grade ≥ 3 lab abnormalities.	As per request from health authority
8.2.7 Audiometry	To add section for audiometry testing, which is to be done prior to weekly cisplatin dosing and follow up if clinically indicated.	As per request from health authority
8.3.4 Pregnancy	Updated reporting of pregnancy information in the CRF.	Updated in line with Sponsor requirements
CCI		
10 Reference list	Added new reference.	Updated to include the current reference list
Appendix 2	Update RECIST criteria to remove the recording of non-target lesions in evaluation visits.	Updated in line with study requirements
Appendix 3	Updated the section to harmonize the period for contraceptive measures for chemotherapy across the protocol as per local guidelines and local product information.	As per request from health authority and IRB
Appendix 5 Study Governance	Added paragraph on applicable regulations to protect personal data and updated the composition of SMC.	Added information to clarify follow-up if regulations to protect personal data are not followed, and to allow additional SMC members, if considered necessary
Appendix 7 Adverse Event	Updated information on use of paper form for SAE reporting, reporting of pregnancies, and reporting of AESIs.	Updated in line with Sponsor requirements
Appendix 8 Clinical Laboratory Test	Removal of alcohol and drug screen.	Assessment not needed for this patient population

Section # and Name	Description of Change	Brief Rationale
Throughout document	Minor editorial and document formatting revisions.	For clarity

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1 Protocol Summary

1.1 Synopsis

Clinical Study Protocol Title: A Single Arm, Open label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants With Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy

Brief Title: Phase 1b safety study of xevinapant, weekly cisplatin, and radiotherapy in participants with unresected LA SCCHN

Rationale: Xevinapant is an inhibitor of IAPs (inhibitor of apoptosis proteins) that has been shown in nonclinical in vitro and in vivo models to have both chemo- and radiosensitizing potential as well as immunomodulatory potential. In unresected LA SCCHN patients, the addition of xevinapant to SoC CRT using Q3W cisplatin (100 mg/m^2) recently showed a statistically significant and clinically meaningful improvement in locoregional control at 18 months compared to placebo with SoC CRT. Following the 36-month analysis, PFS also showed a clinically meaningful improved benefit from xevinapant versus placebo. Furthermore, a clinically relevant improvement in 5-year OS using xevinapant combined with CRT vs the control group was recently presented. The current Phase 1b study aims to assess tolerability and safety of xevinapant when added to QW cisplatin-based (CCI mg/m^2) concomitant CRT in the treatment of previously untreated participants with unresected LA SCCHN.

Objectives and Estimands:

Objectives	Endpoints	Further Estimand Attributes	Ref. #
Primary			
To evaluate tolerability of xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Occurrence of DLT-like events	Population: Treatment naïve patients with LA SCCHN (Stage III, IVA, or IVB) with histologically confirmed diagnosis in at least 1 of the following sites: oropharynx (HPV-negative), hypopharynx, and larynx, eligible to receive weekly cisplatin-based concurrent CRT Treatment: xevinapant, weekly cisplatin, and IMRT followed by xevinapant monotherapy Intercurrent Event Strategy: o Discontinuation/interruption/delay of xevinapant/cisplatin treatment (> 40% of planned cumulative dose missed in DLT-like assessment period) due to reasons other than treatment-related AE (composite strategy: to be considered as DLT-like event) o RT delay > 2 weeks during the DLT-like assessment period due to reasons other than treatment-related AE (composite strategy: to be considered a DLT-like event) Population-Level Summary: o DLT-like event rate and associated CI o Standard summary statistics	1
Secondary			
To characterize safety of xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Occurrence of AEs and treatment-related AEs CCI [redacted]	Population/Treatment: Same as #1	2
To evaluate clinical activity parameters using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1	Objective Response (OR) according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of new anticancer therapy: ignoring assessments after the intercurrent event (while not treated with new anticancer therapy strategy) • Progression according to RECIST 1.1: assessments up to the intercurrent event (while not progressed strategy) Population-level Summary: Response rates (i.e. CRR, ORR) including associated statistics	3

Objectives	Endpoints	Further Estimand Attributes	Ref. #
	PFS according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Death within 2 missing scheduled tumor assessments after last evaluable assessment or start of study intervention will be considered as event (composite strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of subsequent anticancer therapy: ignoring events after the start of a new anticancer therapy (hypothetical strategy) Population-level Summary: Kaplan-Meier estimates including associated statistics	4
	Locoregional control (LRC) according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Death: Assessments before death will be used (treatment policy strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of new anticancer therapy: ignoring events after the start of a new anticancer treatment (hypothetical strategy) Population-level Summary: Same as #4	5
To evaluate time to subsequent cancer treatments in participants treated with xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Time to subsequent systemic cancer treatments	Population/Treatment: Same as #1 Intercurrent Event Strategy/ Population-level Summary: Same as #5	6

Overall Design:

This is a multicenter, single arm, open label, Phase 1b study.

Brief Summary: The purpose of this study is to evaluate the tolerability and safety of xevinapant when added to weekly cisplatin-based concurrent CRT in the treatment of participants with unresectable locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy.

Study details include:

- Study duration: participants to be followed until the last on-study participant reaches his/her 18-month post-first treatment visit (EOS) a decision to end the study has been triggered, or until premature discontinuation from study, whichever occurs first.
- Treatment duration: 18 weeks, consisting of six 3-week cycles.

- Visit frequency: One to 3 visits a week during combination therapy period, once every 3 weeks during xevinapant monotherapy period, and every 3 months during the Follow-up period until EOS.

Since treatment is limited to 18 weeks no continued availability of xevinapant outside of the study protocol is foreseen.

Number of Participants: A total of approximately 40 participants will be assigned to study intervention. It is anticipated to conduct the study in the US, Europe, and Asia-Pacific.

Study Intervention Groups and Duration:

Participants who meet the eligibility criteria will be enrolled and will receive the following treatment:

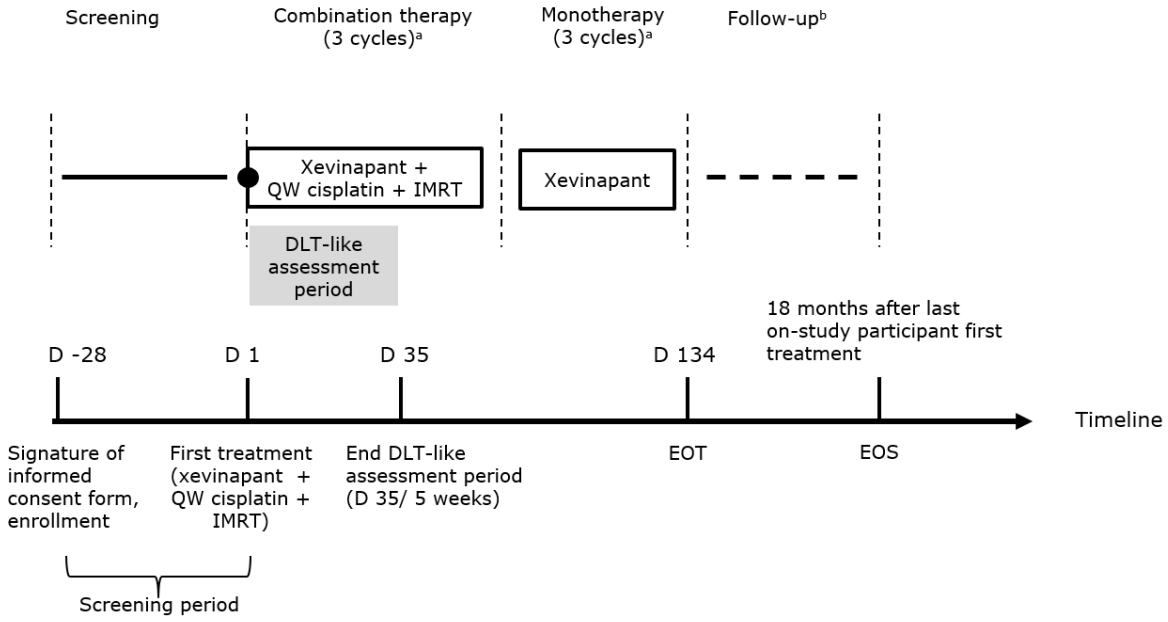
- 3 cycles of xevinapant (oral solution CCI mg/day from Day 1 to 14, per 3-week cycle) + weekly cisplatin (CCI mg/m^2 for 7 weeks on Cycle 1 Day 2 (C1D2), C1D9, C1D16, C2D2, C2D9, C2D16, and C3D2) + IMRT (70 Gy in 35 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of xevinapant (CCI mg/day from Day 1 to 14, per 3-week cycle).

Data and Safety Monitoring /Other Committee: Yes

A Safety Monitoring Committee (SMC) has been appointed for this study. The SMC consists of Sponsor representatives and the Coordinating Investigator.

1.2 Schema

Figure 1 Study Diagram



D=day, DLT=dose-limiting toxicity, EOS=end of study, EOT=end of treatment, IMRT=intensity-modulated radiation therapy, QW=once weekly.

a. Each cycle consists of 3 weeks.

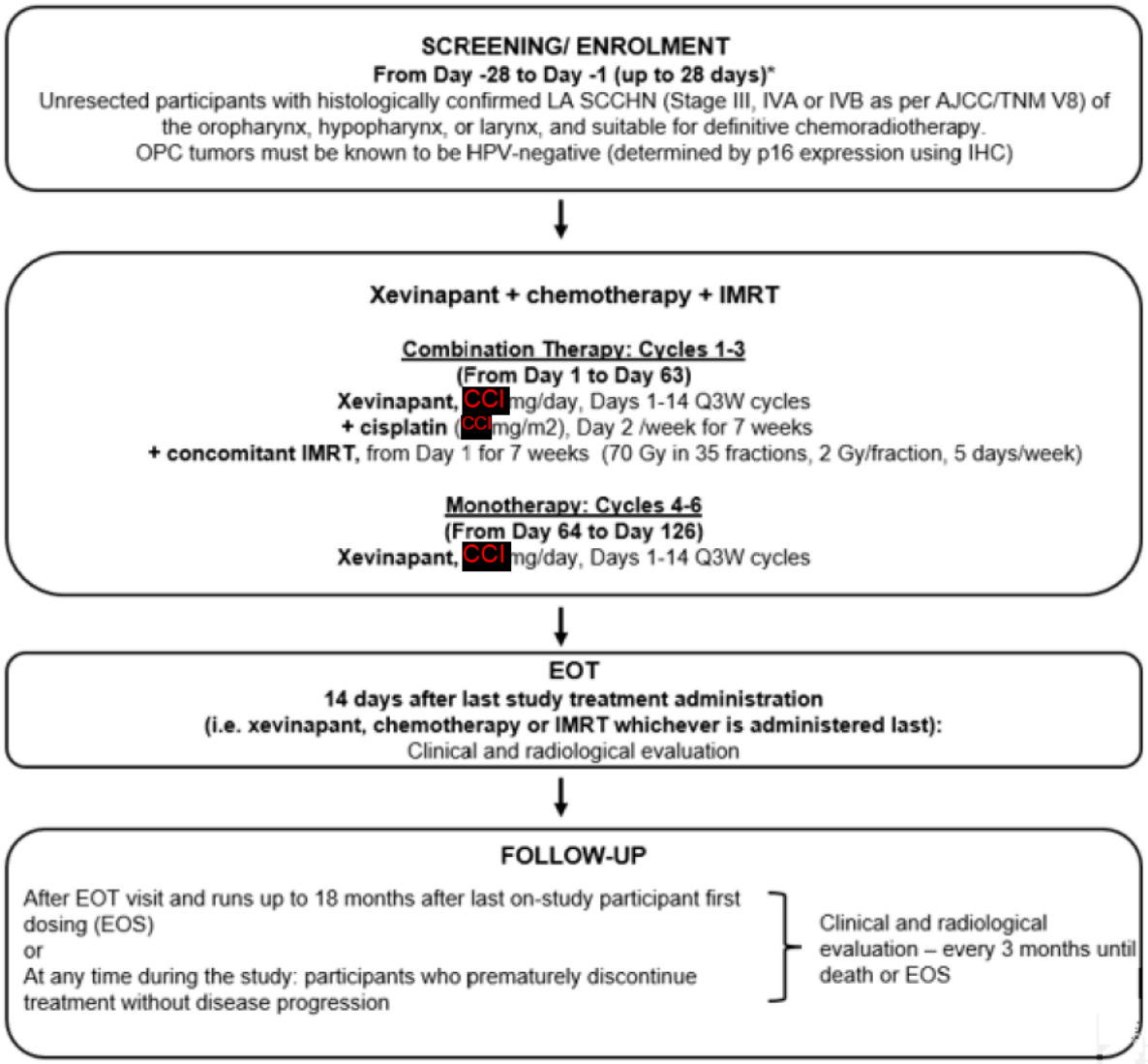
b. Follow-up period starts after EOT visit and runs up to 18 months after last on-study participant first dosing.

Note: Round filled shape at Day 1 indicates start of treatment.

The study flow chart is shown in Figure 2.

Note: For a detailed overview of all visits, assessments, and visit windows, see Table 1, Table 2, Table 3, and Table 4.

Figure 2 Study Flow Chart



CT=computed tomography, EOS=end of study, EOT=end of treatment, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficient virus, HPV=human papilloma virus, IHC=immunohistochemistry, IMRT=intensity-modulated radiation therapy, LA SCCHN=locally advanced squamous cell carcinoma of the head and neck, OPC=oropharyngeal cancer, PET=positron emission tomography, q3w=every 3 weeks.

* Dental examination, audiometry, HBV/HCV/HIV tests, fiberoptic endoscopy, and ^{18}F-FDG-PET scan performed within 4 weeks before ICF signature do not have to be repeated during Screening. See Section 1.3 for details.

1.3 Schedule of Activities

The schedule of the completion of the study visits/procedures is presented in Table 1, Table 2,

Table 3, and Table 4. 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 ICF and can last up to 28 days.

Intravenous (iv) 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 study intervention starts. Dental examination, audiometry, HBV/HCV/HIV tests, fiberoptic endoscopy, and ^{18}F-FDG-PET (^{18}F-FDG-PET/CT is also allowed) scan performed within 4 weeks before ICF signature do not have to be repeated during Screening. If several iv 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 treatment start 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, Table 2,

Table 3, and Section 8.1.

During screening and after study intervention start, laboratory assessments and pregnancy tests should be performed by a local laboratory according to instructions provided in Section 8.2.4.

A participant will be considered as eligible to receive the study interventions after they have signed the ICF and all eligibility criteria have been met. Study intervention administration starts with combination treatment on C1D1. The IMRT plan must be reviewed by the RT-QA Review Center prior to the start of C1D1.

Study procedures must be performed according to the planned visit schedule within the permitted visit windows. Study procedures of the C1D1 visit have a visit window of - 3 days, unless they are required to be performed on first dosing day (C1D1). Other CxD1 visits have a visit window of ± 3 days. During the treatment period, each study visit day and allowed time window will be based on the C1D1 date. The treatment diagram and time windows for visits during the treatment period are presented in Figure 3.

CCI [redacted]

Adequate hydration must be maintained pre- and post-cisplatin infusion according to the following schedule (see Appendix 4 for detailed instructions):

Pre Infusion	Post Infusion
Minimum 2 to 3 hours prior to administration of cisplatin	until a minimum of 2 hours after the administration of cisplatin

The EOT visit will be performed 14 days (± 7 days) after last study intervention administration (i.e. xevinapant, cisplatin, or IMRT, whichever is administered last) or 14 days (± 7 days) after premature discontinuation during treatment but prior to the start of any subsequent anticancer therapy. In case of premature treatment discontinuation, imaging and clinical tumor assessments must be performed according to original schedule (Week 20 for EOT assessment and every 3 months thereafter).

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 intervention or withdrawal from the study due to reasons described in Section 7.

The follow-up period will start after the EOT visit. The 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 will be followed until the last on-study participant reaches their 18-month post-first treatment visit (EOS), or a decision to end the study has been triggered, or until premature discontinuation from study, whichever occurs first. The same is applicable for participants who prematurely discontinue study treatment without disease progression (e.g. unacceptable toxicity). Participants with confirmed disease progression will discontinue the study.

At the EOS, all remaining participants will have an EOS visit unless their last follow-up visit was done less than 6 weeks before.

During the follow-up period, each study visit day and allowed time windows will be based on the C1D1 date.

After completion of the follow-up period, participants who have not discontinued the study prematurely will undergo the EOS assessments ([date of the 18-month visit of the last on-study participant] ± 1 month) and will be considered as having completed the study (see Section 7.2).

If the last on-study participant completes the follow-up (18 months after C1D1), their EOS visit will be performed at the same time as their 18-month visit. In case of premature discontinuation from the study including confirmed disease progression, the participant's EOS visit will be performed when they discontinue from the study.

The following schedules of activities and as assessments are presented:

Table 1: Screening

Table 1 Schedule of Activities: Screening

	Screening	Notes
Study Week	**-4 to -1**	
Study Day	**-28 to -1**	
Informed consent	X	
Medical history	X	
Demographics	X	
Nutritional status	X	According to institutional standards
Dental examination	X	No repeat needed if performed within 4 weeks prior to ICF signature. See Appendix 9.
Audiometry	X	No repeat needed if performed within 4 weeks prior to ICF signature. See Section 8.2.7
Eligibility	X	
Physical examination	X	Complete examination
ECOG PS	X	
Vital Signs	X	Including height and weight
ECG	X	
Laboratory assessments		
Blood hematology	X	Local laboratory
Blood biochemistry – full panel	X	Local laboratory
Coagulation	X	Local laboratory
Pregnancy test	X	Local laboratory. hCG serum at Screening and thereafter from urine for POCBP
Urinalysis	X	Local lab
HPV status (p16)	X	Determined by p16 IHC using CCI [redacted], see Section 8.2.4.1. No repeat needed if performed prior to ICF signature in line with instructions in Section 8.2.4. Mandatory for OPC, optional for other tumor locations. For OPC, CCI [redacted] may be performed, if necessary.
HBV, HCV, HIV test	X	Local laboratory. No repeat needed if performed within 4 weeks prior to ICF signature
SARS-CoV-2 test	X	If applicable, see exclusion criterion (See Section 5.2)
Disease assessments		
Disease History	X	Including tumor staging
^{18}F-FDG-PET	X	No repeat needed if performed within 4 weeks prior to ICF signature
CT or MRI + CT-chest	X	IV contrast-enhanced CT scan or MRI of head and neck AND CT scan of chest
Clinical tumor assessment	X	Ear, nose, and throat examination, and fiberoptic endoscopy. Fiberoptic endoscopy performed within 4 weeks before ICF signature does not have to be repeated during screening
Other clinical assessments		
Concomitant therapy	X	
Adverse events	X	

^{18}F-FDG=[^{18}F]Fluorodeoxyglucose, CT=computed tomography, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, HBV=Hepatitis B Virus, hCG=human Chorionic Gonadotropin, HCV=Hepatitis C Virus, HIV=human immunodeficiency virus, HPV=human papillomavirus, ICF=informed consent form, IHC= immunohistochemistry, iv= intravenous, MRI=magnetic resonance imaging, OPC=oropharyngeal cancer, PET=positron emission tomography, POCBP=Person of Childbearing Potential, SARS-CoV 2=Severe acute respiratory syndrome coronavirus 2.

