Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high-risk for relapse and are ineligible for high-dose cisplatin
Study Number:	MS202359_0002
Protocol Version:	18 October 2023/Version 6.0
Merck Compound:	MSC2735845 (Debio 1143)
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	3
Short Title:	Phase III xevinapant and radiotherapy in resected LA SCCHN, high-risk, cisplatin-ineligible participants
Acronym:	XRAY VISION
Coordinating Investigator:	PPD

Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	FDA Center for Drug Evaluation and Research, IND: 156735 EudraCT: 2022-001144-18
Keywords	Adjuvant RT, Stage III, Stage IVA, Stage IVB, oral cavity, oropharynx, larynx, hypopharynx, unfit

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
6.0	Global	18 October 2023
5.0	Global	25 July 2023
4.0	Global	10 May 2023
3.0	Global	17 August 2022
2.0	Global	28 April 2022
1.0	Original Protocol	23 March 2022

Protocol Version 6.0 (18 October 2023)

Overall Rationale for the Amendment

The main rationale for this protocol amendment is to add PPD adverse event of special interest.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 4	Added revised text "In case of premature treatment discontinuation, the FU7 visit should be performed according to original schedule. Imaging and clinical tumor assessments will also follow original schedule starting from Month 9."	For better clarity
5.1 Inclusion criteria	Updated Inclusion criteria #9 regarding cisplatin ineligibility criteria: For US participants with history of hearing impairment – added text to refer to Appendix 12	To align with country-specific criteria
6.5.1.2 Dose modification xevinapant/ 6.5.2.3 Treatment interruption	Addition that if IMRT is interrupted due to technical or logistical reasons, xevinapant/placebo dosing can continue	In case IMRT is interrupted for technical or logistical reasons, xevinapant/placebo treatment can continue.
8.3.7 AESI	Addition that changes to the AESI list will be included in the IB at the regular annual update	To simplify future management of changes to the AESI list.
PPD	[redacted]	[redacted]
Appendix 6 Study Governance	Added paragraph on applicable regulations to protect personal data	Added information to clarify follow-up if regulations to protect personal data are not followed
PPD	[redacted]	[redacted]
Appendix 12 Country-Specific Requirements	Updated 5.1 Inclusion Criteria #9 for US participants with tinnitus	As per US FDA feedback

CCI [redacted]

Table of Contents

Table of Contents 4
Table of Tables 8
Table of Figures 9
1 Protocol Summary 10
1.1 Synopsis 10
1.2 Schema 12
1.3 Schedule of Activities 15
2 Introduction 30
2.1 Study Rationale 30
2.2 Background 31
2.3 Benefit/Risk Assessment 33
2.3.1 Risk Assessment 34
2.3.2 Benefit Assessment 36
2.3.3 Overall Benefit: Risk Conclusion 37
3 Objectives and Estimands 37
4 Study Design 39
4.1 Overall Design 39
4.2 Scientific Rationale for Study Design 41
4.2.1 Participant Input into Design 44
4.3 Justification for Dose 44
4.4 End of Study Definition 47
5 Study Population 47
5.1 Inclusion Criteria 48
5.2 Exclusion Criteria 52
5.3 Lifestyle Considerations 55
5.3.1 Meals and Dietary Restrictions 55
5.4 Screen Failures 55
5.5 Criteria for Temporarily Delaying the Randomization/ Administration of Study Intervention Administration 56
6 Study Intervention(s) and Concomitant Therapies 56
6.1 Study Intervention(s) Administration 56

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability....58
6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding....59
6.3.1 Study Intervention Assignment....59
6.3.2 Blinding....59
6.3.3 Emergency Unblinding....60
6.4 Study Intervention Compliance....60
6.5 Dose Modification....61
6.5.1 Xevinapant or Placebo Dosing and Administration....61
6.5.1.1 Concurrent Administration to IMRT....61
6.5.1.2 Dose Modification, Interruption and Discontinuation of Xevinapant / Placebo Treatment....62
6.5.1.3 End of Xevinapant / Placebo Treatment....68
6.5.2 Radiotherapy....68
6.5.2.1 General Considerations....68
6.5.2.2 Treatment....68
6.5.2.3 Treatment Interruption....70
6.5.2.4 Management of Acute “Radiation In-Field” Toxicity....70
6.5.2.5 End of IMRT....71
6.6 Continued Access to Study Intervention After the End of the Study....71
6.7 Treatment of Overdose....71
6.8 Concomitant Therapy....71
6.8.1 Permitted Medicines....72
6.8.2 Medications to be Used with Caution with Xevinapant or Placebo....72
6.8.3 Prohibited Medicines....74
6.8.3.1 Recombinant Human Erythropoietin and Derivates....74
6.8.3.2 Food and Herbal Preparations....74
6.8.3.3 Inhibitors/Inducers of P-gp....75
6.8.3.4 CYP3A4/5 Narrow Therapeutic Index Drugs or Sensitive Substrates....75
6.8.4 Other Interventions....76
6.8.4.1 Nutritional Support....76

6.8.4.2 Dental Care 77
6.8.4.3 Pain 77
7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal 77
7.1 Discontinuation of Study Intervention 77
7.1.1 Temporary Discontinuation 78
7.2 Participant Discontinuation/Withdrawal from the Study 78
7.3 Lost to Follow-Up 79
8 Study Assessments and Procedures 80
8.1 Efficacy Assessments and Procedures 81
8.1.1 Radiological Assessment 82
8.1.2 Clinical Assessment 83
8.1.3 DFS Events and Definitions 83
8.1.4 Endpoint Assessment by IRC 84
8.1.5 Quality of Life 85
8.2 Safety Assessments and Procedures 89
8.2.1 Physical Examinations 89
8.2.2 Vital Signs 89
8.2.3 Electrocardiograms 90
8.2.4 Clinical Safety Laboratory Assessments 91
8.2.4.1 HPV Status in Participants with OPC 92
8.2.5 External Data Monitoring Committee 93
8.2.6 Patient Diary 93
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 95
8.3.1 Method of Detecting Adverse Events and Serious Adverse Events 95
8.3.2 Follow-up of Adverse Events and Serious Adverse Events 96
8.3.3 Regulatory Reporting Requirements for Serious Adverse Events 96
8.3.4 Pregnancy 97
8.3.5 Cardiovascular and Death Events 97
8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 98
8.3.7 Adverse Events of Special Interest 98

8.3.7.1 AESIs During the Treatment Period....98
8.3.7.2 Late Onset AESIs During the Follow-up Period (After FU28 Visit up to EOS Visit)....99
8.4 Pharmacokinetics....99
8.5 Pharmacogenomics....100
8.6 Biomarkers....100
8.7 Immunogenicity Assessments....101
8.8 Medical Resource Utilization and Health Economics....101
9 Statistical Considerations....102
9.1 Statistical Hypotheses....102
9.1.1 Primary Objective DFS....102
9.1.2 Secondary Objective OS....103
9.2 Sample Size Determination....103
9.3 Analyses Sets....106
9.4 Statistical Analyses....106
9.4.1 Efficacy Analyses....106
9.4.2 Safety Analyses....111
9.4.3 Other Analyses....112
9.4.4 Sequence of Analyses....112
10 References....115
11 Appendices....120
Appendix 1 Abbreviations....121
Appendix 2 Clinical Laboratory Tests....125
Appendix 3 Conduct of the Study during the COVID-19 Pandemic....127
Appendix 4 Contraception and Barrier Requirements....130
Appendix 5 G8 Questionnaire....132
Appendix 6 Study Governance....133
Appendix 7 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Applied to Adjuvant Studies of Squamous Cell Carcinoma of the Head and Neck....140
Appendix 8 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....144
Appendix 9 Recommended Dental/Oral Evaluations....151

CCI [redacted]

[redacted]

Appendix 12 Country-Specific Requirements....154
Appendix 13 Protocol Amendment History....157
Appendix 14 Sponsor Signature Page....165
Appendix 15 Coordinating Investigator Signature Page....166
Appendix 16 Principal Investigator Signature Page....167

Table of Tables

Table 1 Schedule of Activities: Screening and Combination Treatment Period....18
Table 2 Schedule of Activities: Monotherapy Period....22
Table 3 Treatment Diagram and Time Window for Visits....24
Table 4 Schedule of Activities: DFS Follow-up Visits....25
Table 5 Schedule of Activities: OS Follow-up Visits....28
Table 6 Schedule of Pharmacokinetic Activities....29
CCI [redacted]

[redacted]

Table 9 Dose Prescription....69
Table 10 Anesthetic and Analgesic Drugs to be Used with Xevinapant under Close Medical Monitoring....73
Table 11 Other Drugs to be Used with Xevinapant Under Close Medical Monitoring....73
Table 12 Examples of Prohibited Inhibitors and Inducers of P-gp with Xevinapant / Placebo....75
Table 13 Examples of Prohibited CYP3A4/5 Sensitive Substrates with Xevinapant....76
CCI [redacted]

Table 15 ECG Collection Plan....90
Table 16 Assessments to be Performed by a Central Laboratory or by a Local Laboratory According to Study Visit....92

CCI [redacted]

[redacted]

Table 19 Further Details on Statistical Analysis of Efficacy Estimands Beyond Estimands Attribute Specifications in Section 3 107

Table 20 Statistical Analysis Methods for Safety Endpoints 111

Table 21 Planned Efficacy Analyses and Expected Timing.....112

CCI [redacted]

Table of Figures

Figure 1 Study Diagram 13

Figure 2 Study Flow Chart.....14

Figure 3 Milestone Markers 41

CCI [redacted]

[redacted]

Figure 6 Fixed-Sequence Strategy to Control FWER at 2.5% 1-Sided, where the Arrows Indicate the Alpha Reallocation Applied if the Originating Test Rejects its Null Hypothesis Otherwise Confirmatory Testing is Discontinued.....113

1 Protocol Summary

1.1 Synopsis

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

Short Title: Phase III xevinapant and radiotherapy in resected LA SCCHN, high-risk, cisplatin-ineligible participants

Rationale: Xevinapant is an antagonist 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 unresectable LA SCCHN patients, the addition of xevinapant to standard of care chemoradiotherapy recently showed a statistically significant and clinically meaningful improvement in locoregional control at 18 months compared to placebo and standard of care alone (Sun 2020). Following the 36-month analysis, Overall Survival and Progression Free Survival also showed a clinically meaningful improved benefit from xevinapant versus placebo. The current Phase III study aims to support the approval of xevinapant in combination with radiotherapy for the treatment of high-risk participants with resected LA SCCHN who are ineligible to receive standard cisplatin-based chemoradiotherapy concurrently.

Objectives and Estimands:

Objectives	Estimands	Ref. #
Primary		
To demonstrate improvement in Disease-Free Survival (DFS) with xevinapant compared to placebo when added to RT irrespective of subsequent anticancer therapy	Endpoint: DFS defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled DFS assessments after last evaluable assessment or randomization): • Death from any cause • Objective Disease Recurrence:(earlier date of first imaging or biopsy collection confirming event at a DFS assessment): o Local or regional relapse which is subsequently confirmed by histopathology unless medically contraindicated or medical risk of biopsy deemed too high o Distant metastases. Confirmation of pathology is recommended in case of solitary metastasis (especially in the lung) after considering potential contraindication and/or medical risk associated with biopsy. Population: High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively Treatment: xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo Intercurrent Event Strategy: The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): o Discontinuation of treatment	1

	○ Start of subsequent anticancer therapy Population-Level Summary: Hazard Ratio	
Secondary		
To demonstrate improvement in OS with xevinapant compared to placebo when added to RT followed by subsequent anticancer therapy	Endpoint: OS defined as the time from date of randomization to death Treatment: xevinapant and RT followed by xevinapant followed by subsequent cancer therapy vs. placebo and RT followed by placebo followed by subsequent cancer therapy Population / Population-level Summary / Intercurrent Event Strategy: see Objectives and Estimands	2
To evaluate time to subsequent cancer treatments in participants treated with xevinapant compared to placebo when added to RT	Endpoint: Time to subsequent cancer treatments, defined as time from randomization to start of first subsequent cancer treatment Population / Treatment / Population-level Summary: see Objectives and Estimands Intercurrent Event Strategy The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Occurrence of DFS event	3
To evaluate the safety and tolerability of xevinapant compared to placebo when added to RT	Endpoints: Occurrence of AEs and treatment-related AEs	4
To evaluate tolerability of xevinapant compared to placebo when added to RT followed by xevinapant monotherapy in terms of patient-reported head and neck pain, swallowing, and speech as measured by the EORTC H&N35 sub scales, patient-reported fatigue, physical function, and global health status as measured by the EORTC QLQ C-30 sub scales and EQ-5D-5L VAS	Endpoints: Change from baseline at • end of combination therapy (Day 64) • end of investigational therapy (Day 134) on • EORTC QLQ-HN35 subscale scores (head and neck pain, swallowing, and speech), • EORTC QLQ-C30 subscale scores (fatigue, physical function and global health status), and • EQ-5D-5L VAS Intercurrent Event Strategy: • Permanent discontinuation of investigational therapy: all assessments up to the intercurrent event will be used (while on treatment strategy) • Death: while-alive strategy Population-Level Summary: Difference of least squared mean change from baseline	5

CRT=chemoradiotherapy, ctDNA=circulating tumor DNA, DFS=disease-free survival, EORTC=European Organization for Research and Treatment of Cancer, LA SCCHN=locally advanced squamous cell carcinoma of the head and neck, OS=overall survival, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity Scale, PRO CTCAE=Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, QOL=quality of life, RT=radiotherapy, VAS=visual analog scale.

Overall Design: This is a multicenter, randomized double-blind, placebo-controlled, 2-arm, parallel-group Phase III study.

Brief Summary: The purpose of this study is to demonstrate the superior efficacy of xevinapant vs placebo when added to radiotherapy in the treatment of high-risk participants with resected LA SCCHN who are ineligible to receive cisplatin-based chemoradiation concurrently.

Study details include:

- Study duration: Participants will be followed until the last on-study participant reaches his/her 60-month post-randomization visit, 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.
- Health measurement/observation: Improved Disease-Free Survival.
- Visit frequency: Weekly visit during combination therapy period, once every 3 weeks during monotherapy period, and every 3, 4, or 6 months during the Disease-Free Survival Follow-up period in Year 1, 2 and 3, or 4 and 5 (with telephone contact in between), respectively, and every 3 months (telephone visits allowed) during the Overall Survival Follow-up period.

Xevinapant is not available through an expanded access program.

Number of Participants: A total of approximately 700 participants will be randomly assigned to study intervention. It is anticipated to conduct the study in the US, Canada, Europe, Latin America, and Asia-Pacific.

Study Intervention Groups and Duration: Participants who meet the eligibility criteria will be enrolled and randomized in a 1:1 ratio, using permuted block allocation to Arm A or Arm B and will receive the following treatments:

- **Arm A**: 3 cycles of xevinapant (oral solution 200 mg/day from Day 1 to 14, per 3-week cycle) + IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of xevinapant (oral solution 200 mg/day from Day 1 to 14, per 3-week cycle)

OR

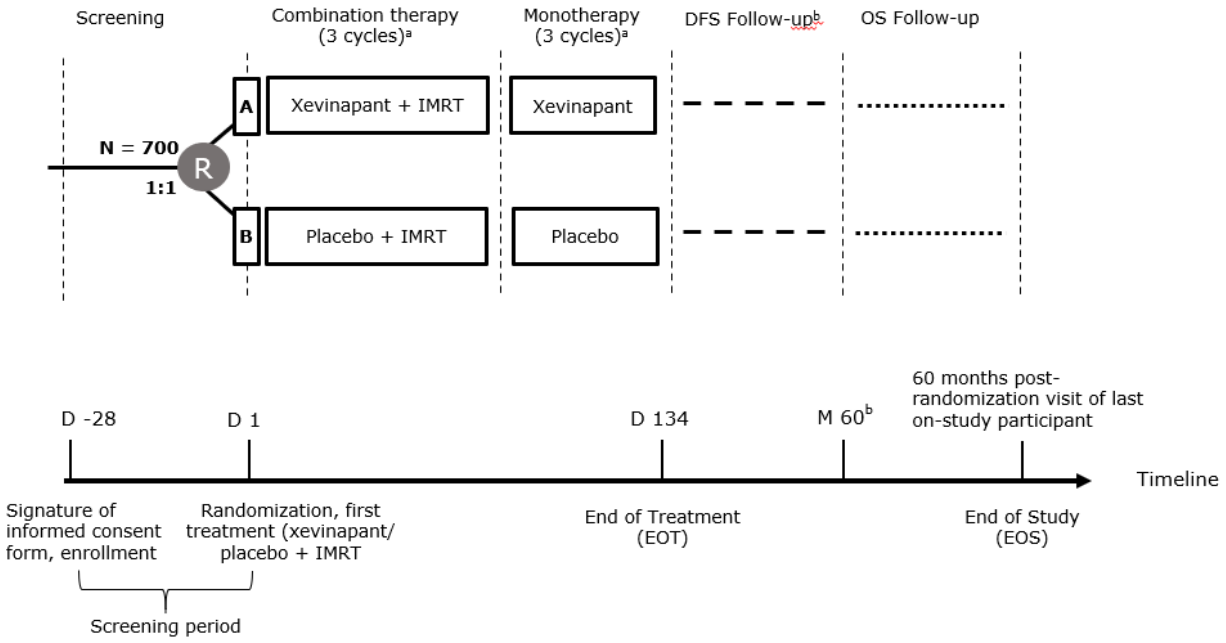
- **Arm B:** 3 cycles of placebo (matching oral solution from Day 1 to 14, per 3-week cycle) + IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of placebo (matching oral solution from Day 1 to 14, per 3-week cycle).

Involvement of Special Committee(s): Yes

1.2 Schema

The overall study design is summarized in Figure 1.

Figure 1 Study Diagram



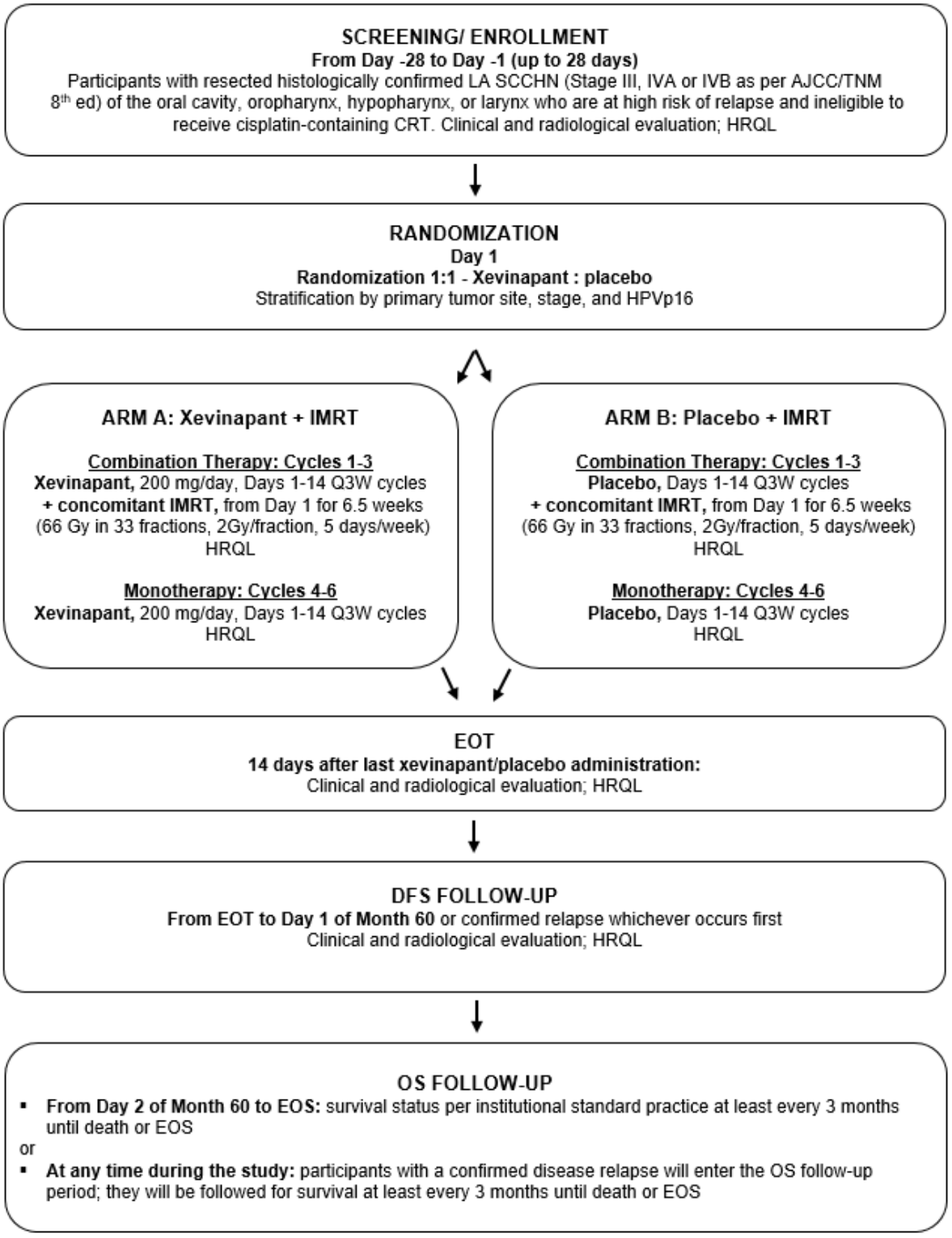
D = day, DFS = disease-free survival, IMRT = intensity modulated radiation therapy, M = Month, OS = overall survival, R = randomization

a Each cycle consists of 3 weeks.
b DFS Follow-up period starts after EOT visit and runs until Month 60 after randomization.

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, Table 4, and Table 5.

Figure 2 Study Flow Chart



CRT=chemoradiotherapy, EOS=end of study, EOT=end of treatment, DFS=disease-free survival, HPV=human papilloma virus, HRQL=health-related quality of life, IMRT=intensity modulated radiation therapy, LA SCCHN=locally advanced squamous cell carcinoma of the head and neck, OS=overall survival, Q3W=every 3 weeks.

1.3 Schedule of Activities

The schedule of the completion of the study visits/procedures is presented in Table 1, Table 2, Table 3, Table 4, and Table 5. 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 until randomization.

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 randomization. Dental examination, audiometry, if required, HIV test, and fiberoptic endoscopy, if appropriate, performed within 2 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 randomization will be used as baseline. For each participant, the same imaging modality must be used throughout the study. Further details on imaging are provided in Table 1, Table 2, Table 4, and Section 8.1.

In addition, the most recent pre-surgery diagnostic/staging CT and/or MRI scans done as a part of SoC should be submitted to the IRC vendor, if available, as well as any recent pre-surgery or baseline PET-CT scan if acquired, to facilitate IRC assessment of any potential macroscopic residual disease at baseline. If biopsy has been performed during screening to exclude presence of residual disease, upon IRC request biopsy reports may be presented to the IRC.

During Screening, results from a central laboratory, including a pregnancy test, should be used to define participant eligibility. The following tests may be obtained locally: HIV test within 2 weeks before ICF signature, HPV status by p16 IHC (Section 8.2.4.1), SARS-CoV-2 PCR and/or antigen test if required, and retest of laboratory abnormalities during the Screening period (Section 8.2.4).

After randomization, laboratory assessments should be performed by a central laboratory designated by the Sponsor, except for the safety laboratory assessments to confirm eligibility for treatment on CxD1 and pregnancy tests, which may be obtained locally, and except for the urinalysis dipstick tests on CxD1, which will be done locally (Section 8.2.4).

A participant will be considered as eligible to receive the study interventions after he/she has signed the ICF, and all eligibility criteria have been met. Randomization can be performed once the participant is eligible, and C1D1 should be within 3 days after randomization. Study intervention administration starts after randomization, with combination treatment on C1D1. The IMRT plan must be approved by the RT-QA Review Center prior to the start of the IMRT.

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 Table 3.

The EOT visit will be performed 14 days (± 7 days) after last study intervention administration (i.e. xevinapant/placebo, 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.

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 DFS follow-up period will start after the EOT visit. The DFS follow-up period must be performed according to the planned visit schedule within the permitted visit windows. Day 1 of study month corresponds to the calendar day of C1D1. In case of premature discontinuation of study intervention (e.g. unacceptable toxicity), efficacy assessments will continue according to original schedule until confirmed disease relapse (Section 8), regardless of start of subsequent anticancer treatment. Participants with confirmed disease relapse will enter the OS follow-up period at time of the confirmation of the event and will be followed up for survival status at least every 3 months, until the EOS (Section 4.4). Survival follow-up can be performed by telephone calls, unless the participant has entered the OS follow-up period earlier than 28 months after start of treatment (e.g. due to PD). In this case, clinic visits are required up to 28 months after start of treatment or until start of next line of anticancer therapy, whichever occurs earlier.

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

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

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

The EOS visit can be performed by telephone call.

The following schedules of activities and assessments are presented:

Table 1: Screening and Combination Treatment Period

Table 2: Monotherapy Period

Table 3: Treatment Diagram and Time Windows for Visits

Table 4: DFS Follow-up Visits

Table 5: OS Follow-up Visits

Table 6: Schedule of Pharmacokinetic Activities

Table 1 Schedule of Activities: Screening and Combination Treatment Period

Study Period	Screening	Combination Therapy Period (Xevinapant / Placebo + IMRT)											Notes
Cycle		1				2				3			
Visit Label	Screening	C1D1	C1D2	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D8	C3D15	
Study Week	-4 to -1	1		2	3	4		5	6	7	8	9	
Study Visit Day	-28 to -1	1	2	8	15	22	23	29	36	43	50	57	From C1D1
Visit Window (Days)	-	- 3d				± 3d				± 3d			C1D1 is triggered by 1st xevinapant/placebo dose
Informed consent	X												
Medical history	X												Including disease history, tumor staging, and SCCHN surgery details. See Section 8.1.
Demographics, height	X												Including G8 questionnaire, if applicable.
Audiometry	X												If required, see Section 5.1.
Archival FFPE tumor sample	X												See Section 8.6
HBV, HCV, HIV test	X												See Section 8.2.4, if applicable.
SARS-CoV 2 test	X												See section 8.2.4, if applicable.
Eligibility	X												
Randomization		X											
Physical examination, weight	X	X				X				X			Complete examination at Screening and EOT.
ECOG PS	X	X				X				X			
Vital signs	X	X	X			X				X			
ECG	X	X		X									See Section 8.2.3 for timepoints.

Study Period	Screening	Combination Therapy Period (Xevinapant / Placebo + IMRT)											Notes
Cycle		1				2				3			
Visit Label	Screening	C1D1	C1D2	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D8	C3D15	
Study Week	-4 to -1	1		2	3	4		5	6	7	8	9	
Study Visit Day	-28 to -1	1	2	8	15	22	23	29	36	43	50	57	From C1D1
Visit Window (Days)	-	- 3d				± 3d				± 3d			C1D1 is triggered by 1st xevinapant/placebo dose
Laboratory Assessments													
Blood Hematology	X	X		X		X		X		X	X		On CxD1 also local tests to confirm eligibility for treatment. See Section 8.2.4.
Blood biochemistry (full)	X	X				X				X			See above and Section 8.2.4. and Appendix 2.
Blood biochemistry (minimum)				X				X			X		See Section 8.2.4 and Appendix 2.
Coagulation	X												
Pregnancy test	X	X				X				X			hCG serum at Screening and thereafter from urine for WOCBP (Section 8.3.4). C1D1 test done within 24 h prior to first dosing (Section 5.1).
Urinalysis	X	X				X				X			See Appendix 2.
HRQOL Assessments													
EQ-5D-5L		X				X				X			
EORTC QLQ-C30, EORTC QLQ-HN35, PGIS		X											
EORTC QLQ-C30 (short), EORTC QLQ-HN35 (short), PGIS						X							See Section 8.1.5.
Patient perception of side effects (Item Library Q168), PRO CTCAE		X		X	X	X		X	X	X	X	X	See Section 8.1.5.

Study Period	Screening	Combination Therapy Period (Xevinapant / Placebo + IMRT)											Notes
Cycle		1				2				3			
Visit Label	Screening	C1D1	C1D2	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D8	C3D15	
Study Week	-4 to -1	1		2	3	4		5	6	7	8	9	
Study Visit Day	-28 to -1	1	2	8	15	22	23	29	36	43	50	57	From C1D1
Visit Window (Days)	-	- 3d				± 3d				± 3d			C1D1 is triggered by 1st xevinapant/placebo dose
Disease Assessments													
HPV status (p16)	X												Mandatory for OPC, optional for other tumor locations; could be analyzed before surgery.
Nutritional status	X					X				X			
Dental examination	X												No repeat if done within 2 wks before ICF signature.
CT or MRI + CT-chest	X												IV contrast-enhanced CT or MRI head and neck AND CT of chest.
Clinical assessment for tumor	X												See Section 8.1.
DFS / OS data collection		X	X	X	X	X	X	X	X	X	X	X	
		All participants will be followed for DFS and OS until death, end of study or withdrawal of consent, whichever comes first. For participants refusing to come to site, a telephone follow-up call is acceptable (only for OS assessment).											
Treatments													
Xevinapant/ placebo		From Day 1 to 14				From Day 1 to 14				From Day 1 to 14			
Patient diary dispensation		X											
IMRT		5 fractions/wk for 6.5 wks											
Other Clinical Assessments													
Concomitant therapy	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	
HRU assessment						X				X			

Study Period	Screening	Combination Therapy Period (Xevinapant / Placebo + IMRT)											Notes
Cycle		1				2				3			
Visit Label	Screening	C1D1	C1D2	C1D8	C1D15	C2D1	C2D2	C2D8	C2D15	C3D1	C3D8	C3D15	
Study Week	-4 to -1	1		2	3	4		5	6	7	8	9	
Study Visit Day	-28 to -1	1	2	8	15	22	23	29	36	43	50	57	From C1D1
Visit Window (Days)	-	- 3d				± 3d				± 3d			C1D1 is triggered by 1st xevinapant/placebo dose
Ancillary Studies													
Blood for xevinapant PK		X	X	X			X	X			X		See Table 6 for timepoints.
CCI													

CxDx=Cycle x Day x, CT=computed tomography CCI DFS=disease-free survival, ECG= electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, EOT=end of treatment, FFPE=formalin-fixed paraffin-embedded, HBV=hepatitis B virus, ICF= informed consent form, hCG=human chorionic gonadotrophin, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HRU= health resource utilization, IMRT=intensity modulated radiation therapy, MRI=magnetic resonance imaging, OPC=oropharynx, OS=overall survival, PGIS=Patient Global Impression of Severity Scale, SARS-CoV 2 =Severe acute respiratory syndrome coronavirus 2; wks=weeks.

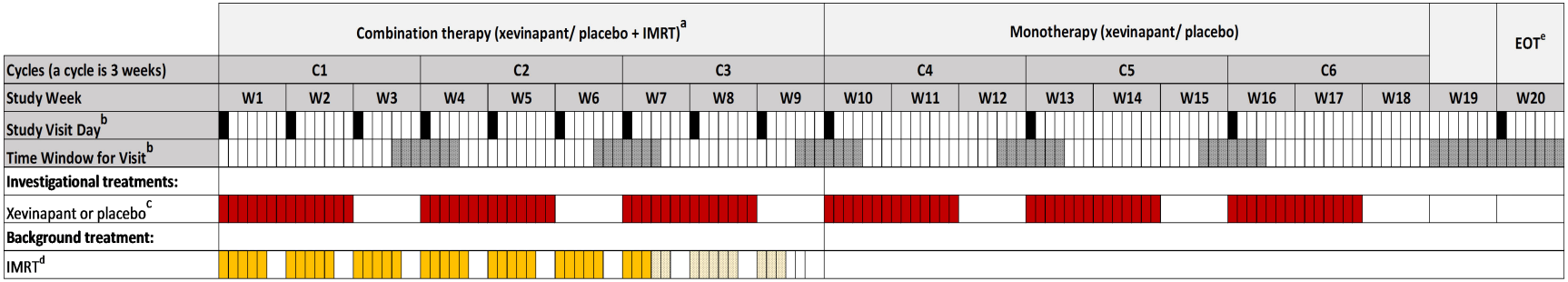
Table 2 Schedule of Activities: Monotherapy Period

Study Period	Monotherapy Period (Xevinapant / Placebo)			EOT Visit	Notes
Cycle	**4**	**5**	**6**		EOT visit will be performed 14 d (± 7 d) after last study intervention administration (xevinapant/placebo), or IMRT whichever is administered 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)
Visit Label	**C4D1**	**C5D1**	**C6D1**	**EOT**	
Study Week	**10**	**13**	**16**	**20**	
Study Visit Day	64	85	106	134	
Visit Window (days)	± 3d	± 3d	± 3d	± 7d	
Physical examination	X	X	X	X	Complete examination at EOT.
ECOG PS	X	X	X	X	
Vital signs, weight	X	X	X	X	
Laboratory Assessments					
Blood hematology	X	X	X	X	On CxD1 also local tests to confirm eligibility for treatment. See Section 8.2.4.
Blood biochemistry (full)	X	X	X	X	See above, Section 8.2.4 and Appendix 2.
Pregnancy test	X	X	X	X	
Urinalysis	X			X	
HRQOL Assessments					
EQ-5D-5L	X	X	X	X	
EORTC QLQ-C30, EORTC QLQ-HN35, PGIS	X			X	
EORTC QLQ-C30 (short), EORTC QLQ-HN35 (short), PGIS			X		See Section 8.1.5
Patient perception of side effects (Item Library Q168), PRO CTCAE	X	X	X	X	Assessed weekly on D1, D8 and D15 in Cycle 4, 5, and 6 (Table 14).
Disease Assessments					
Nutritional status	X			X	
Dental examination				X	
^{18}F-FDG-PET				X	
CT or MRI + CT-chest				X	See Section 8.1.
Clinical tumor assessment.				X	See Section 8.1.
DFS / OS data collection	X	X	X	X	See Table 1.
Treatments					
Xevinapant / placebo	From Day 1 to 14	From Day 1 to 14	From Day 1 to 14		

Study Period	Monotherapy Period (Xevinapant / Placebo)			EOT Visit	Notes
Cycle	**4**	**5**	**6**		EOT visit will be performed 14 d (± 7 d) after last study intervention administration (xevinapant/placebo), or IMRT whichever is administered 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)
Visit Label	**C4D1**	**C5D1**	**C6D1**	**EOT**	
Study Week	**10**	**13**	**16**	**20**	
Study Visit Day	64	85	106	134	
Visit Window (days)	± 3d	± 3d	± 3d	± 7d	
Other Clinical Assessments					
Concomitant therapy	X	X	X	X	
Antineoplastic therapy				X	
Adverse events	X	X	X	X	
HRU assessment	X	X	X	X	
Ancillary Studies					
Blood for xevinapant PK	X	X	X		See Table 6 for timepoints.
CCI					

AESI=adverse events of special interest, CT=computed tomography, CTCAE=Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, CCI CxDx=Cycle x Day x, d=day, DS=disease-free survival, ECG=electrocardiogram, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, EOT=end of treatment, ^{18}F-FDG-PET=2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography, HRU=health resource utilization, IMRT=intensity modulated radiation therapy, OS=overall survival, MRI=magnetic resonance imaging, PGIS=Patient Global Impression of Severity Scale, PRO= patient-reported outcomes, wks=weeks.

Table 3 Treatment Diagram and Time Window for Visits



C=cycle, EOT=end of treatment, IMRT=intensity modulated radiation therapy, W=week.

a On days when IMRT is to be administered, xevinapant / placebo 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 is triggered by the 1st dose administration of xevinapant / placebo. 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 and Table 2).

c Xevinapant / placebo (Section 6.5.1): once daily from D1 to D14 of each cycle (solid red boxes). Xevinapant / placebo should be administered orally, in the morning, preferable 1 to 4 hours before IMRT.

d IMRT should be delivered in 33 fractions over 6.5 weeks, 5 fractions weekly (solid yellow boxes). If IMRT is put on hold due to safety or administrative reason, the 6.5 weeks of IMRT can be administered until Study Week 9 (striped yellow boxes) (Section 6.5.2).

e The EOT visit will be performed 14 days (± 7 days) after last study treatment administration (i.e. xevinapant / placebo, 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: DFS Follow-up Visits

Study Period	Disease-Free Survival Follow-up													Notes
Study Timing	Year 1			Year 2			Year 3			Year 4		Year 5		
Visit Label	FU7	FU9	FU12	FU16	FU20	FU24	FU28	FU32	FU36	FU42	FU48	FU54	FU60	
Study Month	7	9	12	16	20	24	28	32	36	42	48	54	60	
	In case of premature treatment discontinuation, the FU7 visit should be performed according to original schedule. Imaging and clinical tumor assessments will also follow original schedule starting from Month 9.													
Study Visit Day	Day 1 of Study Month ± 2 weeks													
Physical examination, weight	X													
ECOG PS	X		X											
Vital signs	X		X											
Laboratory Assessments														
Blood hematology	X		X											
Blood biochemistry (full)	X		X											
CCI														
HRQOL Assessments														
EQ-5D-5L			X			X			X		X		X	
EORTC QLQ-C30, EORTC QLQ-HN35, PGIS			X			X			X		X		X	Completed within 7 days of DFS event or Month 60 FU visit.
EORTC QLQ-C30 (short), EORTC QLQ-HN35 (short), PGIS		X												See Section 8.1.5.
PGIC			X											
Disease Assessments														
Nutritional status	X		X											
CT or MRI + CT-chest		X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.1.
Clinical tumor assessment		X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.1.

Study Period	Disease-Free Survival Follow-up													Notes
Study Timing	Year 1			Year 2			Year 3			Year 4		Year 5		
Visit Label	FU7	FU9	FU12	FU16	FU20	FU24	FU28	FU32	FU36	FU42	FU48	FU54	FU60	
Study Month	7	9	12	16	20	24	28	32	36	42	48	54	60	
	In case of premature treatment discontinuation, the FU7 visit should be performed according to original schedule. Imaging and clinical tumor assessments will also follow original schedule starting from Month 9.													
Study Visit Day	Day 1 of Study Month ± 2 weeks													
DFS data collection	X	X	X	X	X	X	X	X	X	X	X	X	X	See Table 1.
Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants will be contacted by telephone in Month 39, 45, 51, and 57 (±2 weeks) for survival status.
Other Clinical Assessments														
Concomitant therapy	X	X	X	X	X	X	X							Until FU28 visit or start of next line anticancer therapy, whichever occurs earlier.
Adverse events	X	X	X	X	X	X	X							Until FU28 visit or start of next line anticancer therapy, whichever occurs earlier, including myelodysplastic syndrome, acute myeloid leukemia, or any second malignancy.
New antineoplastic therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy used at occurrence of late onset AESIs and related SAEs								X	X	X	X	X	X	Collect immediately after FU28 visit (Section 6.8). See Section 8.3.7.2 for late onset AESIs.

Study Period	Disease-Free Survival Follow-up													Notes
Study Timing	Year 1			Year 2			Year 3			Year 4		Year 5		
Visit Label	FU7	FU9	FU12	FU16	FU20	FU24	FU28	FU32	FU36	FU42	FU48	FU54	FU60	
Study Month	7	9	12	16	20	24	28	32	36	42	48	54	60	
	In case of premature treatment discontinuation, the FU7 visit should be performed according to original schedule. Imaging and clinical tumor assessments will also follow original schedule starting from Month 9.													
Study Visit Day	Day 1 of Study Month ± 2 weeks													
Late onset AESIs up to EOS and related SAEs								X	X	X	X	X	X	Collect immediately after FU28 visit up to EOS (Table 5). See Section 8.3.7.2 for late onset AESIs.
HRU assessment			X			X			X		X		X	

AESI=adverse events of special interest, CT=computed tomography, CCI [redacted] DFS=disease-free survival, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, EOS=end of study, EOT=end of treatment, FU=follow-up, HRU=health resource utilization, MRI= magnetic resonance imaging, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity Scale, SAE=serious adverse event.

Table 5 Schedule of Activities: OS Follow-up Visits

Study Period	OS Follow-up		Notes
Study Timing	**FUx**	**EOS**	Survival follow-up can be performed by telephone calls
Visit Label	**(where x is number of months post-randomization: at least every 3 months ± 2 weeks)**	**(date of Month 60 visit of last on-study participant) ± 2 months or premature study discontinuation**	
EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-HN35, and PGIS		X	HRQOLs completed within 7 days of DFS event or Month 60 FU visit, as appropriate.
Survival status	X	X	Participants will be contacted shortly before the data cut-off for the primary analysis to provide complete survival data.
Subsequent antineoplastic therapies	X	X	
Concomitant therapy used for late onset AESIs and related SAEs	X	X	See Section 6.8. For AESIs see Section 8.3.7.
Late onset AESIs up to EOS and related SAEs	X	X	See Section 8.3.7.2. For participants who enter the OS FU earlier than 28 months after start of treatment (e.g. due to PD), AEs should also be collected up to 28 months after start of treatment or until start of next line of anticancer therapy, whichever occurs earlier.