Table 2 Schedule of Activities (Combination Treatment Period [Cycles 1 to 3])

Study Period	Combination Therapy Period (Xevinapant, Cisplatin, and IMRT)																						Notes
Cycle	Cycle 1									Cycle 2									Cycle 3				
Cycle Day	1	2	4	8	9	11	15	16	18	1	2	4	8	9	11	15	16	18	1	2	4	8	
Study Week	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	
Study Day	1	2	4	8	9	11	15	16	18	22	23	25	29	30	32	36	37	39	43	44	46	50	
Visit Window (days)	- 3									± 3									± 3				
Physical exam	X									X									X				See Section 8.2.1
ECOG PS	X									X									X				
Vital Signs	X	X			X			X		X	X			X			X		X	X			Including Weight at CxD1
ECG	X			X																			
Audiometry				(X)			(X)			(X)			(X)			(X)			(X)				Only if clinically indicated. See Section 8.2.7
Laboratory assessments																							
Blood hematology	X			X				X		X			X				X		X			X	Local laboratory
Blood biochemistry – full panel	X									X									X				Local laboratory
Blood biochemistry– minimum panel				X				X					X				X						Local laboratory
CCI [redacted]																							
Pregnancy test	X									X									X				Local laboratory
Urinalysis	X									X									X				Local laboratory

Study Period	Combination Therapy Period (Xevinapant, Cisplatin, and IMRT)																						Notes
Cycle	Cycle 1									Cycle 2									Cycle 3				
Cycle Day	1	2	4	8	9	11	15	16	18	1	2	4	8	9	11	15	16	18	1	2	4	8	
Study Week	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	
Study Day	1	2	4	8	9	11	15	16	18	22	23	25	29	30	32	36	37	39	43	44	46	50	
Visit Window (days)	- 3									± 3									± 3				
Disease assessments																							
Nutritional status	X									X									X				See Section 6.8.4.1
CT or MRI																							See Section 8.1
Clinical tumor assessment																							See Section 8.1
Treatments																							
Xevinapant	From Day 1 to 14									From Day 1 to 14									From Day 1 to 14				See Section 6.5.1
Participant diary dispensation	X																						See Section 8.6
Weekly cisplatin		X			X			X			X			X			X			X			See Section 6.5.2
IMRT			5 fractions/week for 7 weeks																				See Section 6.5.3
Other clinical Assessments																							
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Including SAE and AESI
Ancillary Studies																							
Xevinapant blood PK		X			X						X												See details in Table 4

CCI

AESI = adverse events of special interest, CxD1 = Cycle x Day 1, ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, CT = Computed Tomography, IMRT = Intensity-modulated radiation therapy, MRI = Magnetic Resonance Imaging, PK = pharmacokinetic, SAE = serious adverse event.

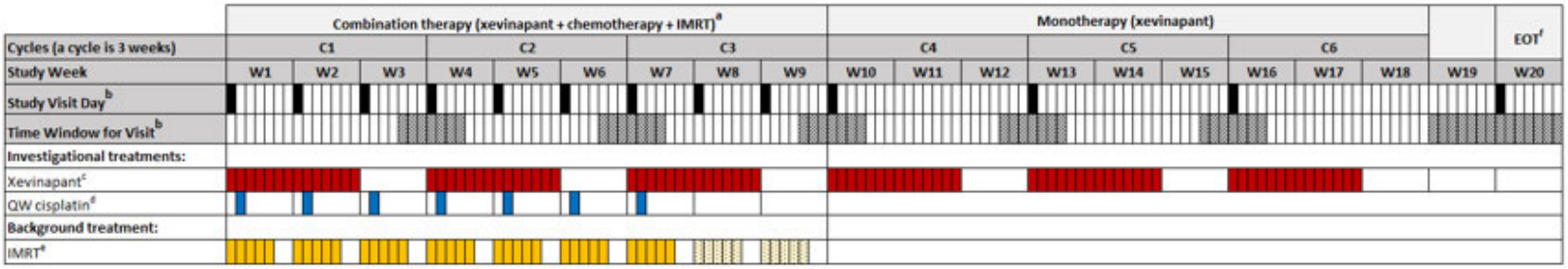
Table 3 Schedule of Activities: Monotherapy Period (Cycle 4 till Cycle 6) and Follow-up Period

Study period	Monotherapy period (Xevinapant)			EOT	FU/EOS	Notes
Cycle	**Cycle 4**	**Cycle 5**	**Cycle 6**			**EOT 14 d (± 7 d) after last study intervention administration (xevinapant, cisplatin), or IMRT whichever is last or 14 d (± 7 d) after premature treatment discontinuation but prior to start of new anticancer therapy. In case of premature treatment discontinuation imaging and clinical tumor assessments must be performed according to original schedule (Week 20 for EOT assessment)" FU at least 3 QM until last on-study participant reaches their 18-month post-first treatment visit (EOS), a decision to end study has been triggered, or until premature discontinuation from study, whichever occurs first. At this point, all remaining participants will have an EOS visit (±1 m) unless last FU visit was done < 6 weeks before.**
Cycle Day	**1**	**1**	**1**			
Study Week	**10**	**13**	**16**	**20**	**3QM**	
Study Day	**64**	**85**	**106**	**134**		
Visit Window (days)	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±2 w/ ±1 m**	
Physical exam	X	X	X	X	X	Complete examination at EOT; until PD
ECOG PS	X	X	X	X	X	Until PD
Vital Signs	X	X	X	X		Including weight
Nutritional status	X			X		See Section 6.8.4.1
Dental examination (See Appendix 9)				X		
Audiometry	(X)					Only if clinically indicated. See Section 8.2.7
Laboratory assessments						
Blood hematology	X	X	X	X		Local laboratory
Blood biochemistry – full panel	X	X	X	X		Local laboratory
Coagulation				X		Local laboratory
Pregnancy test	X	X	X	X	X	In FU every 4 weeks up to 9 months after first treatment
Urinalysis	X			X		Local laboratory
Disease assessments						
^{18}F-FDG-PET				X		See Section 8.1.2
CT or MRI + CT-chest tumor assessment				X	X	Every 3 months until PD or start of next line therapy. See Section 8.1.
Clinical tumor assessment				X	X	Every 3 months until PD or start of next line therapy. See Section 8.1.
Treatments						
Xevinapant	From Day 1 to 14	From Day 1 to 14	From Day 1 to 14			

Study period	Monotherapy period (Xevinapant)			EOT	FU/EOS	Notes
Cycle	**Cycle 4**	**Cycle 5**	**Cycle 6**			**EOT 14 d (± 7 d) after last study intervention administration (xevinapant, cisplatin), or IMRT whichever is last or 14 d (± 7 d) after premature treatment discontinuation but prior to start of new anticancer therapy. In case of premature treatment discontinuation imaging and clinical tumor assessments must be performed according to original schedule (Week 20 for EOT assessment)" FU at least 3 QM until last on-study participant reaches their 18-month post-first treatment visit (EOS), a decision to end study has been triggered, or until premature discontinuation from study, whichever occurs first. At this point, all remaining participants will have an EOS visit (±1 m) unless last FU visit was done < 6 weeks before.**
Cycle Day	**1**	**1**	**1**			
Study Week	**10**	**13**	**16**	**20**	**3QM**	
Study Day	**64**	**85**	**106**	**134**		
Visit Window (days)	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±2 w/ ±1 m**	
Other Clinical Assessments						
Concomitant therapy	X	X	X	X	X	
Antineoplastic therapy				X	X	
Adverse events	X	X	X	X	X	Including SAE and AESI
Ancillary Studies						
CCI						

18F-FDG-PET=[^{18}F]Fluorodeoxyglucose, 3QM=Every 3 months, AESI=adverse events of special interest, CT=computed tomography, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EOS=End of Study, EOT=End of Treatment, FU=Follow-up, MRI=magnetic resonance imaging, PD=progressive disease, SAE=serious adverse event

Figure 3 Treatment Diagram and Time Window for Visits



C=cycle, D=day, EOT=end of treatment, IMRT=intensity-modulated radiation therapy, QW= once a week, W=week.

a. On days when IMRT is to be administered, xevinapant must be administered before IMRT.

b. During the treatment period, each study visit day and allowed time windows will be based on the C1D1 date. C1D1 and C1D2 are triggered by the first administration of xevinapant and QW cisplatin, respectively. These visits should be performed on consecutive days. Crossed gray boxes in the row "Time Window for Visit" represent days around a specific study visit (represented by solid black boxes in the row "Study visit day") where the visit can be rescheduled (see also time windows planned in the SoA, Table 1, Table 2, and,

c. Table 3).

d. Xevinapant once daily from D1 to D14 of each cycle (solid red boxes) CCI [redacted]

e. Cisplatin-based chemotherapy weekly on C1D2, C1D9, C1D16, C2D2, C2D9, C2D16, and C3D2 (see also Section 6.5.2). For participants not eligible to continue with QW cisplatin after dose reduction switch to carboplatin at the next scheduled chemotherapy administration.

f. IMRT should be delivered in 35 fractions over 7 weeks, 5 fractions weekly (solid yellow boxes). If IMRT is put on hold due to safety or administrative reason, the 7 weeks of IMRT can be administered until Study Week 9 (dotted yellow boxes) (also see Section 6.5.3).

g. The EOT visit will be performed 14 days (± 7 days) after last study intervention administration (i.e. xevinapant, chemotherapy, or IMRT whichever is administered last) or 14 days (± 7 days) after premature discontinuation during treatment, but prior to start of any subsequent anticancer therapy.

Table 4 Schedule of Activities: Pharmacokinetic Assessments

Treatment Day	Timepoint	Xevinapant PK Sampling
C1D2	Predose xevinapant (window: less than 1 hour prior to dosing)	X
C1D2	End of cisplatin infusion (window: less than 30 min after end of infusion)	X
C1D9	Predose xevinapant (window: less than 1 hour prior to dosing)	X
C1D9	1-2 hours after end of cisplatin infusion	X
C2D2	Predose xevinapant (window: less than 1 hour prior to dosing)	X
C2D2	1-2 hours after end of cisplatin infusion	X

CXDX=Cycle X Day X, IMRT= Intensity modulated radiation therapy, eCRF= electronic case report form, PK=pharmacokinetic.

CCI [redacted]

On all PK days (C1D2, C1D9, and C2D2), participants take xevinapant at the hospital to ensure predose collection for xevinapant PK at the predose timepoint. On PK days, record time of oral xevinapant dose, volume of xevinapant dose, time of the start and end of cisplatin infusion and time of PK sampling in eCRF.

In addition, record times and volumes of xevinapant dose taken 1 day prior to PK days (such as doses at C1D1, C1D8, and C2D1) in eCRF.

* In case of switch to carboplatin, timepoint is after end of carboplatin infusion.

2 Introduction

Xevinapant is a novel, orally available inhibitor of IAPs that promotes cancer cell death via apoptosis. Xevinapant fosters antitumor immunity and potentially sensitizes tumor cells for various cytotoxic therapies, including chemotherapy, radiotherapy and/or immunotherapy (Serova 2014, Matzinger 2015, Tao 2019).

Nonclinical data suggest xevinapant activity in SCCHN models when combined with radiation as shown by Matzinger (Matzinger 2015). The value of adding xevinapant to conventional Q3W high-dose cisplatin-based chemoradiotherapy in the treatment of previously untreated patients with unresected LA SCCHN was recently investigated in a Phase 2 study (Sun 2020) and its findings are currently being confirmed in a Phase 3 study (Debio 1143-SCCHN-301/MS202359_0006 [TrilynX], NCT04459715).

This study aims to assess safety and tolerability of xevinapant when added to QW cisplatin-based chemoradiotherapy (CRT) in the treatment of previously untreated patients with unresected LA SCCHN.

Detailed information on the chemistry, pharmacology, efficacy, and safety of xevinapant is in the IB.

2.1 Study Rationale

Head and neck cancer is a common cancer; representing approximately 5% of all cancer cases worldwide with an annual incidence of over 878,000 cases and a mortality estimated at 444,000 deaths per year in 2020 (Sung 2021, Ferlay 2021). Definitive treatment options for 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 (Hernandez-Vila 2016, NCCN v1 2023). Among conservative (nonsurgical) treatments, the most widely used standard regimen in this setting consists of high-dose (100 mg/m^2) cisplatin administered Q3W for up to 3 cycles, combined with approximately 70 Gy radiation delivered in 1.8 to 2.0 Gy daily fractions. Although associated with increased toxicity compared to RT alone, this combination is also associated with increased local control rates and OS (Oun 2018). However, Q3W cisplatin (100 mg/m^2) is associated with toxicities such as nephrotoxicity, hematotoxicity, and ototoxicity leading to low treatment adherence. Weekly cisplatin (CCI mg/m^2), administered every week (QW) for up to 7 weeks, is one of the commonly used alternative regimens for Q3W cisplatin (100 mg/m^2) with potentially milder renal and ototoxicity, CCI [redacted]. Furthermore, weekly cisplatin at CCI mg/m^2 requires a less intense hydration regimen compared to high-dose Q3W cisplatin (NCCN v1 2023, Machiels 2020, Bauml 2019).

Xevinapant is an inhibitor of IAPs that has been shown in nonclinical in vitro and in vivo models to have both chemo- and radiosensitizing potential as well as immunomodulatory potential (Serova 2014, Matzinger 2015, Tao 2019). In unresected LA SCCHN patients, the addition of xevinapant to SoC CRT recently showed a statistically significant and clinically meaningful improvement in locoregional control at 18 months compared to placebo with SoC CRT (Sun 2020).

Following the 36-month analysis, PFS also showed a clinically meaningful improved benefit from xevinapant versus placebo. Furthermore, a clinically relevant improvement in 5-year OS using xevinapant combined with CRT vs the control group was recently presented (Tao 2023). The findings of this study are currently being confirmed in a Phase 3 study using standard Q3W cisplatin-based chemoradiation in combination with xevinapant (Debio 1143-SCCHN-301/ MS202359_0006 [TrilynX]).

The purpose of this study is to evaluate the tolerability and safety of xevinapant when added to weekly cisplatin (CCI mg/m^2) based concomitant CRT in the treatment of participants with unresected LA SCCHN.

2.2 Background

Head and neck carcinoma include a variety of epithelial tumors originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx, or larynx. Head and neck cancer is a common cancer representing approximately 5% of all cancer cases worldwide with an annual incidence of over 878,000 cases and a mortality estimated at 444,000 deaths per year in 2020. (Sung 2021, Ferlay 2021). Overall, the highest incidence is observed in patients 65 years of age and older, while for oropharynx and nasopharynx the incidence is higher for those aged 25 to 64 years at diagnosis (www.rarecarenet.eu).

Multidisciplinary treatments, including surgery, RT, and chemotherapy alone, or in combination represent the treatment options for SCCHN patients depending on the disease stage. Locally advanced disease is treated with curative intent and requires multimodal approaches including combined CRT either as adjuvant therapy after tumor resection or as definitive curatively intended treatment. 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 (Machiels 2020, NCCN v1 2023). Every 3-week cisplatin (100 mg/m^2) with concomitant RT is considered the standard systemic regimen in LA SCCHN across countries, irrespective of tumor location (Adelstein 2003, Gregoire 2010).

However, Q3W cisplatin (100 mg/m^2) is associated with both acute and late, often irreversible toxicities, which manifest as detrimental short- and long-term complications for patients and results in low treatment adherence and might not be an optimal treatment for many patients (Porceddu 2020, Espeli 2012). Older, frail patients are often unfit to receive Q3W cisplatin (100 mg/m^2) due to renal, cardiac function, or other comorbidities. Approximately 40% of patients cannot complete the whole 3 planned cycles of Q3W cisplatin (100 mg/m^2) due to toxicity, and a cumulative dose above CCI mg/m^2, which seems enough to produce a therapeutic effect, might not be achieved for those patients (Szturz 2019). Considering SCCHN is more commonly observed in the elderly, development of a less toxic treatment option for those vulnerable patients remains an unmet need.

Weekly cisplatin (CCI mg/m^2) is one of the most commonly selected alternative cisplatin-based chemotherapy regimens due to easier administration and with a potentially better safety and tolerability profile compared to Q3W cisplatin (100 mg/m^2) CCI [redacted]. Weekly cisplatin

(CCI mg/m^2) is considered to show lower hematotoxicity, nausea/vomiting, and nephrotoxicity than the Q3W cisplatin (100 mg/m^2) regimen (Szturz 2019, Sharma 2022). In addition, compliance is higher with a QW cisplatin (CCI mg/m^2) regimen and associated with a significantly higher proportion of patients who received all planned chemotherapy cycles as compared to the Q3W cisplatin (100 mg/m^2) regimen (Szturz 2017).

Due to the pivotal role of RT in many LA SCCHN settings, a lot of focus is being put on research into safe and powerful radiosensitizing agents. In addition, resistance of tumor cells to apoptosis is a major problem in current cancer treatment. Therefore, further development of new molecular anticancer therapies that specifically target resistance of cancer cells to apoptosis is warranted (Nicholson 2000).

IAPs are key endogenous inhibitors of apoptosis, and overexpression of these proteins was detected in numerous cancers, including SCCHN. IAPs have also been shown to interfere with the efficacy of RT (Tamm 2000).

Xevinapant is an inhibitor of IAPs with chemosensitizing, radiosensitizing, and immunomodulatory activities. Nonclinical studies in several in vitro and in vivo SCCHN models demonstrated an efficient antiproliferative activity and a synergistic enhancement of intrinsic cellular radiation sensitivity when xevinapant was combined with RT (Matzinger 2015). These results indicate that xevinapant in combination with RT has a promising therapeutic potential in the treatment of SCCHN.