AESI=adverse events of special interest, DFS= disease-free survival, EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire, EOS=end of study, FU=follow-up, FUP=follow-up period, HRQOL=health-related quality of life, OS=overall survival, PD=progressive disease, PGIS=Patient Global Impression of Severity Scale, SAE=serious adverse event.

Table 6 Schedule of Pharmacokinetic Activities

Treatment Day	Timepoint of Xevinapant PK Sampling	Notes
C1D1	0.5-4 h postdose xevinapant/placebo [b]	On C1D1, C1D2, C1D8, C2D2, C2D8, participants must be at the clinical unit before xevinapant/placebo is administered to ensure PK blood sample collection as per Schedule of Activities. The time of dose on those days and time of the draw for PK assessment must be reported in the eCRF. In addition, time of last dose prior to xevinapant PK collection (i.e. at C1D7, C2D1, C2D7) needs to be recorded in the participant's diary and reported in the eCRF.
C1D2	Predose xevinapant/placebo	
C1D8	Predose xevinapant/placebo [b] and 0.5-4 h postdose xevinapant/placebo [b]	
C2D2	Predose xevinapant/placebo	
C2D8	Predose xevinapant/placebo and 0.5-4 h postdose xevinapant/placebo	
C3D8[a]	At time of blood hematology/ biochemistry laboratory assessments	On C3D8, xevinapant/ placebo dose is encouraged to be taken at home and the time of the last dose prior to PK sample on that day is recorded by participant in the diary and reported in the eCRF. The time of the draw for PK assessment must be reported in the eCRF
C4D1	2-4 h postdose xevinapant/placebo	On C4D1, C5D1, and C6D1 Dose is taken at the hospital. The time of the oral dose and draw for PK assessment must be reported in the eCRF.
C5D1	2-4 h postdose xevinapant/placebo	
C6D1	2-4 h postdose xevinapant/placebo	

CxDx=Cycle x Day x, eCRF=electronic case report form, PK=pharmacokinetics.

Predose sample is taken within 1 hour prior to dosing

a Participants are encouraged to take xevinapant / placebo at home prior to hospital visit at C3D8.

b PK samples at C1D1 (post dose) C1D8 (predose and postdose) are taken after the ECG assessment at the corresponding time point (see Table 15, Section 8.2.3).

2 Introduction

Xevinapant is a novel, orally available antagonist 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 (2015). The value of adding xevinapant to conventional cisplatin-based chemoradiotherapy in the treatment of previously untreated patients with unresected LA SCCHN was recently confirmed in a Phase II study (Sun 2020).

This study aims to confirm the value of adding xevinapant to the treatment of resected locally advanced SCCHN patients with a high-risk of relapse who are ineligible to receive cisplatin-based chemoradiotherapy and who are often treated with radiotherapy.

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

2.1 Study Rationale

The purpose of this study is to demonstrate the superior efficacy of xevinapant vs placebo when added to radiotherapy in the treatment of participants with resected LA SCCHN who are at high-risk for relapse and are ineligible to receive cisplatin-based CRT.

SCCHN is the 7th most common cancer worldwide with an annual incidence of approximately 700,000 and a mortality estimated at 350,000 in 2018 (Bray 2018). The majority of SCCHN patients are diagnosed with locoregional disease, in which RT concurrent with high-dose cisplatin was identified as most effective and thus preferred treatment of choice (NCCN v3 2021). Concomitant chemoradiotherapy has also been established as a SoC for resected patients with a high-risk (due to extra-capsular extension and/or positive margin) of relapse after surgery (Bernier 2004, Cooper 2004, NCCN v3 2021, Machiels 2020). However, a large proportion of these patients are not suitable for standard of care treatment with high-dose cisplatin-based CT concomitant to RT, either due to their age or to their medical/general condition and/or comorbidities (Harari 2014). So, improving the outcome of these patients defines an important unmet clinical need.

Xevinapant is an antagonist 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 unresectable 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 and SoC alone (Sun 2020). Following the 36-month analysis, OS and PFS also showed a clinically meaningful improved benefit from xevinapant versus placebo. In the current study concept, the addition of xevinapant to the SoC regimen of radiotherapy is anticipated to further sensitize SCCHN tumors to the effects of radiotherapy.

The current Phase III study aims to support the approval of xevinapant in combination with radiotherapy for the treatment of high-risk participants with resected LA SCCHN who are ineligible to receive standard cisplatin-based chemoradiation concurrently.

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 cancers are the 7th most common cancer worldwide with an annual incidence of approximately 700,000 and a mortality estimated at 350,000 in 2018 (Bray 2018). In the US alone, 50,000 new cases and 10,000 deaths are reported annually, while in Europe, 140,000 new cases are reported annually (Iglesias Docampo 2018). A vast majority of these cancers (90% to 95%) are SCCHN which are closely associated with alcohol and tobacco use. SCCHN of the oropharynx is also associated with HPV, essentially type 16 infection. Approximately two-third of patients are diagnosed as LA SCCHN (Denaro 2016).

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.

For resected patients with a high-risk of relapse after surgery, due to extra-capsular extension and/or positive margin, adjuvant concomitant chemoradiotherapy (CT-RT) of 66 Gy / 6.5 weeks with concomitant 100 mg/m² cisplatin x 3 cycles has been established as a standard of care (SoC) (Bernier 2004, Cooper 2004, NCCN v3 2021, Machiels 2020).

However, cisplatin is associated with both acute and late, often irreversible toxicities, which are manifested as detrimental short- and long-term complications for patients and result in low treatment adherence and nonoptimal treatment for many patients (Porceddu 2020). In addition, a large proportion of these high-risk patients are not suitable or unfit for receiving cisplatin, due to age and comorbidities but also due to slow recovery and/or complications after surgery (Harari 2014).

Treatment guidelines across Europe and the USA recommend RT as an alternative approach for resected LA SCCHN in patients ineligible to receive cisplatin (NCCN v3 2021, Machiels 2020). The failure rate of RT alone is high and higher than in the corresponding resected high-risk LA SCCHN patients who are able to receive cisplatin (Bernier 2004, Cooper 2004). Improving the outcome of these cisplatin-unfit patients defines an important unmet clinical need to find more efficient and better tolerated therapies.

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 antagonist 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. The synergistic effect of xevinapant combined with RT in vivo was able to cure tumors in 8 of 10 xenografted mice without any apparent toxicity whereas all mice died with RT alone (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 I/II study (Debio 1143-201) and its findings are currently being confirmed in a Phase III study (Debio 1143-301 [TrilynX], MS202350_006). 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. A significant improvement was confirmed at 3 years and xevinapant was found superior to placebo for LRC, PFS, and OS (Bourhis 2020). Overall, the safety profile of xevinapant, when added to high-dose cisplatin and concurrent RT (CRT), was predictable and manageable, and did not jeopardize the delivery of high-dose cisplatin concurrent with standard fractionation RT.

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

This Phase III study aims to confirm the value of xevinapant in the treatment of resected LA SCCHN participants who are ineligible to receive standard cisplatin-based CRT without compromising their health-related quality of life. The nonclinical activity of xevinapant in combination with RT in SCCHN models and the primary analysis results of the Debio 1143-201 study, justifies the clinical investigation of xevinapant in resected SCCHN patients, ineligible to receive high-dose cisplatin when added to SoC of RT.

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

2.3 Benefit/Risk Assessment

As of 31 July 2021, a total of 486 participants with a malignancy have been included and exposed to study treatment (including placebo or CT alone) in studies with xevinapant, of which 105 had received at least 1 blinded dose of xevinapant (200 mg/day, D1 to 14, every 3 weeks) / placebo in combination with CRT and 314 have received at least 1 dose of xevinapant. Of these, 64 participants had received xevinapant as single agent, 150 received xevinapant in combination with CT or CRT, and 100 in combination with immunotherapy. 60 participants received placebo in combination with CT or CRT. 7 patients were included in the cisplatin only arm of Study Debio 1143-SCCHN-202 and were not exposed to xevinapant.

Among the 314 participants with malignancies who had been exposed to xevinapant in scope of the Phase I and II CCI [redacted]

Based on the safety data of the Phase I and Phase II studies, xevinapant doses of up to CCI mg/day were safely combined with either CT or CRT. When used in combination with CT or concomitant CRT, xevinapant appears to be equally well tolerated as CT or CRT alone with respect to Grade ≥ 3 events and TEAEs leading to discontinuation of any of the study treatments and is not associated with an increased frequency of drug-related treatment discontinuation. Data from the placebo-controlled Study Debio 1143-201, where xevinapant or placebo were administered in association with cisplatin and RT, showed an increased risk of mucosal inflammation, dysphagia, weight decrease, radiation skin injury, nausea, tinnitus, vomiting and ALT increase in the xevinapant arm. Dysphagia, mucositis, and anemia were the most common TEAEs, and more frequently manifested as any grade and Grade 3 in the xevinapant group than in the placebo group. Except for Grade 1/2 tinnitus and anemia, treatment with xevinapant was not associated with an increase in other cisplatin-related AEs, such as renal insufficiency, febrile neutropenia, thrombocytopenia, peripheral sensory neuropathy, or severe vomiting.

RT can cause dermatitis, dry skin, dry mouth, mucositis, alopecia, muscle and joint stiffness, diarrhea, dysphagia, anorexia, and fatigue.

When combining xevinapant with RT, overlapping toxicities are anticipated. CCI [redacted] Further, blood count and biochemistry must be regularly investigated for changes and weight must be controlled. Appropriate measures such as monitoring, dose modification schemes and adequate eligibility criteria have been implemented in the protocol (Section 2.3.1) and the anticipated risks are considered manageable.

In summary, based on current available efficacy and safety data available for xevinapant treatment, including the combination with CRT and/or immunotherapy, and for RT alone, the benefit/risk assessment for a study combining xevinapant with RT is expected to be positive.

For additional considerations regarding the benefit/risk assessment during the COVID-19 pandemic, refer to Appendix 3.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of xevinapant may be found in Section 4.2 and the IB.

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


CCI

Eligibility criteria will address the potential risks of QT prolongation and reactivation of latent HIV infection or impaired clearance of HBV/HCV chronic infections. Recommendations for the use of medications that prolong the QT interval is provided. Caution should be exercised when using xevinapant with drugs having a known risk of QTc prolongation. Xevinapant / placebo should be permanently discontinued in case of torsade de pointe or signs / symptoms of serious arrhythmia (Section 6.5.1.2 and 6.8.2).

Despite the chemo-radiosensitizing effect of xevinapant it was shown in the Phase II Study Debio 1143-201 (combining xevinapant and CRT) that TEAEs usually associated with CRT (e.g radiation injury, mucositis, dysphagia, anemia) were manageable with dose modifications and supportive care and did not compromise the delivery of anticancer treatment given with curative intent.

Pregnant and lactating women will be excluded, and WOCBP will have to use highly effective contraception (Appendix 4).

In conclusion, the toxicities of xevinapant in combination with RT are deemed to be predictable and manageable. Participants will be monitored for signs and symptoms and managed accordingly in line with current practices/guideline and specific recommendations made in this protocol. Adequate hematologic/liver function should be confirmed prior to initiation of treatment. Laboratory values and clinical signs or symptoms of toxicities should be closely monitored to allow for early identification and intervention.

2.3.2 Benefit Assessment

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

Xevinapant administered in combination with cisplatin-based CRT in participants with LA SCCHN (Study Debio 1143-201) reached the primary objective for LRC at 18 months and showed clinically and statistically meaningful differences in terms of LRC and PFS, as well as a trend toward improved OS. The 24-month analysis of Study Debio 1143-201 demonstrated that the odds for LRC at 18 months after completing treatment is 2.5 times higher in participants treated with xevinapant compared with participants having received a placebo (odds ratio 2.74; 95% CI: 1.15;6.53, p=0.0232). In addition, a risk reduction of 63% for progression or death was observed in participants treated with xevinapant compared with participants having received a placebo, suggesting a clinically significant improvement in PFS (hazard ratio 0.37; 95% CI: 0.18;0.76; p=0.007). The PFS rate at 24 months after treatment start was 72% in the xevinapant arm and 41% in the placebo arm. Median PFS was not reached in the xevinapant arm at the 24-month analysis cut-off. Results for OS showed the same trend in favor of the xevinapant arm (hazard ratio 0.65; 95% CI: 0.32;1.33). At the 3-year follow-up, this trend was more pronounced. The probability of

PFS at 3 years (Kaplan-Meier estimate) 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 arm compared to the placebo arm (HR=0.33 [95%CI: 0.17-0.67], p=0.0019). Additional follow-up is ongoing and will provide more mature data (refer to the IB for further details).

Nonclinical data suggest that xevinapant acts as a radiosensitizer independent of cisplatin: xevinapant was found to be highly effective in enhancing cell death induced by radiation in 2 SCCHN xenograft models in mice (Matzinger 2015). The addition of xevinapant to standard fractionation RT is therefore expected to provide added benefit to participants over that of RT alone, being the current SoC in the resected SCCHN cisplatin-ineligible patient population.

2.3.3 Overall Benefit: Risk Conclusion

Overall, the toxicities of a study with xevinapant in combination with 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 resected LA SCCHN who are at high-risk for relapse and are ineligible to receive high-dose cisplatin.

3 Objectives and Estimands

Objectives	Estimands	Ref. #
Primary		

To demonstrate improvement in Disease-Free Survival (DFS) with xevinapant compared to placebo when added to RT irrespective of subsequent anticancer therapy.	Endpoint: DFS defined as the time from randomization to the first occurrence of any of the following events (occurring within 2 scheduled DFS assessments after last evaluable assessment or randomization):
	• Death from any cause
	• Objective Disease Recurrence (earlier date of first imaging or biopsy collection confirming event at a DFS assessment):
	  ○ Local or regional relapse which is subsequently confirmed by histopathology unless medically contraindicated or medical risk of biopsy deemed too high
	  ○ Distant metastases. Confirmation of pathology is recommended in case of solitary metastasis (especially in the lung) after considering potential contraindication and/or medical risk associated with biopsy.
	Population: High-risk patients with Stage III, IVA or IVB resected LA SCCHN ineligible to receive high-dose cisplatin-based CRT postoperatively
	Treatment: xevinapant and RT followed by xevinapant vs. placebo and RT followed by placebo
	Intercurrent Event Strategy:
	The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy):
	  ○ Discontinuation of treatment
	  ○ Start of subsequent anticancer therapy
	Population-Level Summary: Hazard Ratio
		1

Objectives	Estimands	Ref. #
Secondary		
To demonstrate improvement in OS with xevinapant compared to placebo when added to RT followed by subsequent anticancer therapy.	Endpoint: OS defined as the time from date of randomization to death Treatment: xevinapant and RT followed by xevinapant followed by subsequent cancer therapy vs. placebo and RT followed by placebo followed by subsequent cancer therapy Population / Population-level Summary / Intercurrent Event Strategy: see Ref. #1	2
To evaluate time to subsequent cancer treatments in participants treated with xevinapant compared to placebo when added to RT.	Endpoint: Time to subsequent cancer treatments, defined as time from randomization to start of first subsequent cancer treatment Population / Treatment / Population-level Summary: see Ref. #1 Intercurrent Event Strategy The endpoint will be analyzed regardless of whether the following intercurrent events had occurred (treatment-policy strategy): • Treatment discontinuation • Occurrence of DFS event	3
To evaluate the safety and tolerability of xevinapant compared to placebo when added to RT.	Endpoints: Occurrence of AEs and treatment-related AEs	4
To evaluate tolerability of xevinapant compared to placebo when added to RT followed by xevinapant monotherapy in terms of patient-reported head and neck pain, swallowing, and speech as measured by the EORTC H&N35 sub scales, patient-reported fatigue, physical function, and global health status as measured by the EORTC QLQ C-30 sub scales and EQ-5D-5L VAS.	Endpoints: Change from baseline at • end of combination therapy (Day 64) • end of investigational therapy (Day 134) on • EORTC QLQ-HN35 subscale scores (head and neck pain, swallowing, and speech), • EORTC QLQ-C30 subscale scores (fatigue, physical function and global health status), and • EQ-5D-5L VAS Population / Treatment: See Ref #1 Intercurrent Event Strategy: • Permanent discontinuation of investigational therapy: all assessments up to the intercurrent event will be used (while on treatment strategy) • Death: while alive strategy Population-Level Summary: Difference of least squared mean change from baseline	5
Exploratory		
To assess the concentration-time profile of xevinapant.	Endpoints: Plasma concentrations of xevinapant during the treatment period Treatment: xevinapant and RT followed by xevinapant	6
CCI [redacted]		

Objectives	Estimands	Ref. #
CCI		
To describe patient-reported outcomes over time.	Endpoints: EORTC QLQ-C30 and HN35, PGIS, PGIC, PRO CTCAE	9

CRT=chemoradiotherapy CCI DFS=disease-free survival, EORTC=European Organization for Research and Treatment of Cancer, HRQOL= health-related quality of life, LA SCCHN=locally advanced squamous cell carcinoma of the head and neck, OS=overall survival, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity Scale, PRO CTCAE=Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, QOL=quality of life, RT=radiotherapy, VAS=visual analog scale.

4 Study Design

4.1 Overall Design

Study Design	Phase III, parallel-group
Control Method	Placebo-controlled
Single or Multicenter	Multicenter
Control Group	Radiotherapy and placebo
Study Population Type	Patients with resected LA SCCHN with high-risk of relapse who are ineligible for treatment with cisplatin
Level and Method of Blinding	Double-blind, matching placebo for xevinapant
Bias Minimalization Method(s)	Study intervention assignment/ randomization via IWRS. Study will be double-blind.
Study Intervention Assignment Method	Randomization and stratification via IWRS. CCI [redacted]
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), the disease-free follow-up period (DFS follow-up) and the OS follow-up period. Each treatment cycle consists of 3 weeks. Participants will be followed up until the last on-study participant reaches his/her 60-month post-randomization 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

This is a multicenter, randomized double-blind, placebo-controlled, 2-arm, parallel-group Phase III study comparing the efficacy and safety of xevinapant versus matched placebo, when administered in combination with standard fractionation IMRT in participants with LA SCCHN histologically confirmed, previously treated by surgery with high risk of relapse, who are unfit to receive cisplatin. The study is designed with the primary objective of demonstrating that treatment with xevinapant in combination with postoperative RT (xevinapant arm – Arm A) is superior to postoperative RT plus placebo (placebo arm – Arm B) (Figure 1) in terms of DFS.

Once a participant has signed the ICF, an identification number will be assigned to him/her and the study-related screening procedures will start. Upon confirmation of eligibility, participants will be enrolled and randomized in a 1:1 ratio, using permuted block allocation to Arm A or Arm B and will receive the following treatments:

- **Arm A**: 3 cycles of xevinapant (oral solution 200 mg/day from Day 1 to 14, per 3-week cycle) + IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of xevinapant (200 mg/day from Day 1 to 14, per 3-week cycle).

OR

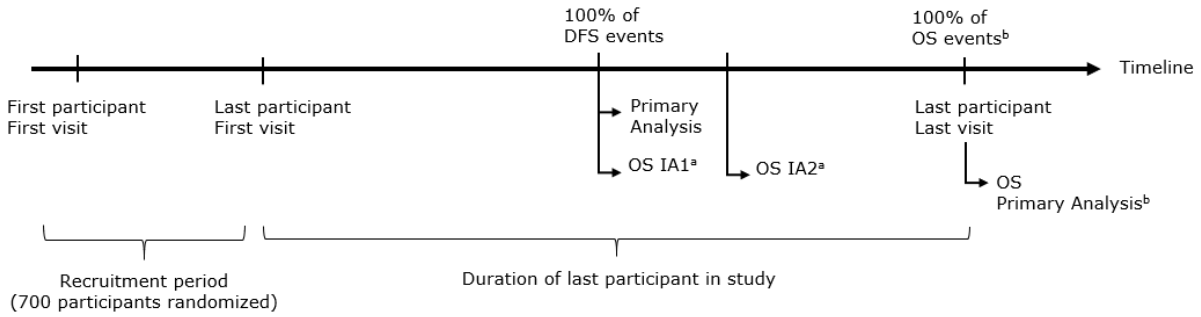
- **Arm B**: 3 cycles of placebo (matching oral solution from Day 1 to 14, per 3-week cycle) + IMRT (66 Gy in 33 fractions, 2 Gy/fraction, 5 days/week), followed by 3 cycles of monotherapy of placebo (from Day 1 to 14, per 3-week cycle).

The schedule of concurrent administration of xevinapant/ placebo and IMRT is presented in the SoA (Table 1 and Table 2) and the treatment diagram (Table 3).

It is planned to randomize approximately 700 adult participants of all sexes. The stratification factors for the randomization are listed above.

The primary analysis is planned when approximately 409 DFS events have occurred (Figure 3). If the study's primary objective is met, an alpha-controlled supplementary DFS analysis will be conducted. If both DFS tests reject their null hypothesis, the key secondary endpoint OS is tested in up to 3 analyses with a primary analysis when the planned number of events are reached (Section 9.4.4) or the last on-study participant reaches the 60-month post-randomization visit, whichever happens first.

Figure 3 Milestone Markers



DFS=disease-free survival, IA=interim analysis, OS=overall survival.

a See Section 9.4.4 for planned OS events at each interim analysis.

b OS primary analysis will be performed when the predefined number of OS events occurred (see Section 9.4.4) or after 60-month follow-up for last on-study participant.

4.2 Scientific Rationale for Study Design

Target Population: Resected LA SCCHN, High-risk, Cisplatin-ineligible

The target population chosen for the study are patients who are expected to significantly benefit from treatment with xevinapant combined with RT, being one of the alternative approaches for cisplatin-ineligible patients in the postoperative setting with a high risk of relapse. In the current study, the high-risk status is defined by the presence after resection of nodal extra-capsular extension (ECE) and/or positive resection margins (R1 or close margin ≤ 1 mm). Participants should not have any macroscopic residual disease (R2), all gross tumor must have been removed by resection, and only a microscopically close margin ≤ 1 mm or microscopically positive margin (R1) on the final resection pathology report are permitted. Participants with R2 resection are excluded from the study.

The SoC for postoperative setting in patient at high risk of relapse, is the concurrent use of cisplatin (100 mg/m^2 once every 3 weeks) with RT (total dose of 66 Gy). However, the positive effect of adding cisplatin CT to radiation in the high-risk setting is modest and is accompanied by significant incremental toxicity (including ototoxicity, nephrotoxicity, neutropenia, nausea). Also, numerous patients do not tolerate and cannot successfully complete the regimen of 100 mg/m^2 cisplatin every 3 weeks during radiation (Cooper 2004, Bernier 2004, Pignon 2009). In addition, many high-risk resected LA SCCHN patients are not considered good candidates for high-dose cisplatin because of advanced age, renal insufficiency, auditory dysfunction, and/or poor performance status (Harari 2014). Therefore, improving the outcome of high-risk resected LA SCCHN patients unfit to receive cisplatin defines an important unmet clinical need.

In this study, 'cisplatin-ineligible' is defined as a combination of the contraindications or warnings of cisplatin as specified in the product information (renal impairment, hearing loss, peripheral neuropathy) (Section 5.1):

- The proposed upper limit of 60 ml/min creatinine clearance is based on relevant publications mentioning a creatinine clearance of 50 ml/min as absolute contraindication for high-dose

cisplatin and clearances of 50 to 59 ml/min as relative contraindication with a high risk for renal toxicity by cisplatin. Hence, cautious treatment with lower doses of cisplatin may be considered based on Investigator judgment (Ahn 2016, Porceddu 2020), which is aligned with some EU Product Information documents in countries participating in this global phase III study. In order to reflect this clinical practice, participants with an eGFR of 50 to 59 ml/min are not automatically excluded from the study (Inclusion criteria #9 and #10).

- Patients with a Grade ≥ 2 audiometric hearing loss or Grade ≥ 2 tinnitus should not receive cisplatin (Ahn 2016) and are therefore considered cisplatin-ineligible (Inclusion criterion #9). Patients with pre-existing hearing loss treated with cisplatin are at higher risk of suffering from deafness at a later time (Vermorken 1983).
- Participants with peripheral neuropathy Grade ≥ 2 are most at risk of cisplatin toxicity, while Grade 3 neuropathy is an absolute contraindication for high-dose cisplatin (Inclusion criterion # 9) (Alvarado-Munoz 2021).
- Elderly patients may be more susceptible to both nephrotoxicity and peripheral neuropathy (refer to cisplatin product information). Advanced age (≥ 70 years) in combination with a poor geriatric score, based on the G8 questionnaire (Score ≤ 14), a validated geriatric screening tool (Bellera 2012),) used as an additional criterion to define ineligibility to cisplatin (Appendix 5).

Target Population: HPV-negative OPC and HPV-positive OPC With Worst Prognosis

SCCHN of the oropharynx is also associated with HPV, essentially type 16 infection. HPV-negative OPC patients do have a worse prognosis and require more and better tailored options to improve overall treatment outcome (Marur 2014, Du 2019). Although HPV-positive OPC patients generally have a better outcome (Perri 2020), HPV-positive advanced stage cancers in heavy smokers are still associated with a poor outcome (Chen 2020, Horwich 2021). Therefore, in this study only OPC participants with poor prognosis are eligible, i.e. HPV-negative OPC or HPV-positive OPC participants who are heavy smokers.

CCI [redacted]

[redacted]

Double-blind Design

This study will use a randomized, double-blind design. To maintain the scientific integrity of the study, the Investigator, the participant and Sponsor/CRO study personnel will remain blinded to the treatment allocation. For the purposes of data presentation to the external DMC, study independent personnel may be unblinded to the study data (for further details see Section 6.3.2).

Randomization is expected to compensate for possible inconsistencies in local assessments, hence minimizing any associated bias.

Endpoints

The primary endpoint of the study is DFS, an accepted endpoint in resectable SCCHN studies, that was shown to be a surrogate endpoint for OS in studies using adjuvant chemoradiotherapy, both at the individual and study level (Michiels 2009). The authors showed a strong correlation between OS and DFS (correlation coefficient of 0.82 [95% CI: 0.82;0.82] for adjuvant CRT) and a strong correlation of the treatment effect between DFS and OS (correlation coefficient of 0.93 [95% CI: 0.85;1.01] for adjuvant CRT), confirming it as a robust surrogate for OS to assess the treatment effect of CRT in randomized studies. DFS will be evaluated by the investigator using imaging and clinical review. CCI [redacted] DFS as assessed by IRC will be used in an alpha-controlled supplementary analysis, if the main analysis yielded a significant treatment arm difference for DFS. The IRC will independently assess both imaging and histopathology data. OS as key secondary endpoint is tested for superiority in a group-sequential design, if both tests for DFS are significant. The other endpoints are secondary endpoints, consistently reported in most large-scale randomized studies for this type of cancer, i.e. time to subsequent cancer therapy, adverse events, and QOL. Exploratory objectives include the potential prognostic and predictive or prognostic value of candidate biomarkers.

PROs

HRQOL can be adversely impacted by SCCHN due to several complications due to treatment and symptoms of disease (Liao 2019). Nonsurgical treatments, especially platinum-based CRT, are extremely difficult for patients to endure, due to extensive negative side effects (Oun 2018). Thus,

improvement in therapy to enhance treatment outcomes without generating incremental detriment to patients' QOL must be a priority in the advancement of SCCHN therapy. In response to this, PROs have been integrated into this study at measurement intervals that represent the appropriate balance between allowing a comprehensive HRQOL assessment across all dimensions in the proposed questionnaires that are broadly relevant to cancer patients as well as questions that are specifically relevant to SCCHN patients as well as a focused assessment of key symptoms from these measures, while remaining cognizant of the burden created for the targeted patient population by administering these questionnaires.

4.2.1 Participant Input into Design

Patient interviews were conducted to understand potential barriers to participation and general reactions to the clinical study design for TrilynX (refer to Study 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. Of note, the 60-month follow-up requirement was not seen as burdensome and is consistent with what the patients would expect.

Additional feedback was obtained from a Patient Advocacy meeting which included patient advocates, who themselves are patients with LA SCCHN, as well as from care givers of patients with LA SCCHN from Europe and the US. Feedback applicable to the current study included the following: patients considered the feeding tubes, which are standard supportive care during radiation, as challenging and added burden on them as they feel physically and emotionally exhausted, but also highlighted that a feeding tube is preferable for food and medication when swallowing is painful. In addition, some patients acknowledged that they felt uncared for 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

Rationale for 200 mg once daily dose:

Integration of nonclinical pharmacology, clinical efficacy and safety profiles, clinical PK/PD, popPK, and exposure-response analyses for efficacy and safety support the recommended Phase III dose (RP3D) selection of xevinapant 200 mg/day administered on Days 1 to 14 of a 3-week cycle with concomitant IMRT, allowing for successive dose reductions to 150 mg and 100 mg for management of toxicities.

Specifically:

- In a Phase II study in participants with high-risk LA SCCHN (Study Debio 1143-201), xevinapant showed significant improvement in LRC at 18 months (LRC18; primary endpoint), OS, and PFS at a dose of 200 mg/day given on Days 1 to 14 of a 3-week cycle in combination with CRT versus CRT alone. Xevinapant chemo-radiosensitizing effects on TEAEs, usually associated with RT, were considered manageable and reversible. In the dose escalation part of

Study Debio 1143-201, CCI [redacted].

- CCI [redacted]
- Exposure-response analyses were conducted based on the pooled datasets of dose escalation and randomized parts of Study Debio 1143-201 (n=62 treated with xevinapant). Logistic regressions showed that probabilities of LRC18, overall response, complete response, and the composite safety endpoint of "mucositis, dysphagia" increased with increasing exposure ($p<0.05$). While statistically significant exposure-response relationships were not discernible for all other evaluated safety endpoints or for time-to-event efficacy end points (PFS, OS, or duration of LRC), the participants in higher exposure subgroups showed a longer duration of LRC.
- Based on available data, the xevinapant exposure range in this study is expected to be consistent with that in Study Debio 1143-201. Currently available urine PK data indicated that about 8 to 11% of xevinapant is recovered unchanged in urine and suggest a low risk for moderate renal impairment to impact PK. Close monitoring of participants with moderate renal impairment will be performed. An external DMC will review available PK exposure and safety data in participants with moderate renal impairment. Assessment of moderate renal impairment as an intrinsic factor on PK via population PK approach is planned once the data in these participants become available.
- Based on the expected MoA of xevinapant in combination with IMRT, conclusions from PK/PD, exposure-response and dose-response analyses of xevinapant efficacy in combination with CRT are expected to be translatable to a xevinapant / IMRT combination, including association between exposure and efficacy endpoints. However, it is noted that the comorbidities that make participants ineligible to receive high-dose cisplatin could also make them more vulnerable to AEs associated with xevinapant / IMRT administration compared to participants eligible to receive cisplatin, as in Study Debio 1143-201. CCI [redacted]

Thus, based on the MoA of xevinapant, the patient population in this study, and all available data to date, the dosing strategy employed for xevinapant / CRT combination in participants with LA SCCHN is also deemed applicable for evaluation of the safety and efficacy of xevinapant in combination with IMRT in participants with resected SCCHN, who are at high risk for relapse and

are ineligible to receive high-dose cisplatin: i.e. 200 mg/day administered on Days 1 to 14 of a 3-week cycle.

Safety monitoring and risk mitigation measures are in place, including individual stepwise dose reductions to 150 and 100 mg (Section 6.5.1).

Rationale for the 7-day off-drug window

The 7-day off-drug window between 2 cycles (Day 1 to 14 of a 3-week cycle) was implemented to reduce the risk for adverse reactions and cumulative toxicity. Xevinapant dosing schedule in all clinical studies included an off-drug window, with the D1 to 14 of a 3-week cycle schedule having one of the highest dosing intensities among schedules studied (refer to the IB). Other investigational IAP antagonists in the clinics, such as CUCDC-427 and ASTX660, use intermittent dosing regimens in clinical studies (Mita 2020, Tolcher 2016). Of note, one participant death due to liver failure was reported in a Phase I study with the investigational IAP antagonist CUDC-427 using a monotherapy continuous twice daily administration schedule (Curis 2014), which triggered a partial clinical hold by US FDA. The amended Phase I study of CUDC-427 with daily 14 day on/7 day off regimen showed an acceptable safety profile in participants with refractory solid tumors (Tolcher 2016).

Based on MoA with RT, i.e sensitization of RT-induced cell death, intermittent dosing with partial target coverage in the off-drug window is unlikely to compromise efficacy. To this end, xevinapant showed efficacy in both SCCHN mouse models and in participant with LA SCCHN in Study Debio 1143-201 using an intermittent dosing regimen. Furthermore, nonclincial studies with ASTX660 in breast cancer models, suggested that regimens with continuous and intermittent dosing have similar efficacy and an improved therapeutic window (Ward 2018).

Population PK/PD modeling based on Phase I data suggested that partial IAP inhibition by xevinapant is maintained during the 7-day off-drug window with the 200 mg/day dose administered on Days 1 to 14 of a 3-week cycle, similar to clinical PK/PD data reported for ASTX660 and CUDC-427 (Tolcher 2016, Mita 2020). Thus, the intermittent dosing regimen selected for xevinapant may allow for maintained sensitization of RT-induced cell death during the 7 day off-drug windows, while reducing the potential of adverse reactions.

CCI [redacted]

[redacted]

CCI [redacted]

IMRT

High-dose RT (60 to 72 Gy) is necessary to potentially cure high-risk resected LA SCCHN patients. Irradiation of critical normal tissue can cause severe side effects 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 dose to 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 SCCHN both in curative and in postoperative locally advanced setting. In the postoperative setting, the recommended radiation dose is 66 Gy over 33 fractions (NCCN v3 2021, Machiels 2020). The dose should follow the ICRU recommendations and using IMRT with boost SIB technique.

4.4 End of Study Definition

The primary completion date is defined as the data cut-off date for the primary DFS analysis when the planned number of events has been reported. After the primary completion date, follow-up continues until the final analysis (Section 9.4) in case the study has reached its primary objective.

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 triggered or after 60 months of FU after randomization of the most recently recruited participant who is still on study, whatever 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 he/she has completed all study parts, including the last visit or the last schedule procedure shown in Section 1.3. Participants will be receiving the appropriate follow-up treatment per institutional standards.

5 Study Population

The study will enroll resected LA SCCHN participants who are at high risk of relapse and are not eligible for cisplatin-based chemoradiotherapy postoperatively.

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant 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 participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative (where allowed by local laws and regulations) has provided written informed consent, as indicated in Appendix 6.

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. Have ECOG PS 0-2 and able to tolerate standard of care IMRT treatment according to Investigator assessment.
	3. Have histologically confirmed squamous cell carcinoma with one of the following primary sites: oral cavity, oropharynx, hypopharynx or larynx. Participants have received surgery with curative intent on these sites in the past 4 to 10 weeks before start of treatment (C1D1) (Note: Participants with 2 or more primary SCCHN tumors are not eligible for this study).
	4. Participants with HPV-negative oropharynx cancers as determined by testing p16 expression using immunohistochemistry (IHC), with oral cavity, hypopharynx or larynx cancers with the following pathological staging (pTNM stage according to the American Joint Committee on Cancer AJCC/TNM Staging System 8th Edition): • pIII or • pIVA or pIVB • OR Participants with HPV-positive oropharynx cancers, as determined by testing p16 expression using IHC, must be smokers > 25 Pack-Year, and must have the following pTNM stage (according to the AJCC/TNM Staging System 8th Edition): • pT3 and pN2 or • pT4 and pN2

Category	Criterion
	OPC participants must have known HPV status as determined by p16 expression using IHC (pathological report should be available). For OPC participants, a positive p16 expression score is defined in Section 8.2.4.1. Note: If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central laboratory.
	5. Archival/preradiotherapy FFPE tumor tissue samples from participant must be provided, if local regulations allow. If an archival FFPE tissue block cannot be provided, at least 15 unstained FFPE tissue slides will be acceptable.
	6. Have no residual disease by CT/MRI and have a high risk of relapse with 1 or 2 of the following criteria, confirmed by local histopathology: • nodal extra-capsular extension (ECE) • positive resection margins (R1 or close margin ≤ 1 mm).
	7. Have a postoperative general condition which allows to perform postoperative radiotherapy.
	8. Are able to swallow liquids or have an adequately functioning feeding tube, gastrostomy, or jejunostomy placed. For participants requiring liquid nutrition at baseline or during the study including the follow-up period, access to liquid nutrition supply should be ensured.
	9. Are unfit to receive high-dose cisplatin by meeting one or more of the following criteria: • eGFR < 60 mL/min /1.73 m^2 (using the CKD-EPI creatinine formula). See Appendix 12 for specific requirements in Japan for CKD-EPI creatinine formula. • History of hearing impairment, defined as Grade ≥ 2 audiometric hearing loss or tinnitus Grade ≥ 2. An audiogram is not required if one of the other criteria meets unfitness to receive high-dose cisplatin. See Appendix 12 for specific requirements in France and the US. • Peripheral neuropathy ≥ Grade 2 • If ≥ 70 years, unfit according to G8 questionnaire (Score ≤ 14) or ineligible for cisplatin treatment due to age limit according to national guidelines.
	10. Have adequate renal, hematologic and hepatic function as indicated by:

Category	Criterion
	• eGFR ≥ 30 mL/min/1.73m² (using the CKD-EPI creatinine formula). See Appendix 12 for specific requirements in Japan for CKD-EPI creatinine formula. • Absolute neutrophil count ≥ 1,000 cells/µL • Platelets ≥ 75,000 cells/µL • Hemoglobin ≥ 9.0 g/dL (blood transfusions during Screening are permitted) • AST and ALT ≤ 2.5 × 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	11. All sexes allowed 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. Please see Appendix 12 for duration of contraception requirements in South Korea. **a. A female participant** • Is not breastfeeding • Is not pregnant (i.e. has a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention) • Is not a WOCBP o If a WOCBP, 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 4 for the following time periods: 1. Before the first dose of the study intervention(s), if using hormonal contraception: o Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her menses; OR, o 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 study intervention is administered) for at

Category	Criterion
	least 3 months, after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period. 4. Female participants using hormonal contraception must also use a barrier contraception method (preferably male condom) due to potential risk of CYP3A4/5 induction by xevinapant which may reduce hormonal contraception efficacy. The Investigator evaluates the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy. **b. A male participant** Agrees to the following during the study intervention period and for at least 3 months after the last dose of study intervention: • Refrains from donating fresh unwashed semen PLUS, either o Abstains from any activity that allows for exposure to ejaculate OR Uses a male condom: o When having sexual intercourse with a WOCBP, who is not currently pregnant, and instructs her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 4 since a condom may break or leak. o When engaging in any activity that allows for exposure to ejaculate.
Informed consent	12. Are capable of giving signed informed consent, as indicated in Appendix 6, which includes compliance with the requirements and restrictions listed in the ICF and this protocol.

ALT=alanine transaminase, AST=aspartate aminotransferase, CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration, CT=computed tomography, ECOG PS=Eastern Cooperative Oncology Group Performance Status, eGFR=estimated glomerular filtration rate, FPPE=formalin-fixed paraffin-embedded, HPV=human papillomavirus, IHC=immunohistochemistry, ICF=informed consent form, IMRT=Intensity modulated radiation therapy, OPC=oropharynx, SCCHN=squamous cell carcinoma of the head and neck, ULN=upper limit of normal.