Based on current understanding of mechanisms of action, the value of adding xevinapant to platinum-based conventional CRT in previously untreated patients with unresected LA SCCHN has been investigated in a Phase 1/2 study (Debio 1143-201) and its findings are currently being confirmed in a Phase 3 study (Debio 1143-SCCHN-301/MS202359_0006 [TrilynX]). Efficacy results from the 2-year primary analysis from Study Debio 1143-201 have shown antitumor activity of xevinapant: participants treated with xevinapant were around 2.5 times more likely to have LRC 18 months after completing treatment, compared with participants having received a placebo. Following the 36-month analysis, PFS also showed a clinically meaningful improved benefit from xevinapant versus placebo. Furthermore, a clinically relevant improvement in 5-year OS using xevinapant combined with CRT vs the control group was recently presented (Tao 2023). Overall, the safety profile of xevinapant, when added to Q3W cisplatin (100 mg/m^2) and concurrent RT (CRT), was predictable and manageable, and did not jeopardize the delivery of Q3W cisplatin (100 mg/m^2) concurrent with standard fractionation RT.

This Phase 1b study aims to evaluate the tolerability and safety of xevinapant when added to QW cisplatin-based CRT in the treatment of participants with unresected LA SCCHN.

Refer to the IB for further details on other non-LA SCCHN Phase 1 studies and on Study Debio 1143-201.

2.3 Benefit/Risk Assessment

Available clinical data with xevinapant originates from studies with participants and patients, presenting different locally advanced or advanced solid tumors or poor prognosis AML, who

received xevinapant as a monotherapy or in combination with other anticancer medicines with or without radiotherapy.

As of 31 July 2022, 314 participants with a malignant disease (excluding participants from the blinded Study Debio 1143-SCCHN-301/MS202359_0006 [TrilynX] and the Investigator-initiated Study CATRIPCA) and 107 healthy participants have received at least 1 dose of xevinapant (ranging from CCI mg/day in 3 main different schedules: D1 to 5 Q3W, D1 to 14 Q3W, or D1 to 10 and D15 to 24 Q4W). When xevinapant was given as a single agent, the MTD was not reached up to doses of CCI mg/day in short-course regimens (D1 to 5 Q3W) or CCI mg/day in extended dosing schedules (D1 to 14 Q3W).

The observed toxicities were in line with those expected in patients with advanced solid tumors, and/or with those observed in patients treated with CT or CRT regimen alone. Importantly, no relevant hematological toxicities other than mild anemia have been reported in studies with xevinapant single agent or in noncytotoxic containing combinations (e.g. immunotherapy with avelumab, nivolumab, or pembrolizumab).

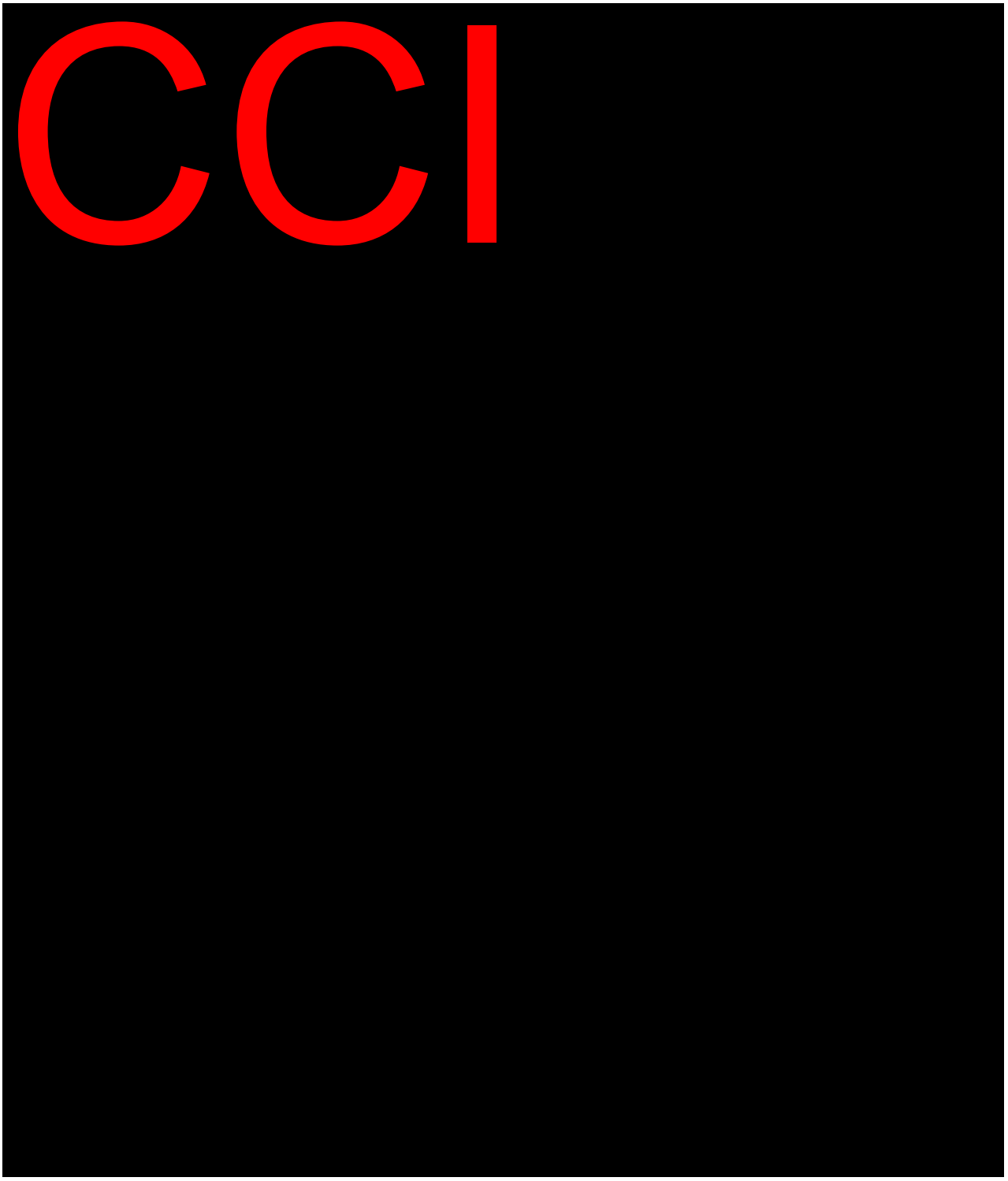
Based on the safety data of the Phase 1 and Phase 2 studies, xevinapant doses of up to CCI mg/day were safely combined with either CT, RT, or both. When used in combination with CT or CRT, xevinapant appears to be equally well tolerated as CT or CRT alone and is not associated with an increased frequency of drug-related treatment discontinuation. Taking into account data from the placebo-controlled Study Debio 1143-201B, where xevinapant or placebo were administered in association with Q3W cisplatin-based CRT (100 mg/m^2), an increased frequency of ALT increase, tinnitus, dysphagia, weight decrease, mucosal inflammation, radiation skin injury, nausea, and vomiting were observed 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.

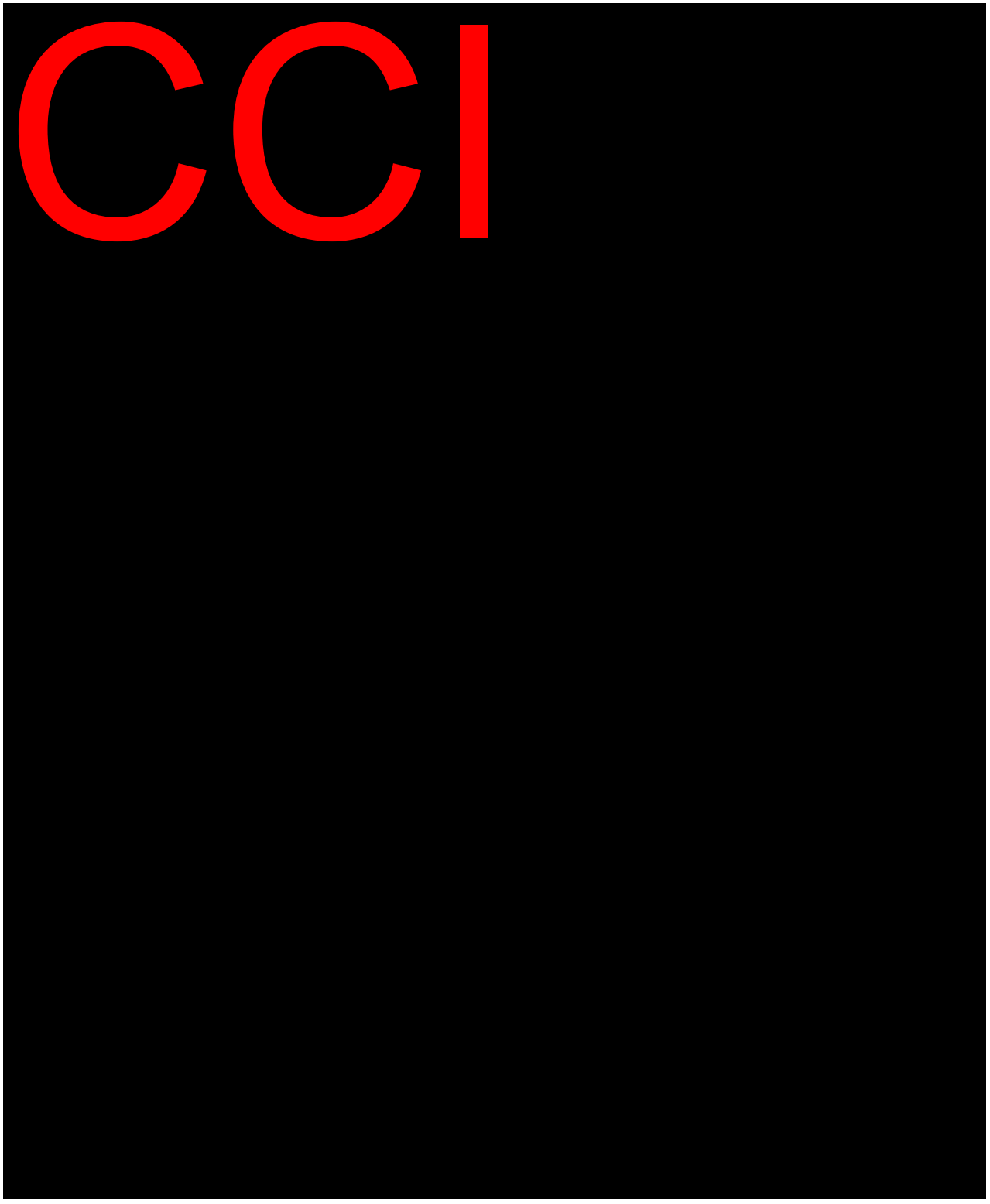
The safety and efficacy of xevinapant (at the recommended Phase 2 dose of CCI mg/day D1 to 14 Q3W) in combination with high-dose platinum-based CRT in previously untreated patients with LA SCCHN, is currently being investigated in the randomized double-blind placebo-controlled Phase 3 Study Debio 1143-SCCHN-301/MS202359_0006 (TrilynX). CCI [redacted]

Additionally, participants in this study will be treated with QW cisplatin, which is considered to have a better safety profile than Q3W cisplatin (100 mg/m^2), especially for hematotoxicity, nausea, and nephrotoxicity (Szturz 2019). Therefore, combination of xevinapant + QW cisplatin (CCI mg/m^2) based CRT is expected to have comparable or better tolerability than xevinapant + Q3W cisplatin (100 mg/m^2).

Based on the available clinical data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment




CCI

2.3.2 Benefit Assessment

The clinical proof of concept of xevinapant in patients with unresected LA SCCHN has been demonstrated by the Phase 2 Study Debio 1143-201. Based on the potential for xevinapant to act as a chemo- and/or radiosensitizer and immune-modulator, CCI

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 as well as clinically relevant improvements in PFS and OS. The 24-month analysis of Study Debio 1143-201B demonstrated that the odds for LRC at 18 months after completing treatment is 2.5 times higher in patients (all heavy smokers, approximately 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]: 2.74 [1.15; 6.53]).

In addition, a risk reduction of 67% for disease progression or death was observed in patients having been treated with xevinapant compared with patients having received a placebo, demonstrating clinically meaningful improvement in PFS (hazard ratio [95%CI]: 0.33 [0.17; 0.67]; p = 0.0019). The PFS rate at 36 months after treatment initiation was 72% in the xevinapant arm and 36% in placebo arm. The median PFS was not reached in the xevinapant arm (95% CI: 37.4; Not Evaluable) versus 16.9 months (95% CI: 7.5; 36.1) in the placebo arm.

Xevinapant combined with CRT showed also a clinically relevant improvement in OS compared to the control group. The OS rate at 5 years (Kaplan-Meier estimate) was 53% (95% CI: 37; 66) in the xevinapant arm versus 28% (95% CI: 15; 42) in the placebo arm, reflecting a 53% reduction in the risk of mortality of any cause in the xevinapant arm compared to the placebo arm (HR = 0.47, [95% CI: 0.27; 0.84], p = 0.0101) (refer to the current version of the IB for further details).

2.3.3 Overall Benefit: Risk Conclusion

Overall, the toxicities of a study with xevinapant in combination with cisplatin and RT are deemed to be predictable and manageable. Considering the measures taken to minimize the risk to participants in this study, the potential risks identified in association with xevinapant are justified by the anticipated benefits that may be afforded to participants with unresected LA SCCHN.

3 Objectives and Estimands

Objectives	Endpoints	Further Estimand Attributes	Ref. #
Primary			
To evaluate tolerability of xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Occurrence of DLT-like events (See Section 8.2.5.1 for definition)	Population: Treatment naïve patients with LA SCCHN (Stage III, IVA, or IVB) with histologically confirmed diagnosis in at least 1 of the following sites: oropharynx (HPV-negative), hypopharynx, and larynx, eligible to receive weekly cisplatin-based concurrent CRT Treatment: xevinapant, weekly cisplatin, and IMRT followed by xevinapant monotherapy Intercurrent Event Strategy: o Discontinuation/interruption/delay of xevinapant/cisplatin treatment (> 40% of planned cumulative dose missed in DLT-like assessment period) due to reasons other than treatment-related AE (composite strategy: to be considered as DLT-like event) o RT delay > 2 weeks during the DLT-like assessment period due to reasons other than treatment-related AE (composite strategy: to be considered a DLT-like event) Population-Level Summary: o DLT-like event rate and and associated CI o Standard summary statistics	1
Secondary			
To characterize safety of xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Occurrence of AEs and treatment-related AEs CCI [redacted]	Population/Treatment: Same as #1	2

Objectives	Endpoints	Further Estimand Attributes	Ref. #
To evaluate clinical activity parameters using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1	Objective Response (OR) according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of new anticancer therapy: ignoring assessments after the intercurrent event (while not treated with new anticancer therapy strategy) • Progression according to RECIST 1.1: assessments up to the intercurrent event (while not progressed strategy) Population-level Summary: Response rates (i.e. CRR, ORR) including associated statistics	3
	PFS according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Death within 2 missing scheduled tumor assessments after last evaluable assessment or start of study intervention will be considered as event (composite strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of subsequent anticancer therapy: ignoring events after the start of a new anticancer therapy (hypothetical strategy) Population-level Summary: Kaplan-Meier estimates including associated statistics	4
	Locoregional control (LRC) according to RECIST 1.1 assessed by Investigator	Population/Treatment: Same as #1 Intercurrent Event Strategy: • Death: Assessments before death will be used (treatment policy strategy) • Discontinuation of treatment: ignoring the intercurrent event (treatment policy strategy) • Start of new anticancer therapy: ignoring events after the start of a new anticancer treatment (hypothetical strategy) Population-level Summary: Same as #4	5
To evaluate time to subsequent cancer treatments in participants treated with xevinapant when added to weekly cisplatin-based CRT in LA SCCHN	Time to subsequent systemic cancer treatments	Population/Treatment: Same as #1 Intercurrent Event Strategy/ Population-level Summary: Same as #5	6

Objectives	Endpoints	Further Estimand Attributes	Ref. #
Tertiary/Exploratory			
To assess the concentration-time profile of xevinapant and its metabolite	Plasma concentrations of xevinapant and its metabolite D-1143-MET1 during the treatment period	Population/Treatment: Same as #1	7
CCI			

4 Study Design

This is a single arm, open label, Phase 1b study of xevinapant in combination with QW cisplatin-based chemotherapy and standard fractionation intensity-modulated radiotherapy to assess safety and tolerability in patients with locally advanced squamous cell carcinoma of the head and neck, suitable for definitive chemoradiotherapy. The study is designed with the primary objective to evaluate tolerability of xevinapant when added to QW cisplatin-based CRT in LA SCCHN.

4.1 Overall Design

Study Design	Single arm
Control Method	None
Single or Multicenter	Multicenter
Study Population Type	Adult patients with LA SCCHN (Stage III, IVA, or IVB) with histologically confirmed diagnosis with 1 of the following primary 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
Level and Method of Blinding	Open label
Bias Minimalization Method(s)	Not applicable
Study Intervention Assignment Method	Not applicable
Data and Safety Monitoring /Other Committee:	An SMC will perform a safety review after 6, 12, and 18 participants have been treated for at least 5 weeks or have experienced a DLT-like event. Additional SMC reviews may be requested by the Sponsor or SMC. See Appendix 5.

Total Duration of Study Participation per Participant	The study includes the screening period (≤ 28 days), the treatment period (combination therapy period followed by the monotherapy period, each consisting of 3 cycles, total of 18 weeks), and a follow-up period. Each treatment cycle consists of 3 weeks. Participants will be followed up until the last on-study participant reaches their 18-month visit or until premature discontinuation from study, whichever occurs first
Provisions for Study Extension or Entry into Roll-Over Studies	Not applicable
Adaptive Aspects of Study Design	Not applicable

Once a participant has signed the ICF, an identification number will be assigned to the participant and the study-related screening procedures will be started. Upon confirmation of eligibility, participants will be enrolled and will receive the following treatments:

- 3 cycles of xevinapant (oral solution CCI mg/day from Day 1 to 14, per 3-week cycle) + QW cisplatin for 7 weeks CCI mg/m^2 on Cycle 1 Day 2 (C1D2), C1D9, C1D16, C2D2, C2D9, C2D16, and C3D2) + IMRT (70 Gy in 35 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of xevinapant (CCI mg/day from Day 1 to 14, per 3-week cycle).

The schedule of concurrent administration of xevinapant, cisplatin, and IMRT is presented in the SoA (Table 2,

Table 3, and the treatment diagram (Figure 3).