5.2 Exclusion Criteria

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

Category	Criterion
Medical Conditions	1. Any condition, including any uncontrolled disease state other than SCCHN that in the Investigator's opinion constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation.
	2. Primary tumor of nasopharyngeal, paranasal sinuses, nasal cavity, salivary, thyroid or parathyroid gland, skin or unknown primary site.
	3. Participant with incomplete surgery i.e. R2 resection (AJCC/TNM Staging System 8th Edition)
	4. Recurrent or metastatic disease (Stage IVC as per AJCC/TNM Staging System 8th Edition).
	5. Known history of infection with HIV. If unknown history of HIV, an HIV screening test must be performed, where allowed by local regulations, and participants with positive serology for HIV-1/2 must be excluded.
	6. Chronically active HBV or HCV infection. The following tests must be performed at the central lab and participants with positive serology must be excluded (Section 8.2.4): • HBV screening tests: both HBsAg and HBcAb (see Appendix 12 for specific requirements in Japan) • HCV screening tests: both HCV-antibody and positive viral load HCV-RNA by PCR
	7. 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.
	8. Known gastrointestinal disorder with clinically established malabsorption syndrome and major gastrointestinal surgery in the last 12 months that may limit oral absorption.
	9. Documented weight loss of > 10% during the last 4 weeks prior to surgery (unless adequate measures are undertaken for nutritional

Category	Criterion
	support), OR plasmatic albumin < 3.0 g/dL. No albumin transfusions are allowed within 2 weeks before randomization.
	10. Active gastrointestinal bleeding, or any other uncontrolled bleeding requiring more than 2 red blood cell transfusions or 4 units of packed red blood cells within 4 weeks prior to randomization.
	11. Active inflammatory disease (including rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, severe extensive psoriasis, inflammatory bowel diseases, pneumonitis, and other autoimmune diseases) requiring ongoing treatment with anti-TNF medication.
	12. 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 randomization. • 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 randomization. • New York Heart Association Grade ≥ 3 congestive heart failure. • Congenital long QT syndrome. • Family history of long QT syndrome. • Symptomatic pulmonary embolism within 6 months prior to randomization. • Ongoing or known history of transient ischemic attacks or stroke within 6 months prior to randomization. • QTc using Fridericia's formula (QTcF) interval > 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).
	13. History of another malignancy prior to randomization, with the following exceptions: • 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,

Category	Criterion
	cervix and/or uterine carcinomas, or T1a squamous esophageal carcinomas. • Prior malignancy treated with curative intent and no relapse and no anti-cancer treatment within the last 3 years and does not have potential to interfere with the safety or efficacy assessments of the study.
	14. Noncompensated or symptomatic liver cirrhosis (Child-Pugh score: B or C).
Prior/Concomitant Therapy	15. Prior definitive, neoadjuvant, concurrent or adjuvant (C)RT to the head and neck region which may jeopardize the primary tumor irradiation plan, or any other prior SCCHN systemic treatment, including investigational agents.
	16. Use of the following: • Prohibited medication. These medications and time window to stop these medications prior to randomization are further specified in Section 6.8.3 • Treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of study treatment or during study treatment • Live attenuated vaccines within 28 days prior to first study intervention administration • Concurrent use of anticancer therapy.
	17. Patients with active immunodeficiency or patients receiving ongoing immunosuppressive therapy.
	18. Any concomitant medication known to prolong the QT interval that cannot be discontinued or replaced by safe alternative medication within 7 days prior to start of treatment.
	19. Major surgical intervention outside the head and neck area within 4 weeks prior to the first dose of study intervention. Biopsies to establish the diagnosis for SCCHN are permitted.
	20. Prior organ transplantation, including allogeneic stem cell transplantation.
Prior/Concurrent Clinical Study Experience	21. Participation in any interventional clinical study within 28 days prior to screening or during participation in this study.
Diagnostic Assessments	22. Known contraindication to undergoing positron emission tomography with ^{18}F-FDG-PET-CT scans, or both contrast-enhanced MRI and contrast-enhanced CT scans.

Category	Criterion
Other Exclusions	23. Known allergy to xevinapant or any excipient known to be present in xevinapant or in the placebo formulation.
	24. Pregnant or nursing (lactating) women.
	25. 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.

(C)RT=(chemo)radiotherapy, HBV=hepatitis B virus, HBcAb=hepatitis B core antigen; HBsAG = hepatitis B surface antigen; HCV=hepatitis C virus, HIV=human immunodeficiency virus, ^{18}F-FDG-PET=2-deoxy-2- [fluorine-18] fluoro-D-glucose positron emission tomography, PCR=polymerase chain reaction; MRI=magnetic resonance imaging, QTcF= QTc using Fridericia's formula; SARS-CoV-2=Severe acute respiratory syndrome coronavirus-2; SCCHN=squamous cell carcinoma of the head and neck.

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 after the final dose: Seville oranges, grapefruit or grapefruit juice, or grapefruit-containing products, St John's Wort (= Hypericum perforatum, millepertuis) and St John's Wort-containing products because of the risk of DDIs with P-gp (Section 6.8.3).

Xevinapant / placebo should be administered orally, 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 one 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 randomization. Dental examination, audiometry, if required, HIV test, and fiberoptic endoscopy, if appropriate, performed within 2 weeks before the last signed ICF do not have to be repeated during screening.

5.5 Criteria for Temporarily Delaying the Randomization/ Administration of Study Intervention Administration

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 allocation to each arm.

Arm Name	A: Xevinapant + IMRT		B: Placebo + IMRT	
Arm Type	Experimental		Placebo comparator	
Arm Description	3 cycles of xevinapant + IMRT followed by 3 cycles of xevinapant		3 cycles of placebo + IMRT followed by 3 cycles of placebo	
Intervention Name	Xevinapant	IMRT	Placebo	IMRT
Type	Drug	Radiation	Placebo	Radiation
Dose Formulation	Oral solution	NA	Oral solution	NA
Unit Dose Strength	CCI of 10 mL containing 200 mg xevinapant (20 mg/mL)	NA	CCI of 10 mL containing placebo	NA
Dose Amount	200 mg	66 Gy	NA	66 Gy
Frequency	Once daily Day 1-14 of a 3-week cycle	2 Gy once daily 5 days/week for a total of 33 fractions	Once daily Day 1-14 of a 3-week cycle	2 Gy once daily 5 days/week for a total of 33 fractions
Route of Administration	Oral	NA	Oral	NA
Use	Experimental	Background intervention	Placebo to xevinapant	Background intervention
IMP/NIMP	IMP	NA	IMP	NA
Sourcing	Provided centrally by the Sponsor	NA	Provided centrally by the Sponsor	NA
Packaging and Labeling	Xevinapant CCI [redacted] will be packed and labeled per all applicable regulatory requirements and GMP Guidelines. Packaging and labeling will be prepared to protect the blinded nature of the study.	NA	Matched placebo CCI [redacted] will be packed and labeled per all applicable regulatory requirements and GMP Guidelines. Packaging and labeling will be prepared to protect the blinded nature of the study.	NA
Former Name	Debio 1143	NA	NA	NA

IMP=investigational medicinal product, IMRT=intensity modulated radiation therapy, NA=not applicable, NIMP=noninvestigational medicinal product.

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, 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.
- Additional instructions for the preparation, handling, storage, and disposal of xevinapant/placebo will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After confirmation of participant's eligibility and at the last practical moment prior to study intervention administration, participants will be centrally allocated to either Arm A or Arm B in a 1:1 ratio using an IWRS and per a computer-generated randomization list. CCI [redacted]

The IWRS will be used to assign unique participant numbers, allocate participants to study intervention group at the randomization visit, and study intervention to participants at each study intervention visit.

Before the study is initiated, the directions for the IWRS will be provided to each site.

6.3.2 Blinding

Blinding Method

The study will be double-blind. At randomization and treatment allocation, a blinded treatment kit number will be allocated by the IWRS to each participant corresponding to their randomization group. Experimental treatment kits will be indistinguishable from the placebo.

Randomization codes will be kept strictly confidential, accessible only to authorized staff (i.e. randomization statistician, unblinded statistician), until the time of unblinding. All other study-related individuals, ancillary site staff, clinical research associates/monitors, the Investigator, IRC, participants, Sponsor (excluding Clinical Trial Supply), and clinical research organization staff will remain blinded to study intervention until after the primary analysis (Section 9.4.4).

Interim analyses before unblinding will be conducted by an external study independent unblinded statistician, programmer, and clinical pharmacologist, who get access to the actual treatment codes only after database is locked to conduct the analyses and provide the external DMC with corresponding results. The external DMC may request unblinded analyses, which are usually masked (i.e. presented by study intervention arm, but actual study intervention is not revealed) for the periodic safety reviews.

Confirmation of the Indistinguishability of the Study Interventions

Xevinapant and matching placebo CCI [redacted] are identical in color and appearance.

Unblinding for Sample Analysis of Special Data

The analytical laboratories responsible for analyses of PK will be unblinded to study treatment codes to enable testing of xevinapant plasma concentration (and metabolite D-1143-MET1) prior to database lock.

Xevinapant and metabolite D-1143-MET1 plasma concentration information that may unblind the study participants will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety is always the first consideration in this decision. The Investigator will be able to break the blind through the IWRS system without prior approval from the Sponsor. The IWRS will be programmed with blind-breaking instructions and will automatically notify the Sponsor in case of unblinding. If the Investigator decides that unblinding is warranted, the Investigator makes every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor will be notified within 24 hours after unblinding. The Investigator will provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated global patient safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding will be recorded in the source documents and eCRF. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 6. If emergency unblinding is required, the participant can continue study treatment unless there are other circumstances that require participant discontinuation.

The Sponsor's global patient safety department will submit any SUSAR reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

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 eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

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 eCRF. Participants will be instructed to return used and unused xevinapant or placebo[redacted] to the site to allow drug accountability by the medical staff.

A record of the number of xevinapant / placebo [redacted] 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 also be recorded in the eCRF. In addition, for each study intervention (xevinapant/ placebo, and IMRT) the reasons for dose modification, interruption, and discontinuation must be recorded in the CRF.

6.5 Dose Modification

6.5.1 Xevinapant or Placebo Dosing and Administration

Xevinapant oral solution at 200 mg/day or matched placebo will be administered once daily from Day 1 to Day 14 of a 3-week cycle, during 6 cycles (Figure 1 and Table 3). Xevinapant / placebo should be administered orally, in the morning (except for days of PK sampling when the dose is taken at the hospital where a specific procedure applies as described below [see also Table 6]). If necessary,[redacted] will be administered [redacted]

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

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

On the days of C1D1, C1D2, C1D8, C2D2, C2D8, C4D1, C5D1, and C6D1 participants must be at the clinical unit before xevinapant / placebo is administered to ensure PK blood sample collection as per SoA (Table 6). The time of dosing on those days and time of the draw must be recorded in eCRF.

On C3D8, xevinapant / placebo dose is encouraged to be taken at home and the time of the last dose prior to PK sample is recorded by participant in the diary and reported in the eCRF.

The treatment schedule of xevinapant / placebo is presented in Table 1, Table 2, and Table 3. Participants will be instructed by the medical staff on how to self-administer xevinapant / placebo at home. The participant should inform the medical staff of any missed or delayed doses. In addition, a Patient Diary will be provided to participants to record xevinapant / placebo intakes at home (Section 6.4 and Section 8.2.6).

6.5.1.1 Concurrent Administration to IMRT

On days when IMRT is to be administered (Table 3 and Section 6.5.2), xevinapant or placebo should be administered in the morning, before IMRT.

If IMRT is put on hold or discontinued due to toxicity, adapt xevinapant / placebo administration as described in Section 6.5.1.2. Otherwise xevinapant / placebo treatment should continue as per protocol.

6.5.1.2 Dose Modification, Interruption and Discontinuation of Xevinapant / Placebo Treatment

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

The guidelines for xevinapant / placebo dose modifications for toxicities considered at least possibly related to study intervention for combination therapy and monotherapy are outlined Table 8. 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.

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

Planned dose (Level 0)	CCI mL/day, corresponds to 200 mg/day of xevinapant
Dose Level -1	CCI mL/day, corresponds to CCI mg/day of xevinapant
Dose Level -2	CCI mL/day, corresponds to CCI mg/day of xevinapant

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

For each participant, a maximum of 2 dose level reductions of xevinapant / placebo will be allowed during the study. These dose reductions only apply to a starting dose of 200 mg/day of xevinapant.

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

The number of treatment days with xevinapant intake should not exceed 14 days per cycle.

- In case of tolerability issues, up to 2 sequential xevinapant dose reductions of CCI [redacted] per step will be allowed, down to a minimum dose of CCI [redacted]. If further dose reduction is required, the participant must be permanently discontinued from xevinapant / placebo administration (IMRT can continue, see Sections 6.5.2.3).
- If the onset of several toxicities leads to conflicting recommendations (as described in Table 8), the most conservative dose adjustment among all toxicities presented must be followed.
- **No re-escalation** of xevinapant / placebo dose after dose reduction will be allowed during the study. Once xevinapant / placebo dose has been reduced, participants 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 / placebo 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 due to toxicity, xevinapant / placebo should be interrupted. If IMRT is restarted, xevinapant / placebo should be resumed at the next originally scheduled intake day of xevinapant / placebo, provided other rules of dose interruption are not met (Section 6.5.2). If IMRT is permanently discontinued due to safety issues, then xevinapant / placebo administration should be maintained.
- Monotherapy treatment period: If a participant requires a xevinapant / placebo dose interruption of more than 21 consecutive days due to study intervention-related toxicities, the Investigator should consider discontinuing the study intervention. If a participant is discontinued from the monotherapy treatment, the EOT visit must be performed. Hereafter, the participant will continue with the study as per schedule and will enter the DFS FU period.
- Xevinapant / placebo interruption or discontinuation during the combination treatment period, will NOT result in IMRT discontinuation.
- Participants who prematurely discontinue from all treatments, i.e. xevinapant / placebo, and IMRT in the absence of an DFS event, will undergo the EOT visit and then enter the DFS follow-up period according to schedule.
- Any dose modification and dose interruption including the reason must be collected on the drug administration form in the eCRF.


CCI


CCI


CCI


CCI

6.5.1.3 End of Xevinapant / Placebo Treatment

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

Note: If IMRT is permanently discontinued due to severe or intolerable toxicities as per Investigator's discretion, then the participant will 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 described in Section 7.1. Procedures for discontinuation from study (not only study intervention) are described in Section 7.2.

6.5.2 Radiotherapy

6.5.2.1 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 nutritional 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.

6.5.2.2 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 6) 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-QA Manual). The IMRT plan must be approved by the RT-QA Review Center prior to the start of the IMRT. A summary of radiotherapy requirements and recommendations is described below.

Initiation of radiotherapy must start 4 to 10 weeks after surgery on C1D1 of xevinapant / placebo. If possible, it is recommended to start treatment within 8 weeks from surgery. 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, and if not possible, co-registration of a postoperative diagnostic CT of the neck with IV contrast is strongly recommended. Co-registration with pre-operative imaging (e.g. CT, PET, MRI) is encouraged to assist with treatment planning, but with caution given anatomical changes related to surgery.

Target volumes must consider all clinical, endoscopic, and imaging information along with surgical and pathologic findings. Since eligible participants must have gross total resections, there will be no GTV.

Clinical target volumes (CTV) will be divided into 2 regions: high risk and low risk; these will be treated at different dose levels using a SIB technique delivered over 33 fractions (Table 9).

Table 9 Dose Prescription

Clinical Target Volume Region	Total Dose	Dose per Fraction	Target
Very High Risk	66 Gy	2 Gy	Regions with positive / close margins and/or extra-capsular extension
Low Risk	54.45 Gy	1.65 Gy	Regions at risk for microscopic / subclinical disease

The delineation of the elective nodal CTV for participants with positive neck nodes can be based on the consensus guidelines published by Gregoire (2006). Additional details will be provided in the RT Manual.

Planning Target Volumes (PTV) will be a uniform 3 to 5 mm expansion to all CTVs to account for interfraction motion and setup uncertainties. The SIB 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.

IMRT (fully described in the RT Manual) is to be started on C1D1 after administration of xevinapant / placebo (Table 1 and Table 3). On days where all treatment components should be administered, IMRT should be administered after xevinapant / placebo administration.

6.5.2.3 Treatment Interruption

Interruption of radiotherapy is strongly discouraged and every attempt should be made to keep the treatment continuous and adhere to the overall treatment time as prescribed (6.5 weeks). Planned radiotherapy interruptions are not allowed. Any interruption must be clearly indicated in the treatment record and reasons should be documented. Radiotherapy may be interrupted for a maximum of 10 treatment days in total to allow resolution / improvement of chemoradiation toxicities such as Grade 4 mucositis or other Grade 3 or 4 in-field treatment-related AEs (for example skin side effects) measured by physical or functional examination, or Grade 4 radiodermatitis (see Section 6.5.2.4 for management of these toxicities).

Treatment interruption due to nonmedical reasons must be minimized and should not exceed 2 consecutive treatment days per interruption. In case of technical reasons (e.g. malfunction of the treatment machine), continued treatment must be ensured, and the use of another unit is recommended.

If IMRT is interrupted due to toxicity, xevinapant / placebo should be interrupted (Section 6.5.1.2), otherwise xevinapant / placebo treatment should continue as per protocol.

No more than 5 fractions will be administered in a given week, unless one previously skipped fraction has to be compensated. If a fraction has to be compensated, it can be administrated at the end of the treatment or it can be compensated during treatment. In the latter case, the fractions should be at least 6 hours apart. Xevinapant / placebo administration should not be compensated.

If IMRT is permanently discontinued due to severe and intolerable toxicities as per Investigator's judgment, then xevinapant / placebo administration must be maintained, and the participant can enter the monotherapy period (Section 6.5.1.3).

6.5.2.4 Management of Acute "Radiation In-Field" Toxicity

If dermatitis, mucositis, or dysphagia occurs, the possibility of IMRT interruption must 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 ≥ 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 must be based on the severity of symptoms, as determined by Radiation Therapy Oncology Group and must be aligned with the recommendations by the Supportive Care Guidelines Group.

6.5.2.5 End of IMRT

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

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 200 mg/day will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose. The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Even if not associated with an AE or a SAE, any overdose is recorded in the eCRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 8.

6.8 Concomitant Therapy

Record in the eCRF all concomitant therapies (e.g. medicines or nondrug interventions) used from the time the participant signs the informed consent until FU28 visit or until the start of next line anticancer therapy, whichever occurs earlier. Record all concomitant therapies used at occurrence of late onset AESIs (Section 8.3.7.2) and related SAEs during the period immediately after the FU28 visit until completion of the study. Record all new antineoplastic therapies (medication, surgery, any further RT) from EOT until completion of the study, 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.

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

6.8.1 Permitted Medicines

The only 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.
- SARS-COV-2 vaccination:
  In case a participant is vaccinated for SARS-COV-2 during the study treatment period, the following actions should be considered:
    - Administer only approved vaccines.
    - Nonreplicating viral vector-based vaccines and mRNA-based vaccines are not considered live attenuated vaccines (exclusion criterion #16) and can be administered during this clinical study. Any future live attenuated vaccine for SARS-COV-2 is prohibited within 28 days prior to the first dose of study intervention and up to 90 days after EOT.
    - Report all SARS-COV-2 vaccine names, and if available, the manufacturer on the ConMed page of eCRF.

6.8.2 Medications to be Used with Caution with Xevinapant or Placebo

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, CYP2Cs (2C8, 2C9, 2C19), 2B6 or 1A2 are recommended to be used under close medical monitoring. Some CYP3A substrates (not prohibited as per Section 6.8.3) 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, 2Cs, 2B6, 1A2, 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
Clopidogrel	Ondansetron (**allowed alternative**: dolasetron, granisetron, tropisetron, palonosetron)
Colchicine	Posaconazole (systemic)
Dabigatran	Riociguat
Digoxin	Valproic Acid
Lansoprazole	

The metabolism and transport of the above listed drugs occurs through CYP3A4/5, CYP2Cs and/or P-gp. As per their product information, the clinical relevance of their co-administration 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 co-administered 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

- 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 randomization or requirement for ongoing treatment with any drug(s) on the prohibited medication list in Sections 6.8.3.1, 6.8.3.2, and 6.8.3.3 or within 3 days prior to randomization for the drugs in Section 6.8.3.4 is an exclusion criterion.
- Treatment with an investigational agent other than xevinapant / placebo or use of an investigational device within 4 weeks of the first dose of study treatment or during study treatment.
- In case of unavoidable concomitant administration of a prohibited medicine during investigational treatment, the need for suspension or discontinuation of xevinapant / placebo must be discussed beforehand with the Sponsor.
- Live vaccines within 28 days prior to the first dose 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, BCG, 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 / placebo.

6.8.3.1 Recombinant Human Erythropoietin and Derivates

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

Nonclinical and clinical studies showed that autocrine or paracrine erythropoietin signaling can enhance cancer invasion in SCCHN and negatively affect patient outcome in terms of OS and localregional PFS (Henke 2003, Lambin 2009).

6.8.3.2 Food and Herbal Preparations

- Grapefruit juice and grapefruit-containing products (P-gp inhibitors, may lead to increased xevinapant exposure) are not allowed during the treatment phase.
- St John's Wort (= *Hypericum perforatum*, millepertuis) and St John's Wort-containing products (P-gp inducers, may lead to decreased xevinapant exposure) are not allowed during the treatment phase.
- Any traditional Chinese medication with approval for use as anticancer treatment (regardless of the type of cancer) will not be permitted. Traditional Chinese medicines for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the

Investigator. However, any traditional Chinese medicines or herbal supplement, known to be strong inhibitors / inducers of CYP 3A4/5 or inhibitors / inducers of P-gp, are not permitted.

6.8.3.3 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 product information 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 / Placebo

International Nonproprietary Name	
Inhibitors	
Amiodarone [a]	Quinidine
Carvedilol	Ranolazine
Clarithromycin	Ritonavir
Dronedarone	Saquinavir and ritonavir
Itraconazole	Telaprevir
Lapatinib	Tipranavir and ritonavir
Lopinavir and ritonavir	Verapamil
Propafenone	
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 randomization need to be closely monitored due to the long half-life of this drug with chronic dosing.

6.8.3.4 CYP3A4/5 Narrow Therapeutic Index Drugs or Sensitive Substrates

The concomitant intake of CYP3A4/5 narrow therapeutic index drugs or sensitive substrates is prohibited, since xevinapant / MET1 has a potential to inhibit CYP3A4/5 (refer to the IB). 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 that are CYP3A4/5 sensitive substrates are listed in Table 13. Note that this is not an exhaustive listing; refer to the product information for other drugs that are narrow 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).

6.8.4 Other Interventions

6.8.4.1 Nutritional Support

All participants must be screened for nutritional risk and early enteral nutrition. Nutrition status must be evaluated as indicated in Table 1, Table 2, and Table 4.

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 v3 2021). 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

7.1 Discontinuation of Study Intervention

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

- Disease relapse (see DFS definition in Section 3).
- 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 survival and/or efficacy assessments.
- Unacceptable toxicity / AEs that result in a significant risk to the participant's safety.
  - Participants who are removed from study 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.
- Initiation of any other cancer therapy.
- Early study termination by the Sponsor, Steering Committee, the Investigator, the IEC/IRB, or the Regulatory Agencies.

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

CCI [redacted]

[redacted]

[redacted].

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy (see DFS and OS follow-up periods in Table 4 and Table 5). The SoA indicates data to be collected at the time of discontinuation of study intervention (Table 2 - EOT visit) and follow-up and for any further evaluations that must be completed. In case of premature treatment discontinuation, the first visit in the DFS FU period starts 1 month after EOT visit. Efficacy assessments including HRQOL will continue to be performed in case of premature discontinuation from study intervention in the absence of a DFS event.

7.1.1 Temporary Discontinuation

See Section 6.5.1.2 (xevinapant / placebo) and Section 6.5.2.3 (RT) for further guidance on temporary discontinuation of treatment.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at his/her own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- 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 the participant until the AE is resolved.

- 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.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records and the eCRF and inform the Sponsor. The samples will be destroyed.
- Premature discontinuation from the study can also be triggered by:
  - Participant lost to follow-up (Section 7.3)
  - Death
  - Early study termination by the Sponsor, Steering Committee, 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 will not be replaced.

7.3 Lost to Follow-Up

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

The following actions 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 should 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.
- Additional survival follow-up information may be collected from participants or their family doctor between routine study visits upon Sponsor request to check on health status and collect survival information.
- **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 should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations 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.
- A participant will be randomized into the study after he/she has signed the ICF, all eligibility criteria have been met, and the IMRT plan has been sent to the RT-QA Review Center (see Appendix 6). The IMRT plan must be approved by the RT-QA Review Center prior to the start of the IMRT.
- 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 6.
- Procedures conducted as part of the participant's routine medical care (e.g. blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

No more than 60 mL of blood may be drawn in a 24-hour period, and no more than 130 mL of blood in a 4-week period.

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.

The long-term storage of samples and imaging data after study completion for future research may be performed with all sample types collected in the study (e.g. PK, pharmacogenomics, biomarkers, or immunogenetic) if the participant consents to optional future medical research.

Order of Assessments

- The participants should be given the QOL questionnaires (Section 8.1.5) to be completed at the scheduled visit before other clinical assessments are conducted.
- ECG readings must be taken prior to blood collection.

Screening Period

Participants will be screened between Days -28 and -1, prior to randomization (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. If ≥ 70 years, G8 questionnaire to be completed.
- Medical history: disease history, previous illness and surgeries (e.g. all during the past year and only major ones prior to that), concomitant illness, relevant medication, therapies stopped or changed at entry into the study, allergies, tobacco use, alcohol use.
- Audiometry: not required if one of the other high-dose cisplatin ineligibility inclusion criteria are met (Section 5.1).
- 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).
- Tumor staging (using the AJCC/TNM Staging System, 8th Ed.) based on radiological imaging and pathological assessment after SCCHN surgery.
- SCCHN surgery details: resection margins (R), positive nodes, risk factors (extra-capsular extension/ positive margin).
- Results from the central laboratory should be used for defining participant eligibility during Screening, except for:
  - HIV test that may be performed by a local laboratory within 2 weeks before ICF signature (Section 8.2.4).
  - HPV status by p16 IHC (mandatory for OPC, optional for other tumor locations) that may be obtained locally (Section 8.2.4.1).
  - SARS-CoV-2 PCR and/or antigen test if required (Section 8.2.4).

8.1 Efficacy Assessments and Procedures

Tumor assessments will be completed using a combination of clinical, radiological and, if appropriate, fiberoptic endoscopy and pathological assessments, integrating in case of a potential tumor relapse, a direct pathologic ascertainment.

Radiographic and clinical evaluations will be conducted with the same schedule in both treatment arms (Table 1, Table 2, Table 4, and Table 5). For radiological assessments, RECIST 1.1 criteria adapted for participants with no residual disease at baseline, including for determination of nodal disease relapse will apply (adapted from Eisenhauer 2009). See Appendix 7 for further details.

At baseline, tumor assessment will require CT scan and/or MRI for head and neck and CT scan of chest. ^{18}F-FDG-PET is required at EOT (Table 2), and at any time if disease relapse is suspected but not proven by CT and/or MRI, or at the Investigator's discretion.

In addition, the most recent pre-surgery diagnostic/staging CT and/or MRI scans done as a part of SoC should be submitted to the IRC vendor, if available, as well as any recent pre-surgery or baseline PET-CT scan if acquired, to facilitate IRC assessment of any potential macroscopic residual disease at baseline.

Tissue (biopsy) confirmation of disease is required for all local and regional suspected disease relapse unless medically contraindicated. When disease relapse is suspected by distant metastasis, confirmation of pathology is recommended in case of solitary metastasis (especially in the lung) unless medically contraindicated. All biopsies will also be reviewed centrally as part of the independent review process (Section 8.1.4). For cases where biopsy is contraindicated or the medical risk assessed as too high, radiological assessment by RECIST 1.1 alone will apply (Appendix 7). Disease relapse on imaging must be confirmed in the absence of histopathological evidence.

After unequivocal disease relapse, participants will enter the OS follow-up period at time of the confirmation of the event (Section 1.3).

8.1.1 Radiological Assessment

For each participant, the same imaging modality for head and neck and for chest must be used throughout the study. The schedule of collection of IV contrast-enhanced CT scan and/or MRI of head and neck (including coverage of the orbits), CT scan of the chest and ^{18}F-FDG-PET scan (from the skull base to proximal upper legs) is provided in Table 1, Table 2, Table 4, and Table 5. Any other site of suspected disease should also be imaged.

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.

If an off-schedule imaging assessment is performed because relapse is suspected or for other reasons, subsequent assessments should be performed in accordance with the original imaging schedule.

For all participants, radiological tumor assessments are to continue until unequivocal disease relapse by imaging according to RECIST 1.1 adjusted for a study wherein no residual disease is expected at baseline, if applicable, or by pathology. Tumor assessments will be performed according to the original schedule regardless of premature treatment discontinuations or treatment delays.

All images will also be reviewed centrally as part of a centralized independent review. Further details will be in an Imaging Charter provided for this study.

The Sponsor may discontinue image transfer to vendor once no further analyses by IRC assessment are planned.

8.1.2 Clinical Assessment

The clinical assessments will include a detailed description of tumor extension and/or nodal extension for palpable nodes in the neck. If appropriate, this should be completed by a fiberoptic endoscopy (by a Head and Neck surgeon) under general anesthesia and biopsy.

For all suspected disease relapse that is detected clinically (by endoscopy), but is not visible on radiographic imaging, an objective evidence supporting disease relapse must be collected and submitted to IRC. Tissue (biopsy) confirmation of disease is required for all local and regional suspected relapse of disease unless medically contraindicated. Photographs and reports from endoscopy procedure should be collected by the site (if available) and both should be submitted to IRC for central review. Please refer to the Imaging Charter for detailed information.

It is recommended that all new distant solitary lesions suspicious for metastatic disease are also biopsied and pathologically confirmed. Prior to performing biopsy, concomitant diseases, location of relapse, coagulation status and concomitant medications must be reviewed for any contraindications in line with local practice.

During the follow-up period the participants will undergo ear, nose, and throat examination, as per the schedule presented in Table 4 and Table 5. Fiberoptic endoscopy, if appropriate, will be done as part of these clinical examinations.

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

8.1.3 DFS Events and Definitions

The reappearance of any lesion with squamous histology, or the development of a new lesion with squamous histology, will be considered a DFS event. CCI [redacted] In the situation where a single pathologic node is driving the progression event and there is no biopsy data, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the "new node" has not resolved, or has significantly increased in size, and truly represents PD, the date of PD would be the date the new node was first documented (Schwartz 2016). CCI [redacted]

A DFS event is defined as follows:

- **Local relapse** is present if recurrent tumor is found at the site of original tumor location. Tumor reappearing within the radiation field (inside the GTV) will be considered local relapse. CCI [redacted] The date of relapse is the date of positive pathology, or the date of imaging detection (including by PET scan, if earliest) subsequently confirmed by biopsy, whichever is first.
- **Regional relapse** is present if recurrent tumor is found at the regional lymph node basins (e.g. neck nodes). CCI [redacted]

The date of relapse is the date of positive pathology, or the date of imaging detection (including by PET scan, if earliest) subsequently confirmed by biopsy, whichever is first.

- **Distant metastasis** is defined as a new lesion of squamous cell histology identified outside the radiation field (outside the PTV) or draining lymph nodes. When disease relapse occurs for distant metastases, confirmation of distant metastasis by pathology is strongly recommended in case of solitary lesions (especially in the lung) unless biopsy is medically contraindicated or the medical risk of biopsy assessed as too high. A solitary speculated lung mass/nodule is a second primary neoplasm and is not a disease relapse event unless proven otherwise by biopsy, i.e. tumor of squamous cell histology. Multiple lung nodules/masses are considered distant metastases and constitute a disease relapse event unless proven otherwise by biopsy, i.e. tumor of non-squamous cell histology. The date of relapse is the date of positive pathology, or the date of imaging detection (including by PET scan, if earliest) subsequently confirmed by biopsy, whichever is first.
- Note: For cases where no histopathological assessment but tumor assessment by imaging is available, any new tumor lesion will be considered a relapse. RECIST 1.1 criteria adapted to a study where there is no residual disease at study entry will be applied for determination of nodal lesions to constitute local, regional or distant relapse. Any lesion of non-squamous origin is considered a second primary cancer. In case of a second primary cancer, DFS data collection should continue as per SoA (Table 2, Table 4, and Table 5), regardless of start of new anticancer therapy.

Good clinical judgment must be used when deciding whether a biopsy is required. If any of the following conditions are met, a biopsy must be done, unless medically contraindicated or medical risk of biopsy deemed too high:

- New lesions on imaging or clinical exam
- Suspicious mucosal changes
- Newly enlarged, regional lymph nodes on clinical exam or imaging
- Areas of unexplained new PET positive FDG-uptake

If a biopsy is not performed a rationale must be entered in the eCRF.

8.1.4 Endpoint Assessment by IRC

An IRC will perform an independent assessment based on all efficacy imaging reading together with central independent review of histopathology. DFS supplementary 2 analyses (Table 19) will use the IRC data for the purpose of significance testing with regards to demonstrate the hypothetical isolated treatment effect as assessed by an IRC, which is implemented to minimize the assessment bias. Further sensitivity analyses will evaluate the robustness of the DFS main analysis with regards to the assessor of DFS.

Hence, all study imaging performed, including any off-schedule imaging, and all histopathological materials should be submitted to the designated vendor(s) promptly after acquisition.

Further details will be described in the Imaging Charter, the Independent Review Charter and histopathology guidelines provided for this study.

8.1.5 Quality of Life

HRQL outcomes are relevant to SCCHN patients, and improvements in their QOL is a significant unmet need. SCCHN can directly affect HRQL due to several side effects of treatment and disease (Liao 2019). All SCCHN patients have to endure QOL limiting surgery and/or very burdensome medical treatments. Surgery is associated with severe negative impact on patients' lives, often resulting in long-term pain, impairment of social functioning and severe depression (Hernandez-Vila 2016). Nonsurgical treatments, especially platinum-based CRT, are extremely difficult for patients to endure, due to extensive negative side effects (Oun 2018). Thus, improvement in therapy to enhance treatment outcomes without generating incremental detriment to patients' QOL must be priorities in the advancement of SCCHN therapy.

Multiple PRO instruments have been used in clinical research to capture different aspects of the disease burden. A systematic literature review of QOL measures in SCCHN performed between 1990 and 2010 identified 57 different disease-specific HRQL measures, another publication has counted a total of 250 different questionnaires which have been used within this indication with varying degrees of specificity including measures which assess individual symptoms such as swallowing (Ojo 2012). The EORTC QLQ-HN35 used in conjunction with the corresponding core cancer module (EORTC QLQ-C30) emerged as the most frequently used instrument for a prospective assessment of HRQL in head and neck cancer patients (Ojo 2012) and have been selected as most relevant for this study population. In addition, the PGIS and PGIC will be included. The PGIS provides a method for classifying participants' perception of overall symptom severity and the PGIC provides a method for classifying participants' perception of overall symptom change over a specified time period, both can be used in exploratory and psychometric analysis.

The FDA has identified symptomatic AEs as a critical component to patient focused drug development. Among the recommendations, systematic assessment of symptomatic AEs by the patient can increase understanding of the patient experience while on treatment and complement clinician reporting (Kluetz 2016). The NCI has created a patient-reported outcomes version of the CTCAE to assess the patient perspective on symptomatic AEs (PRO CTCAE). The PRO CTCAE is a patient-reported measure that ascertains in real time the frequency, severity, interference, and presence/absence of symptomatic toxicities that can be meaningfully reported from the patient perspective. Research indicates the psychometric properties including validity, reliability, responsiveness, and test-retest reliability, are acceptable.

The proposed combination of HRQL instruments is informed by the purpose of capturing both potential treatment-specific, cancer-specific and SCCHN-specific dimensions through nonpreference-based questionnaires as well as the preference-based EQ-5D-5L to inform health economic modeling for health state utility estimates.

Participants should read and complete the PRO instrument independently. All PRO assessments should be completed by the participants as indicated in the SoA. Whenever possible, the PRO

assessments will be completed prior to administration of study intervention. The CRO and the Sponsor will review compliance rates on a regular basis. PROs will not be reviewed or used to inform care decisions nor for safety purposes.

Whenever possible and as appropriate, the PRO instruments should be completed in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-HN35, PGIS, PGIC, patient perception of side effects (Item Library Q168), and PRO CTCAE.

The following will be administered electronically:

EQ-5D-5L

The EQ-5D-5L is a 6-item instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system (5 items) and a single item EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the participant's self-rated health on a vertical VAS. The EQ-5D-5L has 5 response categories: no problems, slight problems, moderate problems, severe problems, and extreme problems. The participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. The responses to each of the 5 dimensions (ranging from 1 to 5) are summarized into a 5-digit profile, which can be converted into a preference-weighted index value and is a key component for discussions with access decision makers.

EORTC QLQ-C30

The EORTC QLQ-C30 is a cancer-specific health-related QOL questionnaire that has been widely used in clinical studies (Kluetz 2016) consisting of 5 function domains and 8 symptoms for a total of 30 items. Development and validation of the EORTC QLQ-C30 has been well documented as a reliable and valid measure of QOL in cancer patients (Aaronson 1993) with widespread use in Europe and the US.

EORTC QLQ-HN35

The EORTC QLQ-HN35 is a disease-specific module capturing HRQL dimensions that affect head and neck cancer patients specifically. It is composed of 7 symptom scales, 6 symptom items, and 5 dummy (yes/no) items (use of painkillers, use of nutritional supplements, use of feeding tube, weight decrease, weight increase), for a total of 35 items. Large international samples (N = 662) indicate the reliability and validity of the instrument (Bjordal 2000).

PGIS

The PGIS is a single, global item assessing the participant's perception of overall symptom severity, using a 5-point scale from "none" to "very severe." The PGIS provides a method for classifying participants as having improved, declined, or not having changed for use in exploratory and psychometric analysis, and to evaluate the sensitivity and responsiveness of individual symptom items and interpret scores on the PRO instruments.

PGIC

The PGIC is a single, global item assessing the participant's perception of overall symptom change. Participants will rate how their symptoms have changed since treatment initiation, using a 5-point scale from "much worse" to "much better." The PGIC provides a method for classifying participants as having much better, much worse, or unchanged symptoms over a particular time interval for use in exploratory and psychometric analysis, and to evaluate the sensitivity and responsiveness of individual symptom items and interpret scores on the PRO instruments.

Frequency of Assessment: EQ-5D-5L

- At the start of each cycle starting with Cycle 1: C1D1, C2D1, C3D1, C4D1, C5D1, C6D1
- At EOT visit
- At 12-month follow-up visit
- At 24-month follow-up visit
- At 36-month follow-up visit
- At 48-month follow-up visit
- At 60-month follow-up visit
- Within 7 days of entering OS follow-up due to DFS event

Frequency of Assessment: EORTC QLQ-C30, EORTC QLQ-HN35, and PGIS

- At C1D1
- At C4D1
- At EOT visit
- At 12-month follow-up visit
- At 24-month follow-up visit
- At 36-month follow-up visit
- At 48-month follow-up visit
- At 60-month follow-up visit
- Within 7 days of entering OS follow-up due to DFS event

Frequency of Assessment: EORTC QLQ-C30 (Short), EORTC QLQ-HN35 (Short) and PGIS

Patients with LA SCCHN consistently indicate head and neck pain, swallowing, speech, fatigue, and sensory problems are impacted by chemoradiotherapy (Curran 2007, Driessen 2018, Bottomley 2014). Trends indicate some symptoms, such as head and neck pain and swallowing, improve in the short term, but then return to baseline following treatment (Driessen 2018). Given the potential variation in symptom experience over the course of treatment, more frequent

assessment of key symptoms will be obtained. Head and neck pain (4 items), swallowing (4 items), speech (3 items), fatigue (3 items), global health status (2 items) and physical function (4 items), will comprise the EORTC QLQ-C30 (short), QLQ-HN35 (short) for a total of 20 items and be assessed at the following timepoints along with the PGIS:

- At C2D1
- At C6D1
- At 9-month follow-up visit

Frequency of Assessment: PGIC

- At the 12-month follow-up visit

Patient Perception of Side Effects (Item Library Q168)

The EORTC provides an item library from which sponsors can select specific items that address gaps not addressed in the established measures. In order to provide an overall picture of treatment side effects, participants will be asked to what extent they have been troubled by side effects from not at all to very much.

PRO CTCAE

PRO CTCAE consists of 124 items representing 78 symptomatic toxicities and has been validated in more than 30 languages. The measure is intended to serve as a complement to the CTCAE used for standard reporting in an effort to more accurately reflect the patient experience. CCI

Frequency of Assessment: Patient Perception of Side Effects (Item Library Q168) and PRO CTCAE

- At C1D1
- Weekly starting with C1D8 through C6D15
- At EOT visit

The measurement intervals of all questionnaires represent the appropriate balance between allowing a comprehensive HRQL assessment of a first-in-class compound across all the dimensions included in the proposed questionnaires, a focused assessment of key symptoms, and the burden created for the targeted patient population by administering these questionnaires at the different time points (and the implied risk of nullifying the analysis due to excessive missing data).

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.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver, spleen, and pancreas) as well as the head, mouth, and neck area.
- Investigators will pay special attention to clinical signs related to previous serious illnesses and AEs requiring a dose modification (Section 6.5).
- Investigators will report findings including late onset AESIs (Section 8.3.7) in the irradiated areas during the DFS and OS FU periods.

8.2.2 Vital Signs

- Blood pressure and participant's position, pulse, respiratory rate, temperature and location of measurement, weight, and height (at Baseline only) will be measured and recorded according to the SoA (Section 1.3).
- 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 15.

Table 15 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 h postdose[b]
Cycle 1	8	predose[a] 0.5-4 h postdose[b]

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

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 8):

- The treatment with xevinapant/ placebo must be interrupted.

- The participant will be monitored including assessment of electrolytes in plasma (potassium calcium and magnesium), treated appropriately and closely followed (ECGs at least 3 times per week) until resolution to within 30 ms from baseline or QTcF < 480 ms.
- Stop any concomitant medication known to cause QTc prolongation.
- The participant will be referred to a cardiologist.
- The Medical Monitor will be consulted prior to administering further xevinapant / placebo doses.
- If the QTcF interval does not return to within 30 ms of baseline or < 480 ms within 14 days, xevinapant / placebo must be permanently discontinued.

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

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

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 2 at the time points 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). Additional coagulation tests may have to be performed prior to tumor biopsy according to local practice.
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted every 3 weeks (C1D1, C2D1, C3D1, C4D1, C5D1 and C6D1) during study intervention administration, as well as at the EOT visit.
- 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 a central laboratory designated by the Sponsor and by a local laboratory, according to instructions shown in Table 16.
- Local laboratory results are only required when central laboratory results are not available in time for study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make a study intervention decision or

response evaluation, the results will be recorded. Also, on CxD1, laboratory assessments required to evaluate suitability for study intervention administration may be evaluated on basis of local laboratory values. These results will be recorded.