It is planned to enroll approximately 40 adult participants of all sexes such that approximately 38 DLT-like evaluable participants are anticipated to be obtained. In case participants drop out of the study for reasons other than DLT-like events earlier than 5 weeks after start of treatment, additional participants may be enrolled to ensure 38 evaluable participants in the DLT analysis set.

The primary analysis is planned when at least 38 participants meet at least 1 of the following criteria (see Section 9.4.4):

- Experience at least 1 DLT-like event, regardless of the administered amount of study intervention/completion in the DLT-like assessment period.
- Receive at least 60% of the planned cumulative dose of xevinapant and cisplatin during the DLT-like assessment period and either complete the DLT-like assessment period or discontinue study or study treatment for non-AE-related reasons.

4.2 Scientific Rationale for Study Design

Target Population: Unresected LA SCCHN

The target population chosen for the study is patients who are expected to significantly benefit from treatment with xevinapant combined with QW cisplatin-based CRT (CCI mg/m^2), being one of the alternative approaches for Q3W cisplatin-based standard CRT (100 mg/m^2) in unresected LA SCCHN. Patients with unresectable or nonresected LA SCCHN have the poorest prognosis and predominantly experience locoregional failures.

Weekly Cisplatin

Cisplatin-based CRT is a standard treatment option, and ESMO and NCCN guidelines on SCCHN recommend the use of CRT when the tumor is unresectable or when surgery is contraindicated (Machiels 2020, NCCN 2023). Although Q3W cisplatin (100 mg/m^2) is considered the standard systemic regimen given concurrently with radiotherapy in LA SCCHN (Adelstein 2003), there is currently no unanimous consensus on the optimal cisplatin regimen (Szturz 2017). Three-weekly cisplatin (100 mg/m^2) is associated with both acute and late, often irreversible toxicities, which manifest as detrimental short- and long-term complications for patients and results in low treatment adherence and not optimal treatment for many patients (Porceddu 2020, Espeli 2012). Although results of controlled studies comparing Q3W vs QW cisplatin-based CRT in this population are still awaited, many local institutions are switching to QW cisplatin (CCI mg/m^2) concurrently used with radiotherapy (CCI) in order to improve compliance and easier control of toxicity as compared to Q3W cisplatin (100 mg/m^2).

In the ongoing Phase 3 study with xevinapant, RT, and cisplatin in unresected LA SCCHN patients (Study Debio 1143-SCCHN-301/MS202359_0006 [TrilynX]), the Q3W cisplatin (100 mg/m^2) regimen is being used. However, since weekly cisplatin is increasing in use in many local institutions, the current study will evaluate if xevinapant with QW cisplatin (CCI mg/m^2) and RT is safe and tolerable to use in the definitive CRT setting.

Single Arm Study

This study will use a single arm, open label design. The data from this study will serve to provide confidence for safe administration of xevinapant in combination with QW cisplatin-based CRT in LA SCCHN patients and to evaluate potential efficacy of this combination.

Primary Endpoint

The primary endpoint of this study is DLT-like events, defined in Section 8.2.5.1. The safety and tolerability will be assessed during the DLT-like assessment period, which is the initial 5 weeks on treatment for each participant. Similar DLT definitions have been used to assess the tolerability and safety of xevinapant in prior studies CCI

4.2.1 Patient Input into Study

Patient interviews were conducted to understand potential barriers to participation and general reactions to the clinical study design for TrilynX (refer to Study Debio 1143-SCCHN-301/MS202359_0006). Key learnings from these interviews were carried over to this study design including the recognition of the importance of providing nutritional monitoring and support.

Additional feedback was obtained from a Patient Advocacy meeting undertaken for the XRay Vision (refer to study MS202359_0002) which included patient advocates (and caregivers), who themselves were patients with LA SCCHN from Europe, Japan, and the US. Key learnings from these meetings have been recognized within this study such as streamlined patient diary and IMP Packaging. In addition, some patients acknowledged that they felt uncared for and isolated after treatment ended. Therefore, regular follow-up, as implemented in this study, is a way to support these patients.

4.3 Justification for Dose

Xevinapant

Xevinapant is to be administered orally without regard to food at CCI mg once daily from Day 1 to Day 14 of a 3-week cycle for 3 cycles in combination with CRT followed by three 3-week cycles of xevinapant monotherapy. Individual stepwise dose reductions to CCI mg are allowed for the management of toxicities. CCI

The selected dose is supported by holistic integration of nonclinical pharmacology, clinical efficacy, and safety data, clinical population PK (popPK) and population PK/PD modeling and simulations, and exposure-response analyses for efficacy and safety (based on data from Study CCI) as described in IB.

Additional xevinapant monotherapy cycles are supported by enhanced antitumor activity with extended monotherapy dosing following the xevinapant + RT combination cycles in an MC38 syngeneic mouse model.

CCI

Cisplatin (Carboplatin, Only in Case of Cisplatin Toxicity as per Table 8)

While the Q3W (100 mg/m^2) regimen for up to 3 cycles delivered concomitantly with IMRT is generally considered the standard (Szturz 2017) and has been widely adopted whenever patients are eligible, there is currently no unanimous consensus on the optimal cisplatin regimen.

Due to the toxicity of the Q3W cisplatin (100 mg/m^2) regimen, many institutions use another recommended regimen of cisplatin instead (QW cisplatin at CCI mg/m^2) CCI [redacted] to improve compliance and easier control of toxicity as compared to Q3W cisplatin (100 mg/m^2). A total cumulative cisplatin dose of CCI mg/m^2 is recommended (Machiels 2020), based on various studies suggesting a sufficient therapeutic effect when this exposure to cisplatin is met (Strojan 2015, Szturz 2019). CCI [redacted]

Therefore, the current study will evaluate if xevinapant with QW cisplatin (CCI mg/m^2) and RT is safe and tolerable to use in the definitive LA SCCHN setting.

Furthermore, in the current study, there is specific guidance for the management of renal impairment depending on grade of severity and first occurrence versus recurrence. (See Table 7).

This includes dose modification of xevinapant, of cisplatin or a switch from cisplatin to an equivalent carboplatin dose (area under the concentration vs time curve [AUC] CCI QW). This regimen is widely accepted and was reported to have similar efficacy (Wilkins 2013).

No PK interactions between xevinapant at CCI mg/day and cisplatin are expected based on data from Study Debio 1143-202 (cisplatin at CCI mg/m^2) and Study Debio 1143-201 (cisplatin at 100 mg/m^2) and consistent with the reported clearance mechanism of cisplatin.

IMRT

High-dose RT (60 to 72 Gy) is necessary to potentially cure patients with LA SCCHN. Irradiation of critical normal tissue can cause severe discomfort with increased acute and late morbidity (Marta 2017). 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 2007). Secondly, to administer a dose to the tumor volume high enough in order not to compromise control rates (Ghosh-Laskar 2016).

According to the NCCN/ESMO guidelines, IMRT is now considered the SoC for treating LA SCCHN. In the curative setting, the recommended radiation dose is 70 Gy over 35 fractions (NCCN v1 2023, Machiels 2020). The dose should follow the International Commission on Radiation Units & Measurements recommendations and using IMRT with simultaneous integrated boost technique.

4.4 End of Study Definition

The primary completion date is defined as the data cut-off date for the primary analysis when a total of 38 participants have completed the 5 weeks DLT-like assessment period or discontinued earlier and are not replaced. After the primary completion date, follow-up continues until the end of study defined below.

The end of the study is defined as the date of the last visit of the last remaining on-study participant. All remaining participants will be taken off study once a decision to end the study has been made or the last remaining on-study participant reaches their 18-month post-first treatment visit, whichever occurs earlier. At this timepoint, all participants who have not previously discontinued from the study prematurely will undergo the EOS assessments as specified in Section 1.3 and will be considered as having completed the study.

A participant has completed the study if they have completed all study parts, including the last visit or the last scheduled procedure shown in Section 1.3. Participants will receive the appropriate follow-up treatment per institutional standards.

5 Study Population

The study will enroll unresected LA SCCHN participants who are eligible for cisplatin-based chemoradiotherapy.

The criteria in Sections 5.1 and 5.2 are designed to enroll only individuals who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether an individual is suitable for this study.

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

Before performing any study assessments that are not part of the individual's routine medical care, the Investigator will confirm that the individual has provided written informed consent, as indicated in Appendix 5.

5.1 Inclusion Criteria

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

Category	Criterion
Age	1. Are ≥ 18 years of age (or based on the country legal age limit for adults if > 18 years) at the time of signing the informed consent.
Type of Participant and Disease Characteristics	2. Having an ECOG PS 0 - 1.
	3. 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, with one of the following primary sites: oropharynx (OPC) (HPV-negative), hypopharynx, and larynx.

Category	Criterion
	4. Evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by CT scan and/or MRI, based on RECIST v 1.1.
	5. For OPC patients, primary tumors must be HPV-negative as determined by p16 expression using immunohistochemistry (IHC) (pathological report should be available, p16 cutoff for determination of HPV status is defined in Section 8.2.4) **Note**: If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory, except for countries where EU IVDR is applicable (see Section 8.2.4).
	6. Able to swallow liquids or has an adequately functioning feeding tube, gastrostomy, or jejunostomy in place. For participants requiring liquid nutrition at baseline or during the study including the follow-up period, access to liquid nutrition supply should be ensured.
	7. Peripheral neuropathy Grade < 2.
	8. Adequate hematologic, renal, and hepatic function as indicated by: • eGFR ≥ 60 mL/min/1.73 m² (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). See also exclusion criteria #9. • 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).

Sex and Contraception/ Barrier Requirements	9. Are of any sex and gender Contraceptive use will be consistent with local regulations on contraception methods for those participating in clinical studies. The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below. **Male study participants:** Agree to the following during the study intervention period and for 6 months or according to local guidelines and/or local product information (whichever is longest), after the last administration of chemotherapy or 3 months after last dose of xevinapant whichever is the latest. • Refrain from donating fresh unwashed semen. PLUS, either: • Abstain from any activity that allows for exposure to ejaculate. OR • Use an external condom: o When having sexual intercourse with a partner of childbearing potential, who is not currently pregnant, and instruct the partner to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 6, since a condom may break or leak. o When engaging in any activity that allows for exposure to ejaculate. **Female study participants:** • Is **not** breastfeeding. • Is **not** pregnant (i.e. has a negative serum or highly sensitive urine pregnancy test, as required by local regulations, within 24 hours before the first dose of xevinapant). If a urine test cannot be confirmed as negative (e.g. an ambiguous result), a serum pregnancy test is required. • Is **not** a POCBP. • If a POCBP, uses a highly effective contraceptive method (i.e. with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 6 for the following time periods:

Category	Criterion
	1. Before the first dose of the xevinapant, if using hormonal contraception: • Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun their menses; **OR**, • Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay. 2. During the study intervention period 3. After the study intervention period (i.e. after the last dose of xevinapant is administered) for 6 months or according to local guidelines and/or local product information (whichever is longest) after the last administration of chemotherapy or 3 months after last dose of xevinapant, whichever is the latest, and agree not to donate eggs (ova, oocytes) for reproduction during this period. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of xevinapant. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.
Informed Consent	10. Are capable of giving signed informed consent, as indicated in Appendix 5, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	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.).

Category	Criterion
	3. Existing need of a hearing aid OR ≥ 25 decibel shift over 2 contiguous frequencies on a pretreatment hearing test as clinically indicated.
	4. 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.
	5. Chronically active HBV or HCV infection. The following tests must be performed and participants with positive serology must be excluded (Section 8.2.4): • HBV screening tests: both HBsAg and HBcAb • HCV screening tests: both HCV-antibody and positive viral load HCV-RNA by PCR.
	6. Other infections (viral [including COVID-19] and/or bacterial and/or mycotic) requiring systemic treatment, including a SARS-CoV-2 positive test during the screening period, either symptomatic, or asymptomatic, PCR, or antigen test proven. **Note**: No test will be required for participants who have completed prophylactic vaccination as per local regulations against SARS-CoV-2 or who have recovered from confirmed COVID-19 within the screening period, as per local regulations.
	7. Known gastrointestinal disorder with clinically established malabsorption syndrome and major gastrointestinal surgery in the last 12 months that may limit oral absorption.
	8. Documented weight loss of > 10% during the last 4 weeks prior to the start of study intervention (unless adequate measures are undertaken for nutritional support), OR plasmatic albumin < 3.0 g/dL. No albumin transfusions are allowed within 2 weeks before the start of study intervention.
	9. 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 the start of study intervention.

Category	Criterion
	10. Active inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis, inflammatory bowel diseases, pneumonitis, and other autoimmune diseases) who are under antitumor necrosis factor treatment.
	11. Impaired cardiovascular function, clinically significant cardiovascular diseases, or clinically significant pulmonary disease, including any of the following: • Ongoing or history of uncontrolled or symptomatic ischemic myocardiopathy within 6 months prior to the start of study intervention. • Known left ventricular ejection fraction < 50%, left ventricular hypertrophy, uncontrolled ventricular arrhythmias, bradycardia (heart rate < 50 bpm). • History of myocardial infarction or severe/unstable angina within 6 months prior to the start of study intervention. • 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 start of study intervention. • Ongoing or known history of transient ischemic attacks or stroke within 6 months prior to the start of study intervention. • QTc using Fridericia's formula (QTcF) interval > 470 ms. • Symptomatic pulmonary disease requiring continuous or intermittent oxygen supply. • Hypertension uncontrolled by medication (i.e. systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg).
	12. History of another malignancy within last 3 years prior to start of study intervention, with the exception of completely resected nonmelanoma cell skin cancer outside the head and neck area or completely resected Stage I breast cancer, or completely resected in-situ nonmuscular invasive bladder, cervix and/or uterine carcinomas, or T1a squamous esophageal carcinomas.

Category	Criterion
	13. Liver cirrhosis (Child-Pugh score: B or C).
Prior/Concomitant Therapy	14. Prior definitive, neoadjuvant, concurrent, or adjuvant (C)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 6.8)
	15. Use of the following: • Prohibited medication. These medications and time window to stop these medications prior to the start of study intervention are further specified in Section 6.8.3. • Treatment with an investigational agent or use of an investigational device within 4 weeks of the start of study intervention or during study intervention • Live attenuated vaccines within 28 days prior to start of study intervention. • Concurrent use of anticancer therapy • 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 study intervention.
	16. Patients with active immunodeficiency or patients receiving ongoing immunosuppressive therapy.
	17. Prior organ transplantation, including allogeneic stem cell transplantation.
Prior/Concurrent Clinical Study Experience	18. Participation in any interventional clinical study within 28 days prior to screening or during participation in this study.
Diagnostic Assessments	19. Known contraindication to undergoing positron emission tomography with ^{18}F-FDG-PET scans or to both contrast-enhanced MRI and contrast-enhanced CT scans.
Other Exclusions	20. Known allergy to xevinapant, cisplatin, carboplatin or any other platinum-based agent, or any excipient known to be present in the formulation of any of these products.

Category	Criterion
	21. Any social, personal, medical, and/or psychologic factor(s), including current alcohol and/or drug abuse that could interfere in the opinion of the Investigator with the observance of the participant to the protocol and/or the follow-up and/or the signature of the informed consent.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Abstain from consumption of the following from 1 day before the start of study intervention until 1 day after the final dose: Seville oranges, grapefruit or grapefruit juice, or grapefruit-containing products, St John's Wort (i.e. Hypericum perforatum, millepertuis) and St John's Wort-containing products because of the risk of DDIs with P-gp (Section 6.8.3).

Xevinapant should be administered orally, early in the morning (see exceptions and further instructions in Section 6.5.1).

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the condition leading to screen failure has resolved and after discussion with the Medical Monitor. Rescreened participants will be assigned a new participant number. Only 1 rescreening is allowed.

Re-testing of participant in cases of physical and/or laboratory parameter 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 rescreened in certain circumstances for enrollment 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).
- 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.

In case of rescreening, the participant will be required to sign another ICF. A new eCRF will be used. All assessments should be repeated according to instructions provided for the initial screening (see Section 1.3 and Table 1). As with initial screening procedures, iv 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 start of study intervention. Dental examination, audiometry, HBV/HCV/HIV test, fiberoptic endoscopy, and ^{18}F-FDG-PET scan performed within 4 weeks before the last signed ICF do not have to be repeated during screening.

5.5 Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention

Not applicable

6 Study Intervention(s) and Concomitant Therapies

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

6.1 Study Intervention(s) Administration

See Section 4.1 for the overall design and timing of the treatments.

Table 5 Study Intervention(s)Administered

Intervention Label	Xevinapant	Cisplatin	Carboplatin (Only Used in Case of Cisplatin Toxicity as per Table 8)	IMRT
Intervention Name	Xevinapant	Cisplatin	Carboplatin	IMRT
Intervention Description	CCI mg oral solution once daily for 14 days of each 3-week cycle	CCI mg/m^2 iv solution once weekly for 7 weeks	Carboplatin solution iv CCI once per week (total platinum dosing should not exceed 7 weeks)	70 Gy total radiation given in 35 fractions delivered 5 days/week for 7 weeks
Type	Drug	Drug	Drug	Radiation
Dose Formulation	Oral solution	Concentrate for solution for iv infusion	Concentrate for solution for iv infusion	NA
Unit Dose Strength(s)	CCI	Vial of 100 mL containing 100 mg cisplatin (1 mg/mL) if provided centrally by the Sponsor. The unit dose can differ if cisplatin is locally sourced.	Vial of 15 mL containing 150 mg carboplatin (10 mg/mL) if provided centrally by the Sponsor. The unit dose can differ if carboplatin is locally sourced.	NA
Dose	CCI mg	CCI mg/m^2	CCI	70 Gy
Dosage Regimen	Once daily Day 1 - 14 of a 3-week cycle	Once weekly for 7 weeks	Once weekly (total platinum dosing should not exceed 7 weeks)	2 Gy once daily 5 days/week for a total of 35 fractions
Route of Administration	Oral	iv infusion	iv infusion	NA
Use	Experimental	Background intervention	Background intervention	Background intervention
IMP or NIMP/AxMP	IMP	IMP/AxMP, depending on local regulation	IMP/AxMP, depending on local regulation	NA
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor or locally by the study site,/CRO, or designee	Provided centrally by the Sponsor or locally by the study site,/CRO, or designee	NA

Intervention Label	Xevinapant	Cisplatin	Carboplatin (Only Used in Case of Cisplatin Toxicity as per Table 8)	IMRT
Packaging and Labeling	Xevinapant will be provided in CCI . CCI and labeled per all applicable regulatory requirements and GMP guidelines.	Depending on the local regulations, cisplatin may either be sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider) and will be packaged/labeled per all applicable regulatory requirements and GMP guidelines.	Depending on the local regulations, carboplatin may either be sourced from a local hospital pharmacy or supplied by the Sponsor (or designated service provider) and will be packaged/labeled per all applicable regulatory requirements and GMP guidelines.	NA
Former Name	Debio 1143	NA	NA	NA

AUC=Area under the curve, AxMP=Auxiliary medicinal product, GMP=good manufacturing practice, IMP=Investigational medicinal product, IMRT=Intensity-modulated radiation therapy, iv=intravenous, NA=not applicable, NIMP=Noninvestigational medicinal product.

Table 6 Study Arm(s)

Arm Name	Single Arm study Combination Therapy: Xevinapant+ cisplatin + concomitant IMRT Monotherapy: Xevinapant
Arm Type	Experimental
Arm Description	Combination Therapy: Xevinapant, QD for 14 days, Q3W cycles, + cisplatin (CCI mg/m^2) Day 2/week + concomitant IMRT Monotherapy: Xevinapant CCI mg QD for 14 days, Q3W cycles
Associated Intervention Labels	Xevinapant Cisplatin Carboplatin (Only used in case of Cisplatin Toxicity) IMRT

IMRT: Intensity-modulated radiation therapy, QD: once a day, Q3W=Every 3 weeks

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

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

- Upon receipt of the study intervention(s), the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Pharmacy Manual.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition, and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, CCI and vial numbers, kit numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) will not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Study Type	
Study using IRT	After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to study intervention using an IRT and per a computer-generated list. The IRT will be used to assign unique participant numbers, allocate participants to study intervention at each study intervention visit. Before the study is initiated, the directions for the IRT will be provided to each site. The site will contact the IRT prior to starting study intervention administration for each participant.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. A member of the study site staff other than the person administering the study intervention will confirm the study intervention dose and study participant identification at the time of dosing.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by monitoring the Patient Diary filled out by the participant after each intake (Section 8.2.6) during the site visits and documented in the source documents and eCRF. Any deviation(s) from the prescribed dosage regimen are recorded in the CRF. Participants will be instructed to return used and unused xevinapant CCI to the site to allow drug accountability by the medical staff.

A record of the number of cisplatin or carboplatin vials administered to the participants and xevinapant CCI and dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates including dates for intervention delays and/or dose reductions will be recorded in the CRF. In addition, for each study intervention (xevinapant, cisplatin [or carboplatin in case of cisplatin toxicity], and IMRT) the reasons for dose modification, interruption, and discontinuation must be recorded in the CRF.

6.5 Dose Modification

6.5.1 Xevinapant Administration

Xevinapant oral solution at CCI mg/day will be administered once daily from Day 1 to Day 14 of a 3-week cycle, during 6 cycles (Table 2,

Table 3, and Figure 3). Xevinapant should be administered orally, preferably in the morning. 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 more than 8 hours after the time of intake, then the participant should skip that dose.

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

On days of PK sampling at C1D2, C1D9, and C2D2, participants should take their doses at the hospital, where the administration of xevinapant will be supervised and recorded by the medical staff. The time of dose administration should be recorded in the eCRF and in the participant's diary for all doses.

The treatment schedule of xevinapant is presented in Figure 3, Table 2 and

Table 3. Participants will be instructed by the medical staff on how to self-administer xevinapant 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 intakes at home. Please refer to Sections 6.4 and 8.2.6 for further details.

6.5.1.1 Concurrent Administration to Chemotherapy and IMRT

CCI [redacted]

On days when IMRT is to be administered without chemotherapy (see Table 2 and Section 6.5.3), xevinapant should be preferably administered before IMRT.

If chemotherapy or IMRT are put on hold or discontinued, please refer to Section 6.5 to adapt xevinapant administration accordingly.

6.5.1.2 Dose Modification, Interruption, and Discontinuation of Xevinapant Treatment

For participants who do not tolerate the study intervention, adjustments to the study intervention dose are permitted to allow the participant to continue on-study intervention according to the guidelines below.

The guidelines for xevinapant dose modifications for toxicities considered at least possibly related to study intervention are outlined in Table 7 and Table 8, 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, nontreatment-related events, or unexpected toxicities may require interruption of study intervention at the discretion of the Investigator.

In case a dose reduction is necessary, the study intervention will be administered as follows:

For each participant, a maximum of 2 dose reductions of xevinapant 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 CCI [redacted] mg/day of xevinapant
- Dose Level 1: CCI [redacted] corresponds to CCI [redacted] mg/day of xevinapant
- Dose Level 2: CCI [redacted] corresponds to CCI [redacted] mg/day of xevinapant

General rules for xevinapant 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] mg/day (CCI [redacted] of oral solution) per step will be allowed, down to a minimum dose of CCI [redacted] mg

CCI of oral solution). If further dose reduction is required, the participant must be permanently discontinued from xevinapant administration (other ongoing treatments can continue, see Sections 6.5.2 and 6.5.3).

- If the onset of several toxicities leads to conflicting recommendations as described in Table 7 the most conservative dose adjustment among all toxicities presented must be followed.
- **No re-escalation** of xevinapant dose after dose reduction will be allowed during the study. Once xevinapant 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 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.
- Combination treatment period: If IMRT is interrupted, xevinapant should be interrupted. If IMRT is restarted, xevinapant should be resumed at the next originally scheduled intake day of xevinapant, provided other rules of dose interruption are not met (see Section 6.5.3.3). If IMRT is permanently discontinued due to safety issues, then xevinapant administration should be maintained, and the participant can enter the monotherapy period. Otherwise, xevinapant 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.
- Monotherapy treatment period: If a participant requires a xevinapant dose interruption of more than 21 consecutive days due to study intervention-related toxicities, the Investigator should consider discontinuing the treatment. If a participant is discontinued from the monotherapy treatment, the EOT visit should be performed. Hereafter, the participant will continue with the study as per schedule and will enter the FU period.
- Chemotherapy discontinuation will **NOT** result in xevinapant discontinuation.
- Participants who prematurely discontinue from all treatments, i.e. chemotherapy, IMRT, and xevinapant, in the absence of disease progression will undergo the EOT visit and then enter the follow-up period according to schedule.
- Any dose modification and dose interruption including the reason must be recorded on the Dosage Administration Record eCRF.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6.5.1.3 End of Xevinapant Treatment

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

Procedures for discontinuation from study (not only study intervention) are described in Section 7.2.

6.5.2 Chemotherapy

All participants will receive cisplatin (CCI mg/m^2) intravenously over at least 90 minutes on Day 2 QW up to a maximum of 7 cycles in total (see administration schedule in Table 2). If body surface area is > 2.00 m^2, the maximum dose per infusion will be capped at a maximum of 80 mg.

A total cumulative cisplatin dose of CCI mg/m^2 is recommended (Machiels 2020), based on various studies suggesting a sufficient therapeutic effect when this exposure to cisplatin is met (Strojan 2015, Szturz 2019) Please consult and follow cisplatin administration instructions provided in your local label and institutional guidelines. The infusion has to be administered with pre- and postinfusion hydration ± mannitol and/or diuretics. Any pre-existing dehydration should be corrected. Please refer to Appendix 3 and Appendix 4 for additional information on cisplatin administration and hydration regimen respectively.

CCI

eGFR (using the CKD-EPI creatinine formula) should be ≥ 60 mL/min/1.73 m^2 before administration of cisplatin at C1D2; retreatment conditions as specified in Table 7 should be met.

Participants should receive at least 1 full cisplatin infusion, such as on C1D2, before dose reduction, or switch to carboplatin.

Standard antiemetic prophylaxis for cisplatin containing regimens is mandatory starting on Day 1 of each chemotherapy containing cycle. Standard antiemetics guidelines (administration of pre- and post-treatment serotonin receptor antagonists, neurokinin-1 receptor antagonists and dexamethasone [or any other corticosteroid at equivalent dose iv] according to the 2016 MASCC and ESMO guideline (Roila 2016) are provided in Section 6.8.1.1; however, the specifics of the regimen are at the discretion of the treating physician, provided adequate control is achieved.

Note: Please refer to Section 6.8.1.1 for the proposed adjusted dosage/schedule for dexamethasone and aprepitant due to perpetrator drug-drug interaction potential of xevinapant via inhibition of CYP3A4.

A participant not eligible to continue with QW cisplatin after dose reduction can switch to carboplatin as per the dose modifications outlined in Table 7 (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.

6.5.2.1 Dose Modification, Interruption, and Discontinuation of Chemotherapy

Permitted cisplatin dose levels:

- Planned dose (level 0): corresponds to cisplatin CCI mg/m^2
- Dose level - 1: corresponds to cisplatin CCI mg/m^2 CCI [redacted]
- Dose level - 2: corresponds to cisplatin CCI mg/m^2 CCI [redacted]

For participants switching to carboplatin: carboplatin AUC = 2 mg·min/mL is allowed.

Please refer to Table 7 for instructions on dose modifications, interruption, discontinuation of chemotherapy, and potential switch to carboplatin in case of toxicity suspected to be related to study intervention.

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 nonhematologic toxicity from the previous treatment cycle. Chemotherapy infusion may be delayed to allow for sufficient recovery time.

6.5.2.2 End of Chemotherapy

Chemotherapy will be administered until completion of the 7 weekly infusions 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** automatically have to result in xevinapant discontinuation or IMRT discontinuation

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

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

Procedures for discontinuation from study (not only study intervention) are described in Section 7.2.

6.5.3 Radiotherapy

6.5.3.1 General Considerations

The general recommendation is to start IMRT as soon as a diagnosis and management decision has been decided.

The following guidelines must be applied:

- **Nutritional support:** Maintaining adequate nutrition is essential during the course of radiotherapy (Section 6.8.4.1).
- **Dental care:** Before the participants start IMRT, dental assessment is mandatory, and appropriate dental care should be provided (Section 6.8.4.2).

Refer to the RT Manual for further guidance.

6.5.3.2 Treatment

Full details of radiotherapy protocol requirements including volumes, OAR, and OAR dose constraints can be found in the RT Manual provided for this study. A QA procedure will be applied for this study. The RT-QA Review Center (Appendix 5) will centrally review the IMRT treatment plan(s) including other treatment-related information submitted by the Investigator to ensure compliance with protocol guidelines and provide feedback to the site (refer to the RT Manual). The IMRT plan must be reviewed by the RT-QA Review Center prior to the start of the IMRT. A summary of radiotherapy requirements and recommendations is described below.

CCI [redacted]

A matched conventional anterior neck field is not permitted. During treatment, daily image-guided radiation therapy (IGRT) is required with either kV or MV guidance.

For CT simulation, the participant must be in a supine position and immobilized with a thermoplastic (or similar) mask that includes the head and neck with strong consideration of the shoulders as well. Intraoral immobilization devices are at the discretion of the Investigator. A slice thickness of 3 mm or less is required and the field of view must extend from the top of skull to the bottom of the carina. Intravenous contrast is recommended at the time of simulation.

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

IMRT will be delivered per Table 9 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 6.5.3.3).
- Elective irradiation (low risk) to locoregional areas, 56 Gy (1.6 Gy/fraction per day, 5 fractions per week [5/7 days]).

Table 9 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

PTV=Planning target volume.

The delineation of the elective nodal clinical target volume for participants with positive neck nodes can be based on the consensus guidelines published by Biau (Biau 2019). Additional details will be provided in the RT Manual.

PTV will be a uniform 3 to 5 mm expansion to all clinical target volumes to account for interfraction motion and setup uncertainties. The simultaneous integrated boost treatment plan will be prescribed to the PTV and coverage requirements are detailed in the Radiotherapy Guidelines. If a PTV is close to the spinal cord or other critical normal tissue, a PTVeval can be created and adjusted for treatment planning purposes. The requirements for organ at risk definition and dose constraints are listed in the RT Manual.

All participants will have daily pretreatment imaging to ensure appropriate repositioning, the details will be described in the RT Manual.

The RT-QA Review Center (Appendix 5) 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 Manual). The RT-QA Review Center will evaluate IMRT delivery and any critical/major deviations from the submitted plan during study intervention period. RT-QA Review Center review of the IMRT plan is requested before starting the first fraction administration.

6.5.3.3 Treatment Interruption

IMRT interruption is strongly discouraged, and every attempt should be made to keep the treatment continuous and adhere to the overall treatment time as prescribed (7 weeks). Planned radiotherapy interruptions are not allowed. 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 6.5.3.4 for management of those toxicities).

Treatment interruption due to a nonmedical reason should be minimized as much as possible and should not exceed 2 consecutive treatment days per interruption (Radiologists 2019). 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 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 monotherapy administration should be maintained, and the participant can enter the monotherapy period.

6.5.3.4 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 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) and access to adequate nutritional support needs to be secured by the Investigator.

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.

6.5.3.5 End of Radiotherapy

Radiotherapy will be administered until completion of the IMRT dose and schedule (see Table 9) planned in the study or until any of the study intervention discontinuation criteria described in Section 7.1 occur.

Note: Radiotherapy discontinuation will not result in xevinapant discontinuation or chemotherapy discontinuation. See further Section 6.5.1.3.

Treatment interruption and permanent discontinuation of any of the components of the study intervention is to be recorded in the Dosing CRF of each component of the study intervention. For each action, the reason must be recorded.

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

Procedures for discontinuation from study (not only study intervention) are described in Section 7.2**.**

6.6 Continued Access to Study Intervention After the End of the Study

Not applicable

6.7 Treatment of Overdose

For this study, any dose of xevinapant greater than CCI mg/day and/or xevinapant intake exceeding 14 days per cycle, any dose of cisplatin higher than CCI mg/m^2 per cycle, or any dose of carboplatin higher than AUC CCI per cycle, will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose. The Investigator will use their clinical judgment to manage any overdose, considering the symptoms, and any site procedures or standards. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the participant should be observed closely for signs of toxicity.

Even if not associated with an AE or SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on an SAE and Overdose Report Form, following the procedure in Appendix 7.

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the signing of the ICF until the EOS visit at the timepoints specified in the SoA (Section 1.3), including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and

herbal supplements, record the name, reason for use, dates administered, and dosing information. For nondrug interventions, record the name, and dates administered.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.8.1 Permitted Medicines

Permitted medicines are the following:

- Medication to prevent or treat concomitant diseases or to treat adverse effects of investigational intervention are allowed unless otherwise specified in the sections below.
- Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless of if it results in a protocol deviation.
- Investigators will assess prior to, or at the beginning of the screening period, whether a participant will be vaccinated against a specific infectious disease (e.g. COVID-19 or mpox infection) that may be a significant risk to the participant during the study before receiving the first dose of study intervention.

In general, Investigators will consider that the vaccination effect may be reduced in participants with cancer and may not lead to protection depending on the extent of the immunocompromised state of the participant, including the impact of prior therapies.

6.8.1.1 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 iv.), 5-HT3 serotonin receptor antagonists and neurokinin-1 receptor antagonists can be administered as per 2016 MASCC and ESMO guideline (Roila 2016). However, dosage/schedule adjustment for both the dexamethasone and aprepitant should be considered, due to elevated plasma concentrations of these drugs fold triggered by xevinapant inhibition of CYP3A4. Strong CYP3A4 inhibitors increased AUC of dexamethasone ~ 3-4 fold and AUC of aprepitant ~ 5 fold, respectively.

For instance, the Investigator can consider the following regimen:

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

- 5-HT3 serotonin receptor antagonists iv., at the appropriate antiemetic dose for highly emetogenic regimens. If ondansetron is used with xevinapant, participant should be monitored closely (see also Section 6.5.2). Alternative 5-HT3 serotonin receptor antagonists should be used, if possible.

- Dexamethasone: 8 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 after cisplatin administration: Dexamethasone 4 mg + aprepitant 80 mg/day ± 5-HT3 serotonin receptor antagonist

Day 3 after cisplatin administration: Dexamethasone 4 mg ± 5-HT3 serotonin receptor antagonist

For participants receiving carboplatin, antiemetic therapy including dexamethasone (or any other corticosteroid at an equivalent dose iv.) and 5-HT3 serotonin receptor antagonists may be administered as per 2016 MASCC and ESMO guideline (Roila 2016). If dexamethasone is used, the modified dosage/schedule described above for cisplatin could also be considered.

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 xevinapant inhibition of CYP3A4 as described above for dexamethasone.

6.8.2 Medications to be Used with Caution With Xevinapant

Drugs With a Known Risk of QTc Prolongation

The potential of xevinapant to prolong the QTc interval has not yet been fully characterized, therefore caution should be exercised when using xevinapant with drugs having a known risk of QTc prolongation (refer to drug's product information or Arizona Center of Education and Research Therapeutics database at website: http://www.crediblemeds.org). Monitoring of electrolyte levels is strongly recommended.

Other Drugs to Be Used Under Close Medical Monitoring

- Drugs that have a narrow therapeutic range or are sensitive substrates of P-gp are recommended to be used under close medical monitoring. Some CYP3A substrates (not prohibited as per Section 6.8.3.1) also require close monitoring. Their metabolism or transport may be modified by xevinapant resulting in potential increased safety events or decreased efficacy. Commonly used drugs are listed below (Table 10 and Table 11). Note that this is not an exhaustive listing; for other drugs metabolized by CYP3A or transported by P-gp, refer to the recommendations of the product information.

Table 10 Anesthetic and Analgesic Drugs to be Used with Xevinapant under Close Medical Monitoring

Drug	International Nonproprietary Name
Anesthetic	Alfentanil Systemic lidocaine Vecuronium
Analgesic	Fentanyl Morphine

- For alfentanil and fentanyl: risk of DDI due to inhibition of CYP3A4/5 and P-gp by xevinapant. The clinical impact is a potential increased exposure, resulting in exacerbated clinical effects of alfentanil and fentanyl at standard doses.
- For lidocaine and vecuronium: risk of DDI due to inhibition of P-gp by xevinapant which might potentiate the effects of anesthetic drugs. If such drugs must be included in an anesthetic protocol, starting, and maintenance doses should be carefully considered.