- 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 8. The laboratory reports will be filed with the source documents.

Table 16 Assessments to be Performed by a Central Laboratory or by a Local Laboratory According to Study Visit

Visit	Central Laboratory Designated by the Sponsor	Local Laboratory
During screening	• HIV test if no local results obtained within 2 weeks before ICF signature • HPV status by p16 IHC if no available report and test not available locally (Section 8.2.4.1) • HBV/HCV tests[a] • Blood hematology • Blood biochemistry • Serum pregnancy test • Urinalysis • Coagulation	• Local results within 2 weeks before ICF signature accepted for HIV test • HPV status by p16 IHC if no available report • SARS-CoV-2 PCR and/or antigen test • Retest of abnormal laboratory assessments • Coagulation as required prior to biopsies as per local practice
CxD1	All blood hematology, blood biochemistry assessments (full panel) and urinalysis[b] mentioned in Appendix 2.	Laboratory assessments required to evaluate suitability for study intervention administration: eGFR, platelet counts, ANC, hemoglobin, ALT, AST, urine pregnancy test (pregnancy test at C1D1, C2D1, C3D1, C4D1, C5D1, C6D1 and EOT).
All visits after randomization, except CxD1	Blood hematology, blood biochemistry (minimum panel), and urinalysis[b] assessments (Appendix 2), to be performed according to schedule presented in Table 1 and Table 2.	Urine pregnancy test, when applicable. Coagulation as required prior to biopsies as per local practice.

ALT=alanine transaminase, ANC=absolute neutrophil count, AST=aspartate aminotransferase, CxDx=Cycle x Day x, eGFR=estimated glomerular filtration rate, IHC=immunohistochemistry, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HPV=human papillomavirus.

a: Interpretation of HBV/HCV tests results will be further clarified in the Laboratory Manual.

b: Dipsticks provided by central laboratory; test done locally. In case of abnormal result, microscopic evaluation at central laboratory. For screening and EOT visit, urinalysis (dipstick and microscopic evaluation) done at central laboratory

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].

- Results obtained prior to the participant's consent to participation in the study are acceptable, provided a report is available. If no report is available for HPV status by p16 IHC, the assessment can be done locally on an archived tumor sample.
- If the site is not able to perform HPV testing by p16 IHC, it will be evaluated by a central pathology laboratory designated by the Sponsor. In this case, randomization into the study can only occur after confirmation of HPV status has been communicated to the site.
- 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 External Data Monitoring Committee

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

8.2.6 Patient Diary

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

On days of PK sampling C1D1, C1D2, C1D8, C2D2, C2D8, C4D1, C5D1, and C6D1 participants must take their doses at the hospital, where the administration of xevinapant / placebo 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 (at home) prior to xevinapant PK collection (i.e. at C1D7, C2D1, C2D7) needs to be recorded in the participant's diary and reported in the eCRF. On days of PK sampling, at C3D8 xevinapant / placebo is taken at home, and the time of last dosing prior to PK sample (C3D8) must be recorded both in the eCRF and the patient's diary.

The treatment schedule of xevinapant or the matched placebo is presented in Table 1, Table 2, and Table 3. Participants will be instructed by the medical staff on how to self-administer xevinapant/matched placebo 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 1. They will be instructed on how to record xevinapant/matched placebo administration (i.e. date and time of the xevinapant/matched placebo 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.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and a SAE are in Appendix 8. The on treatment and late onset AEs of special interest are defined in Section 8.3.7.
- The Investigator and any qualified designees (e.g. Sub-Investigators) 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 SAEs and AESIs 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 8.
- All AEs and SAEs will be collected from the signing of the ICF until the FU28 visit or until the start of next line anticancer therapy, whichever occurs earlier. Late onset AESIs (Section 8.3.7.2) and related SAE will be collected until completion of study at the time points specified in the SoA (Section 1.3) and for AESIs further detailed in Section 8.3.7. 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 8. 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. See Appendix 12 for specific requirements in India.
- 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 his or her 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 8.

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 8.

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 8.

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 towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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 Sub-Investigator 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 review the safety reports and confirm completion of this review. This information will be filed it 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.

For details on SAE reporting, see Appendix 8. See Appendix 12 for specific requirements in India.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 6 months after the last administration of study intervention.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of awareness of pregnancy of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).
- 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 pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. 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 poststudy 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 pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be discontinued from 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 the underlying study disease (SCCHN) and can be serious/life-threatening:

- Recurrence 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 a SAE. These events will be recorded as part of the primary endpoint.

However, the event will be recorded and reported as an AE/SAE (instead of a DRE) as defined in Appendix 8.

8.3.7 Adverse Events of Special Interest

For this study, AESI(s) include the following as described in the Sections 8.3.7.1 and 8.3.7.2. The reporting of AESIs is specified in Appendix 8 and details on criteria and events are in Appendix 10**.**

Based on emerging safety data collected during the study, 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 are encouraged to consult the latest version of the Investigator's Brochure when assessing the need to report an AESI.

All AESIs will be followed up until resolution or stabilization (see Section 8.3.2.).

The site of monitoring during Treatment Period and DFS Follow-up Visits will be in-person/clinic/hospital visits. OS Follow-up visits may be conducted remotely (e.g. by telephone calls) if possible (see Table 1, Table 2, Table 4, and Table 5 for visit schedules). For participants who enter the OS FU earlier than 28 months after start of treatment (e.g. due to PD), the site of monitoring will be in person/clinic/hospital visits up to 28 months after start of treatment or until start of next line of anticancer therapy, whichever occurs earlier.

8.3.7.1 AESIs During the Treatment Period

CCI [redacted]

[redacted]

Reporting of such events as AESI according to the criteria mentioned above will not have any impact on the reporting requirements for other AESIs, SAEs, or SUSARs as defined elsewhere in this protocol.

8.3.7.2 Late Onset AESIs During the Follow-up Period (After FU28 Visit up to EOS Visit)

[redacted]

8.4 Pharmacokinetics

- The following PK parameter will be calculated, when appropriate:

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

Whole blood samples of approximately 2 mL per collection for measurement of plasma concentrations of xevinapant (including its metabolite(s)). Collection times are specified in the SoA. The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration.

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

Randomization codes will be kept confidential and maintained blinded to the Investigators/site personnel, CRO and Sponsor team until the database is locked for primary analysis. However, randomization codes will be disclosed to the third-party laboratory in charge of bioanalytical assays (xevinapant and its metabolite(s)) PK assessments) to prevent analyses of placebo participants' samples and allow PK samples analysis within the samples' stability period and external DMC review.

CCI

CCI

CCI

[redacted]

8.7 Immunogenicity Assessments

Not applicable.

8.8 Medical Resource Utilization and Health Economics

HRU in SCCHN is limited. To generate robust economic information for payers, HRU data collection is included for descriptive purposes. Such data will be used for cost-effectiveness estimations and budget impact analysis of xevinapant to inform commercial payers and HTA

agencies globally. A feasibility study was conducted to ensure the item selection and wording in the study eCRF for the purposes of HRU research was appropriate (Gandola 2021). The HRU variable collection will focus on, but will not be limited to:

- Number of hospitalizations by cause
- Length of hospital stay
- Number of emergency department visits
- Number of stays in intensive care units
- Length of hospital stay in intensive care units
- Number of surgical reconstructions
- Number of subsequent systemic cancer treatments
- Number of participants using feeding tube
- Duration of feeding tube use
- Number of speech/language therapy visits
- Number of swallowing therapy visits
- Number of dental care visits

9 Statistical Considerations

The study will be considered positive if the primary null hypothesis H_0^{DFS} as specified in Section 9.1.1 is rejected (see also Table 19, Table 21, Table 22, Figure 6, and Section 9.4.4).

9.1 Statistical Hypotheses

Only the hypotheses for the primary objective DFS (Section 9.1.1) and the secondary objective OS (Section 9.1.2) are formally tested for statistical significance in a hierarchical testing procedure as outlined in Section 9.4.4. Other statistical tests, confidence intervals and corresponding p-values are provided for exploratory purposes only.

9.1.1 Primary Objective DFS

The hypotheses to demonstrate superiority for the primary endpoint DFS comparing Arm A and B are:

$$H_0^{DFS}: \lambda_A^{DFS}(t) = \theta\lambda_B^{DFS}(t), \theta \geq 1 \text{ versus } H_1^{DFS}: \lambda_A^{DFS}(t) = \theta\lambda_B^{DFS}(t), \theta < 1,$$

where $\lambda^{DFS}(\mathrm{t})$ represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment arms corresponding to the hazard ratio of DFS.

9.1.2 Secondary Objective OS

The hypotheses to demonstrate superiority for the secondary endpoint OS comparing arm A and B are:

$$H_0^{OS}: \lambda_A^{OS}(t) = \theta\lambda_B^{OS}(t), \theta \geq 1 \text{ versus } H_1^{OS}: \lambda_A^{OS}(t) = \theta\lambda_B^{OS}(t), \theta < 1,$$

where λ^{OS}(t) represents the hazard at time t and θ the unknown constant of proportionality of hazards in the treatment arms corresponding to the hazard ratio of OS.

9.2 Sample Size Determination

A total of approximately 700 participants will be randomly assigned to study intervention. The primary DFS analysis to demonstrate superiority of Arm A compared to Arm B is planned when 409 events for the DFS main analysis are reached.

CCI [redacted]


CCI


CCI


CCI


CCI


CCI

9.3 Analyses Sets

The analysis sets are specified below.

Analysis Set	Description
SCR	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
FAS	The FAS will include all randomized participants.
SAF	All participants, who were administered any dose of any study intervention.
PK	All participants, who receive at least one dose of xevinapant, have no relevant protocol deviations or important events affecting PK, and provide at least one measurable postdose concentration.

FAS=full analysis set, PK=pharmacokinetics, SAF=safety analysis set, SCR=screening analysis set.

9.4 Statistical Analyses

Analysis of all data will be performed by the Sponsor or its designee. The results of all study parts will be reported in the clinical study report. Details of the analyses of efficacy, safety, PK, and HRQOL will be presented in the Integrated Analysis Plan, which will be finalized before the database is locked for analysis.

To provide overall estimates of treatment effects, data will be pooled across study centers. The factor 'center' will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of participants randomized at each center.

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. All safety and efficacy endpoints will be summarized by treatment arm.

9.4.1 Efficacy Analyses

All analyses on efficacy endpoints are primarily done on the FAS. Participants will be analyzed according to the treatment assigned at randomization as per the ITT principle.

Details on the analyses for primary and key secondary efficacy estimands are shown in Table 19.

Table 19 Further Details on Statistical Analysis of Efficacy Estimands Beyond Estimands Attribute Specifications in Section 3

Estimand		
Reference #	**Category**	**Statistical Analysis**
Primary		
1 - DFS	Main	**Endpoint:** DFS as assessed by Investigator **Population-Level Summary:** DFS between the 2 study intervention groups will be compared using a one-sided stratified log rank test controlling for a one-sided type I error of 2.5% (see also Section 9.4.4). The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval, estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.
	Sensitivity 1	**Rationale:** Evaluate robustness of treatment effect towards IWRS strata (as used for randomization) and corresponding eCRF variable(s) **Sensitivity Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Use strata from eCRF instead of IWRS
	Sensitivity 2	**Rationale:** Evaluate proportionality of hazards, i.e. whether ratio of hazards is constant over time **Sensitivity Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** • Hazard ratios and confidence intervals from Cox model with piecewise treatment effect • Graphical assessment of residuals from main estimand
	Sensitivity 3	**Rationale:** Evaluate robustness of treatment effect with regard to assessor of DFS **Sensitivity Analysis:** Estimand as defined for main analysis, except for the following change: **Endpoint:** DFS as assessed by IRC according to the same definition as for main estimand
	Sensitivity 4	**Rationale:** Evaluation of the scientific question whether the drug improves DFS irrespective of subsequent anticancer therapy or long time-gap between DFS assessments (pure ITT analysis) **Sensitivity Analysis:** Estimand as defined for main analysis, except for the following changes: **Endpoint:** Use all DFS events regardless of the time since last evaluable assessment or randomization.
	Supplementary 1	**Rationale:** Evaluation of the isolated effect with the study intervention **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Intercurrent Event Strategy:**

Estimand		
Reference #	**Category**	**Statistical Analysis**
		Use the hypothetical strategy for the intercurrent event 'Start of subsequent anticancer therapy', i.e. participants who started subsequent anticancer therapy prior to a DFS event will be censored on the date of the last adequate assessment prior to start of subsequent anticancer therapy
	Supplementary 2	**Rationale:** Evaluation of the hypothetical isolated effect with the study intervention while relying on DFS as assessed by IRC. The corresponding test will be alpha-controlled if main analysis test confirms a significant treatment arm difference for DFS (see also Section 9.4.4). **Supplementary Analysis:** Estimand as defined for main analysis, except for the following changes: **Endpoint:** DFS as assessed by IRC. **Intercurrent Event Strategy:** Use the hypothetical strategy for the intercurrent event 'Start of subsequent anticancer therapy', i.e. participants who started subsequent anticancer therapy prior to a DFS event will be censored on the date of the last adequate assessment prior to start of subsequent anticancer therapy
	Supplementary 3	**Rationale:** Evaluation of the time to local relapse and time to distant metastases as subtypes events for of DFS endpoint while considering the competing risk of death. **Supplementary Analysis:** Estimand as defined for main analysis, except for the following changes: **Population-Level Summary:** Cumulative incidence of both local relapse and distant metastasis over time between the two study intervention groups will be compared in terms of the cause-specific hazard taking the competing risk of death prior relapse into account, including confidence interval, estimated by means of a cause-specific proportional hazards model (multistage approach). Stacked cumulative incidence functions by arm and cause based on a proportional hazards model on the cause-specific hazards will be plotted. Ties will be handled by replacing the proportional hazards model by the discrete logistic model. Further analyses (e.g. subgroup analyses) will be specified in the Integrated Analysis Plan.
	Supplementary 4	**Rationale**: Evaluate treatment effect when adjusting for selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Multivariable Cox regression analysis will be carried out to adjust the treatment effect for relevant baseline factors of potential prognostic impact. The Cox's Proportional Hazard model is defined as: $h(t) = h(0;t) \exp(Xb)$, where $h(0;t)$ defines the baseline hazard function and X defines the vector of explanatory variables and b the unknown vector of regression parameters. The hazard ratios of all selected explanatory variables (note: source should be the clinical database, and not IWRS) and of the treatment effect will be reported including 2-sided 95% confidence intervals. The following baseline variables will be candidates for covariates to be included in the model, in addition to the randomization strata and the treatment effect:

Estimand		
Reference #	**Category**	**Statistical Analysis**
		• Age • Sex • Tumor Stage prior surgery • ECOG PS at baseline • Other Final list of covariates according to the analysis plan. No interactions will be considered.
	Supplementary 5	**Rationale:** Explore interaction of treatment effect and selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Separately for each covariate (as listed in the analysis plan): Interaction derived from unstratified Cox model including treatment effect, baseline covariate, and their interaction Wald-Test
	Supplementary 6	**Rationale:** Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level summary:** Separately for each subgroup level (of baseline variables as listed in the analysis plan, e.g. age, sex, race, ethnicity, and tumor site): Treatment effect based on unstratified Cox model using treatment group as only covariate
Secondary		
2 - OS	Main	**Population-Level Summary:** OS between the two study intervention groups will be compared using a one-sided stratified logrank test controlling for a one-sided type I error of 2.5% in a group-sequential design (see also Table 21, if and only if DFS null hypotheses were rejected. The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval (both adjusted and unadjusted), estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.
	Sensitivity 1	**Rationale:** Evaluate robustness of treatment effect towards IWRS strata (as used for randomization) and corresponding eCRF variable(s) **Sensitivity Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Use strata from eCRF instead of IWRS.
	Supplementary 1	**Rationale:** Explore interaction of treatment effect and selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Separately for each covariate (as listed in the analysis plan):

Estimand		
Reference #	**Category**	**Statistical Analysis**
		Interaction derived from unstratified Cox model including treatment effect, baseline covariate, and their interaction Wald-Test.
	Supplementary 2	**Rationale:** Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level Summary:** Separately for each subgroup level (of baseline variables as listed in the analysis plan, e.g. age, sex, race, ethnicity, tumor site): Treatment effect based on unstratified Cox model using treatment group as only covariate.
3 – Time to subsequent anticancer treatments	Main	**Population-Level Summary:** The treatment effect will be evaluated in terms of the hazard ratio, including confidence interval (both adjusted and unadjusted), estimated by means of a Cox proportional hazards model, stratified by the randomization strata. Randomization strata will be taken as specified and documented in the IWRS and each stratum will define a separate baseline hazard function. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.
	Supplementary	**Rationale:** Explore homogeneity of treatment effect across subgroups defined by selected baseline covariates **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Population-Level summary:** Separately for each subgroup level (of baseline variables as listed in the analysis plan): Treatment effect based on unstratified Cox model using treatment group as only covariate
5 - HRQOL	Main	**Population-Level Summary:** Difference of least squared mean change from baseline based on mixed model for repeated measurements (MMRM) adjusting for randomization strata.
	Supplementary 1	**Rationale:** explore the proportion of disease-free who at least maintain or regain their baseline level for each treatment group at assessments after completion of investigational therapy. **Supplementary Analysis:** Estimand as defined for main analysis, except for the following change: **Endpoint:** As main analysis but considering only assessments after treatment discontinuation prior to recurrence of disease or death **Intercurrent Event Strategy:** The endpoint will be analyzed if none of the following intercurrent events occurred before the time point of interest • Objective disease recurrence: while disease-free strategy • Death: while alive strategy **Population-Level summary:** Proportion of patients who, maintained, or improved compared to baseline on the basis of prespecified criteria at each assessment
Further secondary and exploratory efficacy estimands		

Estimand		
Reference #	Category	Statistical Analysis
		Further exploratory efficacy estimands will be specified in the Integrated Analysis Plan finalized before database lock.

eCRF=electronic case report form, DFS=disease-free survival, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EORTC=European Organization for Research and Treatment of Cancer, EQ=EuroQOL, HRQOL=health-related quality of life, IRC=Independent Review Committee, ITT=intention-to-treat, IWRS=interactive web response system, MMRM=mixed effect model for repeated measures, OS=overall survival, QOL=quality of life, RT=radiotherapy, VAS=visual analog scale.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis set. Analyses will consider participants as actually treated, i.e. received at least one dose of xevinapant vs. received no dose of xevinapant.

Safety endpoints include AEs, clinical laboratory assessments, vital signs, ECG parameters, and ECOG PS. Table 20 provides more details on safety analyses.

Table 20 Statistical Analysis Methods for Safety Endpoints

Estimand Ref #	Statistical Analysis Methods
4 - Safety	Safety will be analyzed on the Safety (SAF) population and will be based on all safety analysis reporting outcomes like AEs, AESIs and laboratory tests outcomes. The safety endpoints will be tabulated using descriptive statistics. Safety will also be tabulated by subgroups. The incidence of AEs which includes AESIs, regardless of attribution, will be summarized by Preferred Term and System Organ Class for each treatment arm, and described in terms of severity according to CTCAE v5 grades and relationship to treatment. Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009). Further details will be provided in the Integrated Analysis Plan.

AE=adverse event, AESI=adverse events of special interest, CTCAE=Common Terminology Criteria for Adverse Events.

9.4.3 Other Analyses

Details on the PK, pharmacogenomics, and biomarker exploratory analyses will be in the Integrated Analysis Plan that will be finalized before database lock.

Pharmacokinetic concentrations of xevinapant and metabolite D-1143-MET1 (in plasma) will be listed by visit/timepoint. In addition, PK data from this study will be pooled with data from other xevinapant studies, as appropriate, for further analysis via modeling and simulation e.g. population PK and exposure-response analyses for efficacy and safety; the details of which will be provided in a separate analysis plan to be finalized before database lock. Integrated PK analyses across studies, will be presented separately from the main clinical study report.

9.4.4 Sequence of Analyses

Regular external DMC safety review meetings are planned after 12 participants have been randomized, treated, and followed up until the end of the combination therapy period and will be held every 4 months during recruitment thereafter and twice a year after recruitment has been completed if not otherwise requested earlier by the Sponsor or the external DMC. The external DMC will also take into consideration available PK data when assessing safety. The planned efficacy and futility analyses are shown in Table 21 and corresponding operating characteristics in Table 22.