Table 11 Other Drugs to be Used with Xevinapant Under Close Medical Monitoring

International Nonproprietary Name	International Nonproprietary Name
Aliskiren	Hydroxyzine
Apixaban	Lamotrigine
Prevacid	Lansoprazole
Clopidogrel	Ondansetron (**allowed alternative**: dolasetron, granisetron, tropisetron, palonosetron)
Colchicine	Posaconazole (systemic)
Dabigatran	Riociguat
Digoxin	Valproic Acid

The metabolism and transport of the above listed drugs occurs through CYP3A4/5 and/or P-gp. As per their product information, the clinical relevance of their coadministration with inhibitors or inducers of such enzymes and transporters is difficult to anticipate. In view of the in vitro DDI profile of xevinapant, the activity, and risk of toxicity of these drugs may be increased when coadministered with xevinapant.

Gastric Mucosal Protectants

Gastric mucosal protectants, if needed, cannot be taken within 2 hours before or 2 hours after xevinapant intake because their concomitant intake may decrease the absorption of xevinapant. Participants must be instructed accordingly.

6.8.3 Prohibited Medicines

6.8.3.1 Prohibited Medications with Xevinapant

- Participants are prohibited from receiving the following therapies during the screening and treatment phases: anticancer systemic chemotherapy, anticancer immunotherapy, or anticancer biological therapy not specified in this protocol.
- Use within 14 days prior to study intervention start or requirement for ongoing treatment with any drug(s) on the prohibited medication list in Sections 6.8.3.1.1, 6.8.3.1.2, 6.8.3.1.3, and 6.8.3.1.5 or within 3 days prior to study intervention start for the drugs in Section 6.8.3.1.4 is an exclusion criterion.

- Treatment with an investigational agent other than xevinapant or use of an investigational device within 4 weeks of the first dose of study intervention or during study intervention.
- In case of unavoidable concomitant administration of a prohibited medicine during investigational treatment, the need for suspension or discontinuation of xevinapant must be discussed beforehand with the Sponsor.
- Live vaccines within 28 days prior to the start of study intervention and up to 90 days after EOT are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- The use of hematopoietic growth factors is prohibited during the concomitant RT phase of the study.
- Other preparations and medications such as those listed in the below sections are strictly prohibited in combination with xevinapant.

6.8.3.1.1 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 2003, Lambin 2009).

6.8.3.1.2 Food and Herbal Preparations

- Grapefruit juice and grapefruit-containing products (P-gp inhibitors) may lead to increased xevinapant exposure.
- St John's Wort (i.e *Hypericum perforatum*, millepertuis) and St John's Wort-containing products (P-gp inducers) may lead to decreased xevinapant exposure.

6.8.3.1.3 Inhibitors/Inducers of P-gp

The concomitant intake of strong inhibitors/inducers of P-gp is prohibited because they may have an impact on the PK disposition of xevinapant (i.e. increase the xevinapant exposure for inhibitors and decrease the xevinapant exposure for inducers). Commonly used drugs are listed below (Table 12). Please note that this is not an exhaustive listing; refer to the label of potential comedications to verify they are not strong inhibitors/inducers of P-gp.

Table 12 Examples of Prohibited Inhibitors and Inducers of P-gp with Xevinapant

International Nonproprietary Name	
Inhibitors	
Amiodarone [a]	Propafenone
Carvedilol	Quinidine
Clarithromycin	Ranolazine
Dronedarone	Ritonavir
Itraconazole	Saquinavir and ritonavir
Lansoprazole	Telaprevir
Lapatinib	Tipranavir and ritonavir
Lopinavir and ritonavir	Verapamil
Inducers	
Apalutamide	Mitotane
Bosentan	Phenobarbital
Carbamazepine	Phenytoin
Efavirenz	Primidone
Enzalutamide	Rifampin
Etravirine	St. John's wort

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers (accessed 16 March 2022).

a. Participants who had long-term use of amiodarone (≤ 6 month) prior to the start of study intervention need to be closely monitored due to the long half-life of this drug with chronic dosing.

6.8.3.1.4 CYP3A4/5 Narrow Therapeutic Index Drugs or Sensitive Substrates

Xevinapant is a strong CYP3A4/5 inhibitor. The drugs listed below should not be coadministered with strong CYP3A4/5 inhibitors. Indeed, there is a risk of clinically significant increased toxicity when the active drug is metabolized by CYP3A4/5 or a risk of decreased efficacy of the concomitant medication when the prodrug is metabolized into the active drug. Commonly used drugs are listed below (Table 13). Please note that this is not an exhaustive listing; refer to label recommendations for other drugs that are low therapeutic index drugs or sensitive substrates of CYP3A.

Table 13 Examples of Prohibited CYP3A4/5 Sensitive Substrates with Xevinapant

International Nonproprietary Name	
Avanafil	Lurasidone
Budesonide	Maraviroc
Buspirone	Midazolam
Conivaptan	Naloxegol
Darifenacin	Nisoldipine
Darunavir	Quetiapine
Dasatinib	Saquinavir
Dronedarone	Sildenafil
Ebastine	Simvastatin
Eletriptan	Sirolimus
Eplerenone	Tacrolimus
Everolimus	Ticagrelor
Felodipine	Tipranavir
Ibrutinib	Tolvaptan
Indinavir	Triazolam
Lomitapide	Vardenafil
Lovastatin	

Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers (accessed 16 March 2022).

6.8.3.1.5 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 intervention. 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.

6.8.3.2 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 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.

Please also refer to the local product information for cisplatin or carboplatin, as applicable.

Medications to be used with caution

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

6.8.4 Other Interventions

6.8.4.1 Nutritional Support

All participants must be screened for nutritional risk and need of early enteral nutrition. Nutrition status must be evaluated as indicated in Table 1, Table 2, and

Table 3.

Maintaining adequate nutritional support is essential during the radiotherapy and monotherapy period. Participants must receive dietary advice to help maintain their weight during the course of radiotherapy. In case of important swallowing difficulties and/or weight loss exceeding 5% to 10%, a feeding tube is recommended, either a percutaneous endoscopic gastrostomy or nasogastric tube can be placed. The Investigator needs to ensure that the participant has access to nutritional support.

A feeding tube is mandatory if the participant has Grade ≥ 3 dysphagia.

6.8.4.2 Dental Care

Participants 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 (NCCN v1 2023). 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 in Appendix 9.

6.8.4.3 Pain

The management of pain should be done according to severity and recommended drugs as per institutional guidelines. Review Table 10 before using concomitant medications.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the entire study is specified in Appendix 5.

7.1 Discontinuation of Study Intervention

Study intervention (i.e. xevinapant, cisplatin, 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.
- Participant withdrawal of consent for treatment.
- Participants may voluntarily discontinue one or several of the study interventions at any time. If such discontinuation occurs, every effort should be made by the Investigator to determine the primary/underlying reason for this decision, which should be recorded in the eCRF. The participant should be encouraged to remain on study to be followed for efficacy assessments.
- Unacceptable toxicity/AEs that result in a significant risk to the participant's safety.
- Participants who are removed from study intervention due to AEs must 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, only after discussion with Sponsor.
- Noncompliance that is deemed by the Investigator or the Sponsor to compromise participant safety or study integrity.
- Pregnancy (Section 8.3.4).
- 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, SMC, the Investigator, the IEC/IRB, or the Regulatory Agencies.

The primary reason for study intervention discontinuation must be recorded in the eCRF.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed (

Table 3- EOT visit).

7.1.3 Temporary Discontinuation

See Section 6.5.1.2 (xevinapant), Section 6.5.2.1 (cisplatin), and Section 6.5.3.3 (RT) for further guidance on temporary discontinuation of treatment.

7.1.4 Rechallenge

See Section 6.5.1.2 for details on study intervention restart or rechallenge criteria.

7.1.4.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Are Met

Study intervention restart or rechallenge after liver clinical safety laboratory test stopping criteria are met by any participant in this study are not allowed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at their own request or 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").
- At the time of study discontinuation, if possible, a discontinuation visit will be conducted, as listed in the SoA. The SoA specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed.

- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- If a participant requests the destruction of any biological samples still remaining, the Investigator will document this in the site study records and inform the Sponsor. The samples will be destroyed.
- Participants may voluntarily withdraw consent for study participation at any time. If such withdrawal occurs, every effort must be made by the Investigator to determine the primary/underlying reason for this decision which must be recorded as reason in the form in the eCRF i.e. if the underlying reason for the decision is toxicity (e.g. AE) this must be recorded as such and the Investigator has to follow-up with the participant until the AE is resolved.
- Premature discontinuation from the study can also be triggered by:
  - Participant lost to follow-up (Section 7.3)
  - Death
  - Disease progression
  - Early study termination by the Sponsor, SMC, the Investigator, the IEC/IRB, or the Regulatory Agencies
- Should a participant be withdrawn from the study, EOS assessments must be performed prior to any further therapeutic intervention, whenever possible. Results of these assessments must be recorded in the eCRF, together with a description of the reasons for study discontinuation.

Participants who prematurely discontinue, for reasons other than DLT-like events earlier than 5 weeks after start of treatment, may be replaced.

7.3 Lost to Follow-Up

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

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

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or will continue in the study.
- Before a participant is deemed “lost to follow-up”, the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant’s medical record.
- If the participant continues to be unreachable, he/she will be deemed as “lost to follow-up”.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA. It may be necessary to perform these assessments at unscheduled timepoints if deemed clinical necessary by the Investigator.
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential, and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 5.
- Procedures conducted as part of the participant's routine medical care and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria, were performed within the time frame defined in the SoA, and if reviewed, and approved by the Sponsor.
- A participant will be allowed to receive study intervention 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 Appendix 5). The IMRT plan must have been reviewed by the RT-QA Review Center prior to the start of the IMRT.
- About 250 mL of blood total will be taken throughout the study. Up to 50 mL of blood may be drawn at certain visits. These blood samples will be used for the following purposes: clinical laboratory tests, PK, CCI [redacted]. The volume of collected blood might increase due to repeat collections that may be necessary.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the CSR.

Order of Assessments

- ECG readings must be taken prior to blood collection.

Screening Period

Participants will be screened between Days -28 and -1, prior to start of study intervention (Day 1 [-3 days]). Activities and procedures to be performed at Screening are detailed in the SoA (Section 1.3). Screening-specific procedures include:

- Demography: birth year, age at informed consent, sex, race (only where allowed by local law/regulations), and ethnicity.
- Medical history: previous illness and surgeries (e.g. all during the past year and only major ones prior to that), concomitant illness, relevant medication/ therapies, allergies, tobacco use, alcohol use.
- Eastern Cooperative Oncology Group Performance Status: assessed at Screening to assess eligibility (Section 5.1) and then assessed according to the SoA (Section 1.3).
- Disease history and tumor staging (using the AJCC/TNM Staging System, 8th Ed.) based on radiological imaging. Please refer to Section 8.1.1 for further details on radiologic imaging.
- Results from the local laboratory should be used for defining participant eligibility during Screening.
- Dental examination, audiometry (if required), HBV/HCV/HIV tests, fiberoptic endoscopy and ^{18}F-FDG-PET scan performed within 4 weeks before ICF signature do not have to be repeated during screening.
- Intravenous 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 study intervention starts.
- HPV status by p16 IHC (mandatory for OPC, optional for other tumor locations) does not have to be repeated if performed prior to ICF signature in line with instructions in Section 8.2.4.1.

8.1 Efficacy Assessments and Procedures

Assessment of tumor response to treatment will be assessed locally according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as described in Appendix 2 but will also take into consideration clinical, anatomopathological, and functional assessments of the tumor.

Tumor assessments (clinical and radiological) should be continued until disease progression (as per RECIST v1.1) occurs, next line of anticancer treatment is started, or EOS, whichever occurs first as per SoAs (Table 1, Table 2, and

Table 3) and are scheduled, after the EOT visit, every 3 months.

Participants who progress (as per RECIST v1.1) or who start next line of anticancer treatment will discontinue the study. If study intervention is permanently discontinued in participants without disease progression according to RECIST v1.1 (e.g. unacceptable toxicity), the participant will remain in the study to be evaluated for safety and efficacy. The SoA indicates data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed (

Table 3-EOT visit). Efficacy assessments will continue to be performed until disease progression, start of next line therapy, or EOS, whichever occurs first.

8.1.1 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 iv 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, Table 2, and

Table 3.

^{18}F-FDG-PET scan is preferred to facilitate pre-and posttreatment evaluation of metabolic response and the need for posttreatment neck dissection. If physical examination and imaging suggest residual disease at the primary site at EOT, a biopsy should be performed whenever possible 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 and selection of at least 1 measurable nodal or non-nodal lesion. The assessment of participants at baseline according to RECIST v1.1 is covered in Appendix 2.

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 complete response and progression based on RECIST v1.1 is also defined in Appendix 2.

Images may be collected retrospectively from the investigational sites in case it is later determined that an independent read is appropriate.

8.1.2 Radiological/Clinical Assessment at EOT and Follow-up

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

- ^{18}F-FDG-PET or ^{18}F-FDG-PET/CT scans for determining the overall clinical outcomes and the need for nodal dissection (^{18}F-FDG-PET 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, Table 2, and

Table 3.

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 ± 2 weeks).

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 scan at Baseline, with a positive ^{18}F-FDG-PET scan 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 scan in this study are supplied in Appendix 2.

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 as per institutional guidelines, and MRI and/or CT as per the schedule CT as per the schedule presented in

Table 3.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting, and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the brief physical examination as well as neurological systems, and will be done at screening and EOT.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver, spleen, and pancreas) as well as the head, mouth, and neck area, and will be done during treatment and follow-up visits.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Blood pressure and participant's position during measurement; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g. television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, and QT. If QTcF is not automatically measured, it can be calculated separately.
- A standard single 12-lead ECG will be recorded after 10 minutes of supine rest according to the schedule shown in Table 14.

Table 14 ECG Collection Plan

Study Visit or Cycle	Day	Time Relevant to Dosing
Screening	-28 to -1	NA
Cycle 1	1	predose[a] 0.5-4 hours postdose
Cycle 1	8	predose[a] 0.5-4 hours postdose

ECG=electrocardiogram, NA=not applicable.
a To be performed prior to all predose blood collection.

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

- 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 relevant to QT interval (e.g. QTcF prolongation > 30 ms compared to baseline, or QTcF interval > 500 ms, Torsade de Pointe, ventricular tachycardia, ventricular fibrillation, flutter) or any other new clinically significant cardiac abnormality, triplicate ECG readings will be performed including the already abnormal ECG reading. If the abnormal ECG finding is confirmed after triplicate ECG readings, the participant must be referred to a local cardiologist.

Significant QTcF prolongation is defined as an interval > 500 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 7 and Table 8):

- CCI [redacted]
- 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 < 480 ms.
- CCI [redacted].
- The participant will be referred to a cardiologist.
- The Medical Monitor will be consulted prior to administering further xevinapant doses.
- CCI [redacted]

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:

- CCI [redacted]
- 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.
- CCI [redacted]
- The participant will be referred to a local cardiologist.

8.2.4 Clinical Safety Laboratory Tests

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 8 at the timepoints listed in the SoA. All samples will be clearly identified.
- The following tests are only performed at Screening: coagulation, HBV, HCV, HIV tests and SARS-CoV-2 test (PCR or antigen test, if applicable). Additional coagulation tests may have to be performed according to local practice.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted according to the schedule in Table 1, Table 2, and,
- Table 3.
  - Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention.

- Additional tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by the local laboratory. For HPV testing, see additional instructions in Section 8.2.4.1.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does **not** meet the AE definition, as specified in Appendix 7. The laboratory reports will be filed with the source documents.

8.2.4.1 HPV Status in Participants with OPC

- In participants with OPC, tumor HPV status should be determined by p16 IHC.
- For OPC participants, p16 expression 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].
- p16 IHC results obtained prior to the participant's consent to participation in the study are acceptable, pathological report should be available.
  - If the report is not available for HPV status by p16 IHC, for countries where EU IVD Regulation (IVDR) is applicable, only local lab testing on an CCI [redacted] is allowed.
  - For countries not falling under the EU IVD Regulation (IVDR), the assessment can be done locally CCI [redacted]. If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory.
- The results of existing local data must be captured on the appropriate eCRF upon enrollment into the study after the participant has signed the ICF.
- For non-OPC participants, if tumor HPV status is available, this can also be captured on the eCRF as well; for these participants if no result is available, it is not needed to have the HPV status assessed.

8.2.5 Safety Monitoring Committee (SMC)

The SMC will perform a safety review after 6, 12, 18, and 38 participants have been treated for at least 5 weeks or have experienced a DLT-like event. For the SMC review after 18 participants the tolerability of treatment will be assessed using the DLT-like criteria (Section 8.2.5.1) during the initial 5 weeks for each participant (DLT-like assessment period). Additional SMC reviews may be requested by the Sponsor or SMC. In addition, the SMC will decide upon stopping of the study:

- In case of unacceptable toxicity
- In case of treatment related death without possible alternative causality.

For further details, see Section 9.2 and Appendix 5.

8.2.5.1 Definition of DLT-like Events

DLT-like events are defined as any of the following laboratory abnormalities or treatment-related AEs occurring during the DLT-like assessment period of 5 weeks that are assessed as related to study intervention:

- Asymptomatic CTCAE Grade 4 neutropenia that persists > 7 days
- CTCAE Grade ≥ 3 febrile neutropenia
- Grade 4 Thrombocytopenia without bleeding lasting ≥ 5 days or Grade ≥ 3 thrombocytopenia with bleeding or requiring platelet transfusion.
- CTCAE Grade ≥ 3 nonhematologic toxicity, including but not limited to:
  - CCI [redacted]
  - CTCAE Grade 4 dermal toxicity or mucositis if it interferes with study intervention delivery.
- A dose of less than 60% of the planned cumulative dose of xevinapant or cisplatin in the respective treatment cycle due to treatment-related AE occurring during the DLT-like assessment period.

  Note: If dose reduction at the start of a next treatment cycle of xevinapant /cisplatin/carboplatin is required according to dose modification guidelines (Section 6.5.1.2), it is considered as a new planned dose.
- RT delay > 2 weeks due to a treatment-related AE occurring during the DLT-like assessment period
- CTCAE Grade 2 or higher ototoxicity worsening by 2 grades or more from baseline if deemed treatment limiting by the investigator
- Any occurrence of drug-induced liver injury (DILI) meeting the Hy's law criteria (i.e. defined as aminotransferases > 3 × ULN, alkaline phosphatase < 2 × ULN, total bilirubin ≥ 2 × ULN, with no other reason to account for these abnormalities)
- CTCAE Grade ≥ 3 laboratory abnormalities
- Any other life-threatening toxicity
- Grade 5 toxicity

Exceptions:

1. Grade 3/4 nausea, vomiting, and diarrhea will be considered DLT-like events only if they persist for at least Grade 3 for > 3 days despite optimal therapy. Grade ≥ 3 fatigue and anorexia will not be considered DLT-like events
2. 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 DLT-like events unless if it leads to permanent discontinuation of treatment as assessed by the investigator.

3. CTCAE Grade ≥ 3 lab abnormalities that are not interfering with study intervention delivery according to investigator assessment will not be considered DLT-like events.
4. Grade ≥ 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
5. Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
6. Amylase increases originating from the salivary gland will also not be considered DLT-like events.

The SMC will confirm any DLT-like event.

8.2.6 Patient Diary

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

On days of PK sampling, C1D2, C1D9, and C2D2 participants must take their doses at the hospital, where the administration of xevinapant will be supervised and recorded by the medical staff both in the eCRF and in the patient's diary. In addition, time of last dose taken prior to xevinapant PK collection (i.e. at C1D1, C1D8, C2D1) needs to be recorded in the participant's diary, if taken at home, and all need to reported in the eCRF.

The treatment schedule of xevinapant is presented in Table 2 and

Table 3. Participants will be instructed by the medical staff on how to self-administer xevinapant at home. The participant should inform the medical staff of any missed or delayed doses.

The diary will be dispensed to the participants according to the schedule presented in Table 2. They will be instructed on how to record xevinapant administration (i.e. date and time of the xevinapant intake should be recorded in the diary).

Participant 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.

8.2.7 Audiometry

An audiometry must be performed at screening. In addition, hearing clinical evaluation and audiometry should be performed if clinically indicated at C1D8, C1D15, C2D1, C2D8, C2D15, C3D1, and at any time 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 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and SAE are in Appendix 7.
- The Investigator and any qualified designees (e.g. Subinvestigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up all AEs, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 7
- All AEs and SAEs will be collected from the signing of the ICF until the EOS/follow-up visit at the timepoints specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 7. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in their condition.

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 7.

AE data will be obtained by querying the participant and checking the AESI list (Section 8.3.7) and will be based on the physical examination. Particular focus should be on the gastrointestinal system, hepatobiliary system, kidneys, pancreas, mucosae in head neck area, skin, and eyes.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined in below sections) will be reported on an ongoing basis in the appropriate section of the eCRF.

All SAEs must be additionally documented and reported using the appropriate report form as specified in Appendix 7

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 7.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators within 15 days.
- An Investigator or Subinvestigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g. Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will read it and confirm completion of this activity. This information will be filed in the Investigator's Site File, and the IRB/IEC will be notified, if appropriate, according to applicable local laws/regulations and site SOPs.
- In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious adverse event that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

Details on SAE reporting is specified in Appendix 7.

8.3.4 Pregnancy

- Details of all pregnancies in participants and participant's partners will be collected after the start of study intervention and until 6 months after the last administration of chemotherapy or 3 months after last dose of xevinapant corresponding to time needed to eliminate study intervention(s) (e.g. 5 terminal half-lives) after the last dose of study intervention.
- If a pregnancy is reported, the Investigator will record the pregnancy information in the CRF which will be reported to the Sponsor within 24 hours after awareness of the participant's or partner's pregnancy (after obtaining the necessary signed partner's informed consent).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication, or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant /partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/ partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants /partner, they may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.5 Cardiovascular and Death Events

No dedicated collection of cardiovascular TEAEs is planned for this study. Potential cardiovascular adverse events will be recorded according to standard TEAE documentation and reporting process. Death will not be collected as SAE but only be recorded as outcome of a TEAE.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with SCHNN and can be serious/life-threatening:

- Progression of the underlying SCCHN.
- Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded as part of the secondary endpoint.

- However, the event will be recorded and reported as an AE/SAE (instead of a DRE) as defined in Appendix 7.

8.3.7 Adverse Events of Special Interest

All AESIs during the treatment period should be recorded promptly to the Sponsor and in the eCRF within 24 hours. Nonserious AESIs should be reported on an AESI form. In addition, serious AESIs must be documented on an SAE form. All SAEs must be reported as specified in Appendix 7.

Based on emerging safety data collected during this and other xevinapant studies, changes to the AESI list might be required. Should this be the case, an updated list will be included in the Investigator's Brochure at the regular annual update. Thus, Investigators should consult the latest version of the Investigator's Brochure when assessing the need to report an AESI.

The AESIs for this study are defined below according to study period (also refer to the IB for any updates).

For this study, AESI(s) include the following as listed in Section 8.3.7.1and Section 8.3.7.2.

CCI

CCI

8.4 Pharmacokinetics

8.4.1 Blood Sampling and Bioanalysis

- Samples are collected only where allowed by local law/regulations.

On all PK days (C1D2, C1D9, and C2D2; Table 4) participants take xevinapant at the hospital to ensure predose collection for xevinapant PK at the predose timepoint.

Whole blood samples of approximately 3 mL per collection for measurement of plasma concentrations of xevinapant (including metabolite[s], such as D-1143-MET1) will be collected.

Collection times are specified in the Pharmacokinetic Assessments SoA (Table 4). The actual date and time (24-hour clock time) of each sample collection will be recorded in the eCRF to calculate actual time elapsed since the prior dose administration. On PK days, record time of oral xevinapant dose, time of start and end of cisplatin infusion, and time of PK sampling for each sample in eCRF. In addition, record time of previous dose prior to PK sampling day (such as dose taken on C1D1, C1D8, C2D1) in eCRF or patient diary if taken at home. Volumes of doses taken on PK sampling days and prior dose needs to be recorded in eCRF (C1D1, C1D2, C1D8, C1D9, C2D1, and C2D2).

- The quantification of xevinapant in plasma will be performed using a validated bioanalytical method. In addition, metabolite(s) (such as D-1143-MET1) will be measured. Concentrations will be used to evaluate the PK of xevinapant and D-1143-MET1 via population PK approaches.
- Remaining samples collected for analyses of xevinapant (including metabolite[s] such as D-1143-MET1) may also be used to evaluate safety or efficacy related to concerns arising during or after the study, including safety laboratory assessment and cisplatin concentrations.

Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the end of study are specified in the respective ICF.

8.4.2 PK Parameters

The following PK parameters will be calculated, when appropriate:

Symbol	Definition
C_{trough}	The concentration observed at the end of a dosing interval immediately before next dosing (xevinapant)

- Other PK parameters might be added based on emerging data. Details will be in the IAP. Concentration data may be used for integrated data analyses across studies, such as population PK and CCI [redacted], efficacy, and/or safety analyses and reported separately from the main CSR.

8.5 Genetics and/or Pharmacogenomics

Not applicable

CCI [redacted]

CCI [redacted]

8.7 Immunogenicity Assessments

Not applicable

8.8 Health Economics

Not applicable

9 Statistical Considerations

Details of these analyses will be specified in the IAP.

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

9.2 Sample Size Determination

A total of approximately 40 participants will be treated with study intervention such that approximately 38 DLT-like evaluable participants are anticipated to be obtained. Participants who prematurely discontinue, for reasons other than DLT-like events earlier than 5 weeks after start of treatment, may be replaced.

The tolerability will be assessed using the DLT-like criteria (Section 8.2.5.1) during the initial 5 weeks for each participant (DLT-like assessment period). The SMC will review the safety data. If the incidence of DLT-like adverse events is < 40% at the SMC review with 18 participants and the primary analysis, treatment will be determined to be tolerable. If the incidence of DLT-like adverse events is ≥ 40% at the SMC review with 18 participants and the primary analysis, SMC will make a recommendation based on a comprehensive assessment of all available data. In the SMC review with 6 and 12 participants or any in non-pre-specified SMC review, the occurrence of DLT-like

events will be evaluated qualitatively, but the tolerability of the treatment will not be determined using the 40% threshold of DLT-like events due to the small sample size.

The threshold of 40% is based on the previous DLT-like event rate of 33% observed in the xevinapant arm in Study CCI [redacted] In general, a threshold of 30% is used in early oncology first in human studies; however, 40% is considered appropriate for this study, because the cisplatin, and IMRT based backbone treatment is known to already have a certain level of toxicity. CCI [redacted]

The sample size is determined by having a set of DLT-like adverse event evaluable participants of a size, which provides an estimated incidence proportion of DLT-like adverse events below the threshold of 40% with a likelihood of 80%, if the true underlying incidence proportion would be at 30%. Based on the simulation study, the actual such probability at SMC with 18 participants is 85.9% and actual limit of observed DLT-like events is 7 events (38.9%, CI: 17.3; 67.3). The following table summarize the results for entire study (i.e. probability of both SMC and PA result in a proportion below 40%) with varying sample size:

Table 15 Sample Size Calculation

N	Probability		
	x (%)	95% CI	P(X ≤ x | p = 0.3)
37	14 (38.8)	[17.3, 67.3]	81.0%
38 (selected)	15 (39.5)	[22.5, 57.5]	83.0%
39	15 (39.5)	[24.0, 58.8]	82.0%
40	15 (38.5)	[23.4, 57.6]	80.6%

N=total of DLT-like evaluable participants, x=observed DLT-like adverse events (here limit for x/N ≤ 0.4), p=true underlying incidence proportion for DLT-like adverse events, CI=Exact (Clopper-Pearson) confidence interval, P(X ≤ x | p = 0.3)=probability to observe a DLT-like adverse event incidence proportion below 40%).

9.3 Analysis Sets

The analysis sets are specified below.

Table 16 Analysis Set

Analysis Set	Description
SCR	All participants who provided informed consent, regardless of the study intervention status in the study.

Analysis Set	Description
DLT	All participants who were administered any dose of any study intervention and meet at least 1 of the following criteria: • Experienced at least one DLT like event confirmed by the SMC during the DLT like assessment period or for whom the composite ICE strategy led to a DLT like event, regardless of the administered number of doses of study intervention/completion in the DLT like assessment period. • Received at least 60% of the planned cumulative dose of xevinapant and cisplatin during the DLT-like assessment period, regardless of the completion in the DLT-like assessment period.
FAS/SAF	All participants who were administered any dose of any study intervention.
PK	All participants, who receive at least 1 dose of xevinapant, have no relevant protocol deviations or important events affecting PK, and provide at least 1 measurable postdose concentration.

DLT=dose-limiting toxicity, FAS=full analysis set, PK=pharmacokinetic, SAF=safety, SCR=screening.

9.4 Statistical Analyses

In general, continuous variables will be summarized using number (n), mean, median, standard deviation, minimum, and maximum. Time-to-event data will be summarized based on Kaplan-Meier estimates, including but not limited to median (and 95% CI), frequency of participants with events, at risk, rate (and 95% CI) at predefined timepoints. Categorical variables will be summarized using frequency counts and percentages. Proportions are calculated based on the number of participants in the analysis set of interest, unless otherwise specified in the Integrated Analysis Plan. If not explicitly stated, no imputation is used in the analyses.

9.4.1 Efficacy Analyses

All analyses on efficacy endpoints are primarily done on the FAS/SAF.

Reference #	Category	Statistical Analysis
Secondary		
3 – Objective Response	Main	Objective response rate (ORR), defined as the number of participants having reached a best overall response (BOR) of CR or PR will be calculated along with the corresponding 2-sided exact Clopper-Pearson 95% CI per treatment group. Further details will be provided in the Integrated Analysis Plan.
4 – PFS 5 – LRC 6 - Time to subsequent cancer treatments	Main	PFS is defined as the time from date of the first treatment until date of the first documentation of PD or death due to any cause, whichever occurs first. LRC is defined as the time from date of the first treatment until date of the first occurrence of progression at the site of the primary tumor or the locoregional lymph nodes. Time to subsequent systemic cancer treatments is defined as time from date of the first treatment administration until the start date of the first subsequent systemic cancer treatment for SCCHN. Evaluations of tumor response are based on either according to RECIST v1.1 or based on clinical assessment (radiological or clinical, as assessed by Investigator). Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics (median, survival time, and survival rate estimates at 3 and 6 months and every 6 months thereafter if applicable) including the corresponding 2-sided CIs. Further details will be provided in the Integrated Analysis Plan.

BOR=best overall response, CI=confidence interval, CR=complete response, LRC=Local-regional control, OR=overall response, ORR=overall response rate, PD=progressive disease, PFS=progression-free survival, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumor, SCCHN=squamous cell carcinoma of the head and neck.

9.4.2 Safety Analyses

All safety analyses will be performed on the FAS/SAF except for the analysis of the primary endpoint, which will be performed on the DLT analysis set.

Reference #	Statistical Analysis
Primary	
1 – Occurrence of DLT-like events	DLT-like events are defined in Section 8.2.5.1. All DLT-like events that occurred in the analysis population during the DLT-like assessment period of each participant will be analyzed. The number and proportion of participants experiencing DLT-like events in the analysis population will be reported together with the corresponding Clopper-Pearson 95% CI.
Secondary	
2– safety	TEAEs are defined as AEs emerging or worsening after start of treatment until 30 days after end of treatment. Adverse events will be coded according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs will be graded by the Investigator using the NCI-CTCAE (Version 5) toxicity grades. TRAEs will be defined as any AE considered as related to study treatment. Incidence of TEAEs which includes AESIs and TRAEs summarized by SOC and PT.

Reference #	Statistical Analysis
	Laboratory results will also be classified by Grade according to NCI-CTCAE. Worst on treatment grades as well as shifts to worst on treatment grades will be summarized. Measurements without NCI-CTCAE grading will be summarized by above, within, and below normal limits. Vital parameters, weight, and ECOG performance status and corresponding changes from baseline will be presented as descriptive statistics by timepoint. Further details will be provided in the Integrated Analysis Plan.

AE=adverse event, AESI=adverse events of special interest, CI=confidence interval, ECOG=Eastern Cooperative Oncology Group, MedDRA=Medical Dictionary for Regulatory Activities, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, PT=Preferred Term, SOC=System organ class, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event.

9.4.3 Other Analyses

Details on the analyses of plasma concentrations of xevinapant (including metabolite[s], such as D-1143-MET1) during the treatment period will be in the IAP that will be finalized before database lock.

9.4.4 Sequence of Analyses

The sequence of planned analyses is as shown in Table 17.

Additional analysis during the study might be conducted, e.g. for publication or decision making purposes. More details will be described in the IAP and SMC Charter.

Table 17 Sequence of Planned Analysis

	Analysis
SMC	The SMC will review available data during study conduct. The cutoff for the SMC reviews will be triggered when 6, 12, and 18 participants have been treated for at least 5 weeks (DLT-like assessment period) or have experienced a DLT-like event. Additional SMC reviews may be requested by the Sponsor or the SMC.
Primary analysis	The cutoff will be triggered when at least 38 participants meet at least 1 of the following criteria: • Experience at least 1 DLT-like event, regardless of the administered amount of study intervention/completion in the DLT-like assessment period. • Receive at least 60% of the planned cumulative dose of xevinapant and cisplatin during the DLT-like assessment period and either complete the DLT-like assessment period or discontinue study.
Follow-up analysis	Follow-up analyses to report further efficacy and safety data will be done once the End of Study has been reached as defined in Section 4.4.

DLT=dose-limiting toxicity, SMC=Safety Monitoring Committee.

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11 Appendices

Appendix 1 Abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AJCC	American Joint Committee on Cancer
AxMP	auxiliary medicinal product
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BOR	best overall response
CDMO	Contract Development Manufacturing Organization
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Corona virus disease-19
CR	complete response
CrCL	creatine clearance
CRF	case report form
CRO	clinical research organization
CRR	complete response rate
CRT	chemoradiotherapy
CSR	clinical study report
CT	clinical trials, computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interactions
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DRE	disease-related events
EAC	Endpoint Adjudication Committee

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
END	elective neck dissection
EOT	end of treatment
ESMO	European Society for Medical Oncology
ER	emergency room
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded
FU	follow-up
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factors
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human Chorionic Gonadotropin
HCP	healthcare provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
IAP	integrated analysis plan or inhibitor of apoptosis proteins
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IMRT	intensity-modulated radiation therapy

IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	interactive response technology
IVDR	In Vitro Diagnostic Medical Device Regulation
LA SCCHN	locally advanced squamous cell carcinoma of the head and neck
LRC	locoregional control
MASCC	Multinational Association of Supportive Care in Cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	noninvestigational medicinal product
OPC	oropharyngeal cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic, progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	permeability glycoprotein
PK	Pharmacokinetic
POCBP	Person of Childbearing Potential
PR	partial response
PS	performance status
PT	preferred term
PTV	planning target volume
QTcF	corrected QT interval by Fridericia' formula
QTL	quality tolerance limit
QW	Weekly
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumor

RT	Radiotherapy
RT-QA	RadioTherapy Quality Assurance
SAE	serious adverse event
SAF	Safety
SCCHN	squamous cell carcinoma of the head and neck
SCR	Screening
SDV	source data verification
SMC	Safety Monitoring Committee
SoA	schedule of activities
SoC	standard of care
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
ULN	upper limit of normal

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 Applied to This Study in Locally Advanced SCCHN

The text below was derived from Eisenhauer 2009 and Schwartz 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 ^{18}F-FDG -PET scanning to complement CT/MRI scans in assessment of progression (particularly possible 'new' disease.) However, the use of ^{18}F-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 1 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 nonmeasurable 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-target 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 except ^{18}F-FDG-PET scan should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. ^{18}F-FDG-PET scan performed within 4 weeks before ICF signature could be used at baseline evaluation. 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 nontarget lesions. Nodes that have a short axis < 10 mm at baseline are considered nonpathological and should not be recorded or followed.

A sum of diameters (longest for nonnodal 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.

- *Nontarget Lesions*

All other lesions (or sites of disease) including pathological lymph nodes should be identified as **nontarget lesions**. Measurements are not required, except short axis of nodes and then only to confirm or exclude pathological enlargement: these lesions should be subsequently assess all together as complete response, noncomplete response, or progressive disease. Progressive disease has to be unequivocal, and based on the entire nontarget lesion burden, unless there is only 1 nontarget lesion. Multiple nontarget 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 18 below.

Table 18 Response Status Definition for Target Lesions at Each Timepoint

Observed disease	Response	Abbreviation
Disappearance of all target lesions except pathological lymph nodes. All pathological nodes (target or nontarget) 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
1 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 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 Nontarget Lesions*

While some nontarget 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 19 below:

Table 19 Response Status Definition for Nontarget Lesions at Each Timepoint

Observed disease	Response	Abbreviation
Disappearance of all nontarget lesions except for lymph nodes. All lymph nodes must be nonpathological in size (< 10 mm short axis)	Complete Response	CR
Persistence of 1 or more nontarget Lesions	Neither complete response nor progressive disease	Non-CR/non-PD
Unequivocal progression of existing nontarget lesions	Progressive disease	PD
No nontarget lesions seen at baseline	No nontarget lesions	NA
Assessment not possible due to inadequate or missing images	Not Evaluable	NE

- *Special points*

When the participant has both target and nontarget lesions. To achieve 'unequivocal progression' on the basis of the nontarget disease, there must be an overall substantial worsening in nontarget 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 nontarget lesions is insufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only nontarget 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 nontarget 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 secondary endpoints of this study.