Table 21 Planned Efficacy Analyses and Expected Timing

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

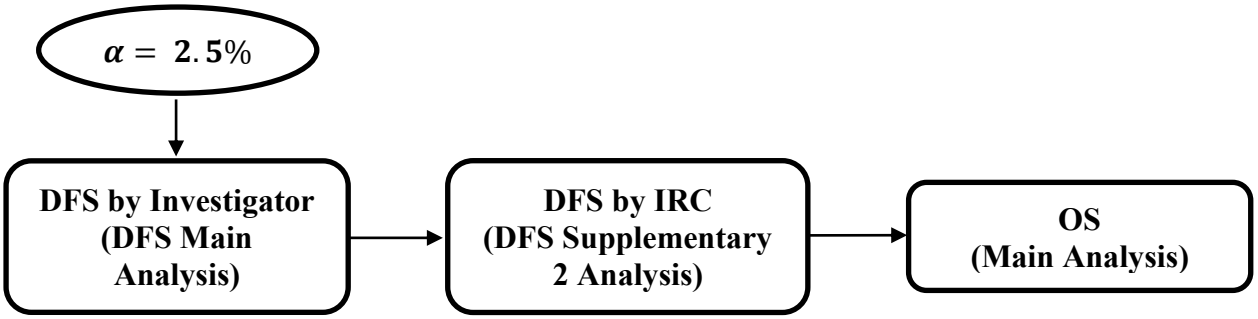
DFS=disease-free survival, OS=overall survival, IF=information fraction, IA=interim analysis, PA=primary analysis, FPI=date of first participant randomized.

a Projections based on assumptions as per Section 9.2.
b OS IA1 is conducted on same data set (and data cut-off date) as DFS PA.
c OS PA is conducted at the earlier of reaching the planned number of events or end of study (Section 4.4).

As shown in Figure 6, a fixed-sequence strategy is used to test first the null hypothesis H_0^{DFS} (Section 9.1.1) at 1-sided alpha of 2.5% while planning for a total number of 409 DFS events as assessed by Investigator in the DFS main analysis, which uses Investigator assessment and the treatment-policy strategy for the intercurrent event 'Start of subsequent anticancer therapy'. If and only if H_0^{DFS} can be rejected in the main analysis, the full alpha is reallocated to test H_0^{DFS} according to 'DFS supplementary 2' analysis as specified in Table 19 on the same data set,

which uses the IRC assessment and hypothetical strategy for the intercurrent event 'Start of subsequent anticancer therapy' (i.e. censoring on the date of the last adequate assessment prior to start of subsequent anticancer therapy). If and only if that second test rejects H_0^{DFS}, the null hypothesis H_0^{OS} (Section 9.1) is confirmatory tested in a group-sequential design with interim analyses as planned in Table 21, which uses alpha-spending according to Lan-DeMets with O'Brian-Fleming-like boundaries planning for a total number of 495 OS events at primary analysis. That procedure achieves a strong control of the FWER at 2.5% one-sided according to Glimm (2010). Table 22 shows the operating characteristics and decision boundaries for the confirmatory interim and primary analyses as planned.

Figure 6 **Fixed-Sequence Strategy to Control FWER at 2.5% 1-Sided, where the Arrows Indicate the Alpha Reallocation Applied if the Originating Test Rejects its Null Hypothesis Otherwise Confirmatory Testing is Discontinued**



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

Thus, the hierarchical (alpha-controlled) testing strategy is as follows:

- Primary testing: DFS as assessed by Investigator (DFS Main Analysis according to Table 19)
- Secondary testing: DFS as assessed by IRC (DFS Supplementary Analysis 2 according to Table 19)
- Tertiary testing: OS (Main Analysis according to Table 19)

CCI

CCI

DFS primary analysis is event driven. The first OS interim analysis will be combined by using data from the same data cut-off date when the planned number of DFS events (Table 21) is reached for DFS PA. In case H_0^{DFS} is rejected at DFS PA and alpha can be reallocated to test H_0^{OS} without stopping at OS IA1, the second OS interim analysis will be conducted when the planned number of OS events (Table 21) is reached. The primary OS analysis is latest conducted (if H_0^{OS} could not be rejected before and study did not stop for futility on OS) on all data collected until the end of the study with all OS events collected even if the planned 495 OS events are not reached (but the total of the so far not used alpha will be considered for calculation of the efficacy boundaries at that stage to control FWER at 2.5%). Since the observed number of events at interim analyses may not be exactly equal to the planned number of events, the efficacy boundaries will be updated based on the actual number of observed events using if applicable the prespecified alpha-spending functions to maintain the control of the FWER. The final analysis will be conducted on all data collected until the end of study.

Pooled and blinded efficacy data will be used for event projections to allow for in-time preparation of the efficacy analyses according to the planned event numbers in Table 21. The cut-off date will be the date on which approximately the planned number of events are expected in the FAS based on the latest event projection, if the approximate event number can be confirmed by a blinded data review meeting before (partially) locking the data base.

Continuous cleaning is implemented throughout the conduct of the clinical study for all participant data collected, though an extra cleaning period is foreseen according to the external DMC Charter and other relevant documents for each external DMC review as well as all analyses listed in Table 21. In particular, the high-quality expectation for regulatory filing is provided on all dimensions of collected participant data at all prespecified efficacy interim analyses.

10 References

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI 1993;85(5):365-76.

Ahn MJ, D'Cruz A, Vermorken JB, et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review. Oral Oncol 2016;53:10-6

AJCC Cancer Staging Manual, Springer Ver[la]g, 8th ed. 2017, Table of Contents.

Alvarado-Munoz JF, Falco A, Morales AR, et al. Platinum ineligibility in squamous cell carcinoma of the head and neck: consensus from Central America and the Caribbean. Future Oncol 2021;1963-1971. Epub

Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23:2166-72.

Bernier J, Domenge C, Ozsahin M, et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. N Engl J Med 2004;359:1945-52.

Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer 2000;36:1796-807.

Bottomley A, Tridello G, Coens C, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. Cancer 2014;120(3):390-8.

Bourhis J, Sun X, Le Tourneau C, et al. 3-Years follow-up results of double-blind randomized phase II comparing concurrent high-dose cisplatin chemo-radiation plus Debio 1143 (xevinapant) or placebo in high-risk patients with locally advanced squamous cell carcinoma of the head and neck. Ann Oncol 2020;31(S4):S1168. Abstract.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394-424.

Brouwer CL, Steenbakkers RJ, Bourhis J, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol 2015;117(1):83-90.

Chen SY, Massa S, Mazul AL, et al. The association of smoking and outcomes in HPV-positive oropharyngeal cancer: A systematic review. Am J Otolaryngol 2020;41:1-7. Epub.

Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937-44.

Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clinical Trials. 2009 Oct;6(5):430-40.

Curis, Inc. United States securities and exchange commission Form 10-K. Transition report pursuant to section 13 or 15(d) of the securities exchange Act of 1934. Washington, D.C, December 31, 2014.

Curran D, Giralt J, Paul M et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007;25:2191-7.

Denaro N, Merlano MC, Russi EG. Follow-up in Head and Neck Cancer: Do More Does It Mean Do Better? A Systematic Review and Our Proposal Based on Our Experience. Clin Exp Otorhinolaryngol 2016;9(4):287-97.

Driessen CML, Groenewoud JMM, de Boer JP, et al. Quality of life of patients with locally advanced head and neck cancer treated with induction chemotherapy followed by cisplatin-containing chemoradiotherapy in the Dutch CONDOR study: a randomized controlled trial. Support Care Cancer 2018;26:1233-42.

Du E, Mazul AL, Farquhar D, et al. Long-term Survival in Head and Neck Cancer: Impact of Site, Stage, Smoking, and Human Papillomavirus Status. Laryngoscope 2019;129(11):Epub.

CCI [redacted]

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228-47.

Elad S. The MASCC/ISOO Mucositis Guidelines 2019 Update: introduction to the first set of articles. Support Care Cancer 2019;27:3929-31.

Gandola AE, Orfanos P, Ait Sarkouh R, et al. Healthcare resource utilization (HRU) survey to inform HRU data collection alongside the double blinded TrilynX study evaluating xevinapant in combination with chemoradiotherapy versus placebo plus chemoradiotherapy in patients with previously untreated locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). ISPOR, Europe 2021, Poster.

Ghosh-Laskar S, Yathiraj PH, Dutta D, et al. Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: Long-term results. Head Neck 2016;38:E1481-7.

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2010;29:219-28.

Gregoire V, Eisbruch A, Hamoir M et al. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol 2006;79(1):15-20.

Harari PM, Harris J, Kies MS et al. Postoperative chemotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation therapy oncology Group RTOG-0234.J Clin Oncol 2014; 32(32):2486-95.

Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1255-60.

Hernandez-Vila C. Current prognosis and quality of life following surgical treatment for head and neck squamous cell carcinoma. Plast Aesthet Res 2016;3:203-10.

Horio M, Imai E, Yasuda Y, et al. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis 2010;56(1):32-8

Horwich P, Gundale A, Patin S, et al. Impact of smoking on stage-specific survival in human papilloma virus-associated oropharyngeal squamous cell carcinoma. Head Neck 2021;43(9):2698-704.

Iglesias Docampo LC, Arrazubi Arrula V, Baste Rotllan N, et al. SEOM clinical guidelines for the treatment of head and neck cancer (2017). Clin Transl Oncol 2018;20(1):75-83.

Jellema AP, Slotman BJ, Doornaert P, et al. Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007;69(3):751-60.

Kluetz PG, Slagle A, Papadopoulos EJ, et al. Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms. Clin Cancer Res 2016;22(7):1553-8.

Lambin P, Ramaekers BLT, van Mastrigt GAPG, et al. Erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. Cochrane Database Syst Rev 2009;3:CD006158:1-27.

Liao LJ, Hsu WL, Lo WC, et al. Health-related quality of life and utility in head and neck cancer survivors. BMC Cancer 2019;19(1):425. Epub.

Machiels J-P, Leemans CR, Golusinski W, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Anns of Oncology 2020;31(11):1462-75.

Marta GN, Saad ED. Assessment of quality of life in phase III trials of radiotherapy in localized or locally advanced head and neck cancer over the past 17 years. Ann Palliat Med 2017;6(1):73-80.

Marur S and Burtness B. Oropharyngeal squamous cell carcinoma treatment: current standards and future directions. Curr Opin Oncol 2014;26(3):252-8.

Matzinger O, Viertl D, Tsoutsou P, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, in TNFα-mediated in head and neck squamous cell carcinoma. Radiother Oncol 2015;116:495-503.

CCI [redacted]

Michiels S, Le Maître A, Buyse M, et al. Surrogate endpoints for overall survival in locally advanced head and neck cancer: meta-analyses of individual patient data. Lancet Oncol 2009;10:341-50.

Mita MM, LoRusso PM, Papadopoulos KP, et al. A Phase I Study of ASTX660, an Antagonist of Inhibitors of Apoptosis Proteins, in Adults with Advanced Cancers or Lymphoma. Clin Cancer Res 2020;26(12):2819-26.

CCI

NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 3.2021.

Nicholson DW. From bench to clinic with apoptosis-based therapeutic agents. Nature 2000;407:810-6.

Ojo B, Genden EM, Teng MS, et al. A systematic review of head and neck cancer quality of life assessment instruments. Oral Oncol 2012;48(10):923-37.

Oun R, Moussa YE , Wheate NJ . The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans 2018;47:6645-53.

Perri F, Longo F, Caponigro F, et al. Management of HPV-Related Squamous Cell Carcinoma of the Head and Neck: Pitfalls and Caveat. Cancers (Basel) 2020;12:975. Epub.

Peterson DE, Boers-Doets CB, Bensadoun RJ, et al. ESMO Guidelines Committee. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015;26:(S5):v139-51.

Pignon JP, Maitre AL, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.

Porceddu SV, Scotte F, Aapro M, et al. Treating patients with locally advanced squamous cell carcinoma of the head and neck unsuitable to receive cisplatin-based therapy. Front Oncol 2020;9:1522.

Radiologists. The timely delivery of radical radiotherapy: guidelines for the management of unscheduled treatment interruptions. Fourth edition. Clin Oncol (R Coll Radiol) 2019;1-37.

CCI

Schwartz LH, Litiere S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132-7.

Serova M, Raballand AT, Albert S, et al. Effects of Debio 1143, a novel oral IAP inhibitor, in monotherapy and in combination with platinum drugs in human SCCHN tumor specimens. In: Proceedings of t^{he} 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2014;74(19):Abstract.

Sun XS, Tao Y, Le Tourneau C, et al. Debio 1143 and high-dose cisplatin chemoradiotherapy in high-risk locoregionally advanced squamous cell carcinoma of the head and neck: a double-blind, multicentre, randomised, phase 2 study. Lancet Oncol 2020;21:1173-87.

Tamm I, Kornblau SM, Segall H, et al. Expression and prognostic significance of IAP-family genes in human cancers and myeloid leukemias. Clin Cancer Res 2000;6(5):1796-803.

Tao Z, McCall NS, Wiedemann N, et al. SMAC Mimetic Debio 1143 and Ablative Radiation Therapy Synergize to Enhance Antitumor Immunity against Lung Cancer. Clin Cancer Res 2019;25(3):1113-1124.

The R Project for Statistical Computing. The R Foundation. https://www.r-project.org/. Accessed October 2023.

Tolcher AW, Bendell JC, Papadopoulos KP, et al. A Phase I Dose-Escalation Study Evaluating the Safety Tolerability and Pharmacokinetics of CUDC-427, a Potent, Oral, Monovalent IAP Antagonist, in Patients with Refractory Solid Tumors. Clin Cancer Res 2016;22(18):4567-73.

Vermorken JB, Kapteijn TS, Hart AAM, et al Ototoxicity of cis-diamminedichloroplatinum (II): Influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol 1983;19 (1):53-58

Ward GA, Lewis EJ, Ahn JS, et al. ASTX660, a Novel Non-peptidomimetic Antagonist of cIAP1/2 and XIAP, Potently Induces TNFα-Dependent Apoptosis in Cancer Cell Lines and Inhibits Tumor Growth. Mol Cancer Ther 2018;17(7):Epub.

CCI [redacted]

WHO Guidelines for the Pharmacological and Radiotherapeutic management of cancer pain in adults and adolescents, 2018.

11 Appendices

Appendix 1 Abbreviations

^{18}F-FDG-PET	2-deoxy-2- [fluorine-18] fluoro-D-glucose positron emission tomography
ADR	adverse drug reaction
AESI	adverse events of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
Bpm	beats per minute
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CrCl	creatinine clearance
CRO	contract research organization
CRT	chemoradiotherapy
CT	computed tomography
CCI	[redacted]
CTV	clinical target volume
CxDx	cycle x day x
DDI	drug-drug interaction
DFS	disease-free survival
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECE	extra-capsular extension
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EORTC QLQ-C30	European Organization for research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ-HN35	European Organization for research and Treatment of Cancer Quality of Life Head and Neck Module
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQOL 5 Dimension 5 Level Health-Related Quality of Life Measure
ESMO	European Society for Medical Oncology
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded

FPI	date of first participant randomized
FU	follow-up
FWER	family-wise error rate
GCP	good clinical practice
GI	gastroinstestinal
GTV	gross tumor volume
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotrophin
HCP	healthcare practitioner
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HRQoL/HRQL	health-related quality of life
HRU	health resource utilization
IA	interim analysis
IAP	inhibitor of apoptosis proteins
IB	Investigator's Brochure
ICF	informed consent form
ICRU	International Commission on Radiation Units
IEC	Independent Ethics Committee
IF	information fraction
IGRT	image guided radiation therapy
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IMRT	intensity modulated radiation therapy
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intention-to-treat
IV	intravenous
IWRS	interactive web response system
LA SCCHN	locally advanced squamous cell carcinoma of the head and neck

LRC	locoregional control
MMRM	mixed effect model for repeated measures
MoA	mechanism of action
MRI	magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NIMP	noninvestigational medicinal product
OPC	oropharynx
OS	overall survival
PA	primary analysis
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity Scale
PK	pharmacokinetics
PRO	patient-reported outcomes
PRO CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PT	preferred term
PTV	planning target volumes
PTVeval	planned target volume evaluation
QA	Quality Assurance
QoL	quality of life
QTcF	QTc using Fridericia's formula
QTL	quality tolerance limits
RECIST	Response Evaluation Criteria in Solid Tumors
RT	radiotherapy
SAD	short axis diameter
SAE	serious adverse event
SAF	safety analysis set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SCCHN	squamous cell carcinoma of the head and neck
SIB	simultaneous integrated boost

SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse events
TEN	toxic epidermal necrolysis
ULN	upper limit of normal
VAS	visual analog scale
VMAT	volumetric modulated arc therapy
WOCBP	women of childbearing potential
wk(s)	week(s)

Appendix 2 Clinical Laboratory Tests

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

Laboratory Assessments	Parameters			
Blood Hematology	Platelet count Hemoglobin Hematocrit Erythrocytes (RBC)		Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH)	White blood cell count (absolute/%) with differential • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Blood Biochemistry[1] (full panel)	Blood urea nitrogen/ urea Creatinine Glucose C reactive protein Uric acid	Potassium Sodium Calcium Magnesium Amylase Albumin Lipase	Aspartate aminotransferase[1] Alanine aminotransferase[1] Alkaline phosphatase[2] Phosphate	Bilirubin (total) (if > ULN: direct bilirubin as well) Protein (total) eGFR (calculated)
Blood Biochemistry[1] (minimum panel)	Blood urea nitrogen / urea Creatinine Amylase	Potassium Sodium Magnesium Lipase	Aspartate aminotransferase[1] Alanine aminotransferase[1] Alkaline phosphatase[2]	Bilirubin (total) (if > ULN: direct bilirubin as well)
Notes: [1] 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. [2] If alkaline phosphatase is elevated, consider measuring the alkaline phosphatase isoenzymes.				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, leukocytes by dipstick • Microscopic examination (only at Screening and End of Treatment, at other visits only if blood or protein is abnormal).			
Coagulation	• Prothrombin Intl. Normalized Ratio, if applicable (e.g. under oral anticoagulation medication) • Activated partial thromboplastin time • Fibrinogen			
Other Screening Tests	• Follicle Stimulating Hormone (for females, as needed, if not WOCBP). • Serum hCG pregnancy test (as needed for a WOCBP) during screening, local urine test thereafter. • HBsAg and HBcAb (see Appendix 12 for specific requirements in Japan). • HCV-antibody and HCV-RNA by PCR.			

Laboratory Assessments	Parameters
	• HIV 1/2 antibodies. • HPV status by p16 IHC • SARS-CoV-2 (RNA by PCR and/or antigen test) (see Section 5.2 when test is applicable)
All study-required laboratory assessments will be performed by a central laboratory, except for the laboratory tests to confirm eligibility for treatment on CxD1 which may be obtained locally (eGFR, platelet counts, absolute neutrophil count, hemoglobin, alanine transferase, aspartate aminotransferase, urine pregnancy test [pregnancy test at C1D1, C2D1, C3D1, C4D1, C5D1, C6D1 and EOT]). See Section 8.2.4 for further instructions.	

Appendix 3 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 #7 "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 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. However, all procedures related to the primary endpoint (clinical and radiological evaluations as listed in Section 8.1) should be performed at the study site.
- 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 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 4 Contraception and Barrier Requirements

Definitions:

WOCBP:

A woman 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 study intervention, 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 female 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 female on HRT and whose menopausal status are in doubt will be required to use one 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 WOCBP 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 the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

- Male or female 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, except for Japan (for details see Appendix 12).

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 (male or female 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, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure from friction).

Appendix 5 G8 Questionnaire

G8 Questionnaire		
	Items	**Possible Answers (Score)**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0: severe decrease in food intake
		1: moderate decrease in food intake
		2: no decrease in food intake
B	Weight loss during the last 3 months	0: weight loss > 3 kg
		1: does not know
		2: weight loss between 1 and 3 kgs
		3: no weight loss
C	Mobility	0: bed or chair bound
		1: able to get out of bed/chair but does not go out
		2: goes out
E	Neuropsychological problems	0: severe dementia or depression
		1: mild dementia or depression
		2: no psychological problems
F	Body Mass Index (BMI [weight in kg] / (height in m^2)	0: BMI < 19
		1: BMI = 19 to BMI < 21
		2: BMI = 21 to BMI < 23
		3: BMI = 23 and > 23
H	Takes more than 3 medications per day	0: yes
		1: no
P	In comparison with other people of the same age, how does the patient consider his/her health status?	0: not as good
		0.5: does not know
		1: as good
		2: better
	Age	0: > 85
		1: 80-85
		2: < 80
	TOTAL SCORE	**0 – 17**

Source: Bellera 2012.

Appendix 6 Study Governance

Financial Disclosure

Investigators and Sub-Investigators 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; HIPAA 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 re-consented 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 his/her 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 in the US, Canada, Europe, Latin America, 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, ePRO