Evaluation of Disease Status at Each Postbaseline 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, nontarget lesions and new lesions, and is shown in Table 20 below.

Table 20 Timepoint Assessment of Disease Status by Imaging for Participants With Measurable Disease at Baseline.

Timepoint Response in:			Overall Timepoint Response
Target Lesions	Nontarget 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 21 below.

Table 21 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
Nontarget 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/ or videos.

Appendix 3 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 4). 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.

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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 participants 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 6 months or according to local guidelines and/or local product information (whichever is longest) 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 6 months or according to local guidelines and/or local product information (whichever is longest) 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.

Appendix 4 Cisplatin Hydration Guidelines

Adequate hydration must be maintained from 2 to 3 hours prior to administration until minimum of 2 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 for a period of 2 to 3 hours, with a total amount of at least 1 L.

Hydration after termination of the administration of cisplatin:

- Intravenous infusion of another 2 liters for a period of at least 2 hours.
- Additional hydration on days 2 and 3 post-cisplatin dosing as per institutional guidelines.

Efforts to maintain urine output to 100 mL/hour on the day of cisplatin administration is important and forced diuresis should be required as appropriate, by taking the increase or decrease in in-out balance and body weight into account. 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 postcisplatin 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 posthydration regimen (recommended 1,000-1,500 mL on days 2 to 3 post-cisplatin dose) is requested whenever possible in those participants with risk factors for renal toxicity, e.g. proteinuria, diabetes, and hypertension.

CCI [redacted] Attention should also by paid to any signs of dehydration (insufficient urine outputs) or conditions leading to a potential dehydration like diarrhea, vomiting, undernutrition, infection/fever.

CCI [redacted]

Appendix 5 Study Governance

Financial Disclosure

Investigators and Subinvestigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or their representative will explain the nature of the studyincluding the risks, and benefits, to the participant, and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; privacy and data protection requirements, where applicable; and the IRB/IEC or study center.
- The medical record 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. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be reconsented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative. The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing, and inspection purposes.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable) who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that their medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

- The Investigator and Sponsor will comply with all applicable regulations to protect personal data. If a data security breach occurs at the site, the Investigator will inform the Sponsor within 24 hours after becoming aware of the event. The Sponsor will manage the breach in accordance with their processes, including where applicable regulatory authority and/or IRB/EC notification.

Study Administrative

Site and country selection will be based on historic enrollment data and the results of a feasibility assessment. It is anticipated to be conducted in the US, Europe, and Asia-Pacific. Sites will include clinical centers and academic centers, mostly in an outpatient setting.

The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

- Several activities are outsourced to third-party service providers. These providers and activities include, but are not limited to a CRO, central laboratory, RT-QA review center, and CDMO.
- Drug supply and distribution are handled via CDMO including regional depots.

Details of structures and associated procedures will be defined separately in an Integrated Study Management Plan and the associated functional study plans.

Safety Monitoring Committee

An SMC will be formed in this study before the start of study intervention of the first participant and will assess the tolerability and safety during the study (See Section 8.2.5 and 9.2 for details). The SMC consists of Sponsor representatives (including, but not limited to the Medical Responsible, the Patient Safety Strategy Lead, and the Biostatistician), the coordinating Investigator, and external experts, if applicable. The full membership, mandate, and processes of the SMC will be detailed in the SMC charter.

RT-QA Review Center

1 or more RT-QA Review Centers will be identified. The responsibilities of the RT-QA Review Center can include:

- Reviewing and provide suggestions to IMRT plan(s) before starting the first fraction administration to ensure IMRT requirements compliance.

A RT-QA 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.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

- The protocol, protocol amendments (if applicable), ICF, IB, and other relevant documents (e.g. advertisements) will be submitted to an IRB/IEC for review and approval before the study is initiated.
- Any protocol amendments (i.e. changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide their emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard process established for Investigators.

  When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24 hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator

Publication

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

Dissemination of Clinical Study Data

- Following the primary analysis, a clinical study report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations. Further analyses will be reported in a CSR addendum, if applicable.
- Posting of data on ClinicalTrials.gov, the Clinical Trial Information System (CTIS), and all other required registries is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.
- No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Data Management Plan.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

CCI [redacted]

- QTLs will be predefined and documented in the Risk-based Monitoring and Operations Plan to help support the identification of systematic issues that could potentially impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTL thresholds and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Clinical Operating Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for the required length of time after study completion, per all applicable regulations, institutional policies, or contractual agreement.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data, and its origin is found in Clinical Operating Plan.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further development of the Sponsor’s compound.
- Sponsor discontinuation of the study due to an unacceptable risk, any relevant toxicity, or negative change in the risk/benefit assessment.

The Sponsor will decide which study procedures/assessments that are not related to participant safety will be discontinued. If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

Appendix 6 Contraception and Barrier Requirements

Definitions:

POCBP:

A participant is of childbearing potential (fertile) following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g. amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of xevinapant, consider additional evaluation.

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a participant not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement (> 40 IU/L or 40 mIU/mL) is required.
- A participant on HRT and whose menopausal status are in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent Sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

Contraception Guidance:

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- IUD
- IUS
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

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

Highly Effective Methods That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation
  - Oral
  - Injectable
- Sexual abstinence: a highly effective method **only** if defined as refraining from intercourse during the entire period of risk associated with xevinapant. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Barrier Methods (to be used in addition to a highly effective method)

- External or internal condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide]

Notes:

Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants.

Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with the study intervention(s), which may reduce the efficacy of the contraceptive method. As such, 1) barrier methods (external or internal condom with or without spermicide; cap, diaphragm, or sponge with spermicide) in addition to hormonal contraception or 2) a non-hormonal intrauterine device must be used". If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are **not** acceptable methods of contraception for this study. External and internal condoms cannot be used together (due to risk of failure from friction).

Appendix 7 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events Meeting the AE Definition
• Any abnormal laboratory test results (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition per the Investigator's medical and scientific judgment, are considered clinically significant in the medical and scientific judgment of the Investigator (e.g. not related to progression of underlying disease, but may be leading to study intervention discontinuation). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator. • Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for their condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.

SAE Definition

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

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

a. Results in death.

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma

(e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.
f. Other situations • Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs, AESIs, or DLTs.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • 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. All participant identifiers, except the participant number, will be redacted on these copies before submission to Sponsor. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

  Do not confuse an AE that is assessed as severe with an SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Investigators will reference the NCI-CTCAE, version 5.0 (publication date: 27 Nov 2017), a descriptive terminology that can be used for AE reporting.

A general grading (severity/intensity; hereafter referred to as severity) scale is provided at the beginning of the above referenced document, and specific event grades are also provided.

If the severity for an AE is not specifically graded by NCI-CTCAE, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5, using their best medical judgment.

The 5 general grades are:

- Grade 1 or Mild
- Grade 2 or Moderate
- Grade 3 or Severe
- Grade 4 or Life-threatening
- Grade 5 or Death

Any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE. However, a laboratory abnormality of Grade 4, such as anemia, or neutropenia, is considered serious only if the condition meets one of the serious criteria specified below.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g. sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change their causality assessment after considering follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE form, specified below, to report the event within 24 hours. • The site will enter into the electronic system the SAE data within 24 hours after becoming aware of the event. It is expected that the Investigator/Subinvestigator signs off this data in the system and any relevant associated data (e.g. additional laboratory tests, medical records, diagnostic reports, histopathological examinations, or consultation with other health care professionals) will be entered as soon as it becomes available. • After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department. • By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.
SAE Reporting by a Paper Form
• SAE reporting on a paper report form may be used as a back-up method for an EDC system failure. The paper form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.

- The paper form will be transmitted to the Sponsor or its designee within 24 hours by email or facsimile (fax to mail).
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the paper form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, and hospital discharge letter) may be required in addition.

Recording and Reporting of DLTs

- Each event that meets the DLT criteria, as specified in Section 8.2.5.1, will be recorded in the CRF within 24 hours after awareness of the event.
- Serious DLTs will be reported in an expedited manner, using the SAE reporting process, as specified above.
- Notification of each DLT related event (nonserious and serious) will be reported to the Sponsor or its designee within 24 hours from the date of awareness.

Reporting of AESIs

- Serious and nonserious AESIs will be recorded by the site within 24 hours in the CRF, using the same process as stated in the section above “Reporting of SAEs”.
- Paper report forms may be used as a back-up method for an EDC system failure and will be transmitted to the Sponsor or its designee within 24 hours by facsimile (fax to mail) or email.

Reporting of Pregnancies

- Pregnancy and abnormal pregnancy outcomes (participant/partner/child/fetus) will be recorded in the CRF and submitted to the Sponsor within 24 hours. Specific guidance is provided in the CRF Completion Guideline.
- Paper report forms may be used as a back-up method for an EDC system failure and will be transmitted to the Sponsor or its designee within 24 hours by facsimile (fax to mail) or email.

Appendix 8 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

Laboratory Assessment	Parameters	
Biochemistry[1] (full panel)	Albumin	Glomerular Filtration Rate, Calculated[d]
	Alanine Aminotransferase[a]	Glucose
	Alkaline Phosphatase[b]	Lipase
	Amylase	Potassium
	Aspartate Aminotransferase[a]	Sodium
	Total Bilirubin	Protein
	Direct Bilirubin[c]	Blood urea nitrogen/urea
	Calcium	C-reactive protein
	Creatinine	Uric acid
		Magnesium
Biochemistry[1] (minimum panel)	Alanine Aminotransferase[a]	Lipase
	Alkaline Phosphatase[b]	Potassium
	Amylase	Sodium
	Aspartate Aminotransferase[a]	Blood urea nitrogen/urea
	Total Bilirubin	Magnesium
	Direct Bilirubin	
	Creatinine	
CCI		
a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Table 8.		
b If alkaline phosphatase is elevated, consider measuring the alkaline phosphatase isoenzymes		
c Only If total Bilirubin > ULN		
CCI		
Hematology	Hematocrit	Platelets
	Hemoglobin	Mean corpuscular volume (MCV)
	Leukocytes with Differential:	Mean corpuscular hemoglobin (MCH)
	Neutrophils (absolute/%)	Erythrocytes (RBC)
	Lymphocytes (absolute/%)	
	Monocytes (absolute/%)	
	Eosinophils (absolute/%)	
	Basophils(absolute/%)	
Coagulation	Prothrombin Intl. Normalized Ratio, if applicable (e.g. under oral anticoagulation medication)	
	Activated partial thromboplastin time	
	Fibrinogen	
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, leukocytes by dipstick.	
	Microscopic examination (if blood or protein is abnormal).	
Contraception and Pregnancy	Follicle Stimulating Hormone (for females, as needed, if not POCBP)	
	Serum or highly sensitive urine] hCG pregnancy test (as needed for a POCBP). Serum hCG pregnancy test during screening, local urine test thereafter [Note: urine testing at a local	

Laboratory Assessment	Parameters	
	laboratory will be standard for the protocol. If required by local regulations or the IRB/IEC, serum testing will be done instead].	
Serology	HBsAg and HBcAb	HPV status by p16 IHC
	HCV-antibody and HCV-RNA by PCR	SARS-CoV-2 (RNA by PCR and/or antigen test) (see Section 5.2 when test is applicable)
	HIV 1/2 antibodies	

CCI [redacted]

HBcAb=Hepatitis B core antibody, HBsAg=Hepatitis B surface antigen, hCG=human Chorionic Gonadotropin, HCV=Hepatitis C Virus, HIV=human immunodeficiency virus, HPV=Human papillomavirus, IEC=Independent Ethics Committee, IHC=immunohistochemistry, IRB=Institutional Review Board, MCH=Mean corpuscular hemoglobin, MCV=Mean corpuscular volume, PCR=polymerase chain reaction, POCBP=Person of Childbearing Potential, RBC=red blood cell, SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2, ULN=upper limit of normal.

All study-required laboratory assessments will be performed by a local laboratory. For HPV testing, see Section 8.2.4. CCI [redacted]

CCI [redacted]

Appendix 9 Recommended Dental/Oral Evaluations

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 participant 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 postradiation osteonecrosis.
  - Preventing oral candidiasis.

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

Appendix 10 Conduct of the Study During the COVID-19 Pandemic

Benefit/Risk Assessment of the Conduct of the Study During the COVID-19 Pandemic

Efficacy results from the 36-month analysis of Debio 1143-201 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 54% in the xevinapant group compared to the placebo group (hazard ratio 0.46 [95% CI: 0.19; 1.13], p=0.0893).

Xevinapant + CRT treatments also demonstrated a 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 67% in the risk of disease progression or death in the xevinapant group compared to the placebo group (hazard ratio 0.33 [95% CI: 0.17; 0.67], p=0.0019).

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: 50; 78) in the xevinapant arm versus 51% (95% CI: 35; 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=0.0271.

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 CCI mg/day were safely combined with either chemotherapy, RT, or both. In Study Debio 1143-201, xevinapant was administered to participants with LA SCCHN in combination with cisplatin and standard RT. An increased risk of nausea, mucosal inflammation, dysphagia, weight decrease, radiation skin injury, tinnitus, hyperlipasemia, elevation of transaminase, and Grade 3 anemia was observed versus placebo. Nevertheless, the safety profile of xevinapant used in combination with CRT remained acceptable and manageable.

The COVID-19 pandemic globally affected the society in many aspects, including the conduct of clinical studies. While cancer patients are a subpopulation at increased risk during the pandemic, they are also a patient population in urgent need of receiving treatment for their disease. Therefore, during the COVID-19 pandemic, the decision to start cancer treatment is very individual and relies on a thorough benefit/risk analysis per patient by the treating physician.

Recommendations for Mitigation Measures During the COVID-19 Pandemic

Considerations for participants' eligibility

The safety of the clinical study participants is of primary importance. The individual benefit-risk 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. Furthermore, special attention should be paid to those participants with additional risk factors for more serious COVID-19.

Recommendations for the initiation of study intervention

In the context of the study protocol exclusion criteria #6 "Other infections (viral [including COVID-19] and/or bacterial and/or mycotic) requiring systemic treatment", a COVID-19 diagnostic test (PCR or antigen test) is mandatory during Screening, except for participants who have completed vaccination against SARS-CoV-2 or who have recovered from confirmed COVID-19 at Screening, as per local regulations. The result of this diagnostic test should be available before randomization. If the test is positive, irrespective of the absence or presence of symptoms, the initiation of the study intervention should be postponed until any existing symptoms have resolved and a follow-up test (PCR or antigen test) is negative.

If initiation of treatment is postponed, study intervention should not be started before a negative COVID-19 test result. Additionally, in case of symptoms, study intervention 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 confirmed COVID-19 cases should be reported as an AE even if they are asymptomatic.

Recommended study procedures in case of COVID-19 pandemic in study site area

Recommendations for the management of participants enrolled in the study during the COVID-19 pandemic are listed below. There might be specific national legislation and guidance in place, which can be considered to complement these recommendations, or may take priority over these recommendations.

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

Certain study assessments, especially those related to safety, such as ECGs and blood monitoring (Section 8.2) can be exceptionally performed in institutions other than the study site. More specifically, these assessments can exceptionally be performed at different local laboratories or relevant clinical facilities authorized/certified (as legally required nationally) to routinely perform such tests, if this can be done within local rules on social distancing.

This decision will be at the Investigator's discretion, based on an assessment of potential risk of SARS-CoV-2 infection between a visit to the study site versus a visit to another institution.

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

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

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

The sites must inform the CRO and the Sponsor immediately about the implementation of any of the above adaptations or measures.

In case a participant becomes infected with SARS-CoV-2 during the treatment period, the Investigator must consider any study treatment modification in the best interest of the participant and in accordance with the protocol (Section 6.5.1.2;Table 7 and Table 8). This includes an evaluation of potential DDI if the use of concomitant medications is necessary to manage COVID-19 (Section 6.8). 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 eCRF.

Note: in case of study intervention discontinuation, it is 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 exceptional and justified cases and only if strictly necessary, rSDV can take place. For Germany specific: In case of rSDV implementation, 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

The above 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 measures will be captured in the Trial Master File for the study and will be described in the clinical study report.

These rules will not apply once the COVID-19 pandemic will be declared to have ended in the applicable country.

Appendix 11 Country-specific Requirements

Not applicable

Appendix 12 Protocol Amendment History

The information for the current amendment is on the title page.

Appendix 13 Sponsor Signature Page

Study Title:	A Single Arm, Open Label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants with Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy
Regulatory Agency Identifying Numbers:	IND:14330 EU trial number: 2023-505796-76-00
Clinical Study Protocol Version:	27 November 2023/Version 2.0

I approve the design of the clinical study:

PPD

Name, Academic Degree:	PPD
Function/Title:	
Institution:	Merck, Biopharma Co. Ltd.
Address:	Arco Tower 4F 1-8-1 Shimomeguro Meguro-ku Tokyo 153-8926, Japan
General Merck Phone Number:	PPD
General Merck Fax Number:	Not applicable

CCI

Appendix 14 Coordinating Investigator Signature Page

Study Title:	A Single Arm, Open label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants with Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy
Regulatory Agency Identifying Numbers:	IND:14330 EU trial number: 2023-505796-76-00
Clinical Study Protocol Version:	27 November 2023/Version 2.0
Site Number:	

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 laws.

PPD

Name, academic degree:	Nabil F. Saba MD, FACP
Function/Title:	Professor and Vice Chair, Hematology, and Medical Oncology The Lynne and Howard Halpern Chair in Head and Neck Cancer Research, Co-Director H&N CA Multidisciplinary Program
Institution:	Winship Cancer Institute, Emory University
Address:	1365-C. Clifton Road NE, Atlanta, GA 30322, USA
Telephone number:	PPD
Fax number:	
E-mail address:	

CCI [redacted]

Appendix 15 Principal Investigator Signature Page

Study Title:	A Single Arm, Open label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants with Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy
Regulatory Agency Identifying Numbers:	IND:14330 EU trial number: 2023-505796-76-00
Clinical Study Protocol Version:	27 November 2023/Version 2.0
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: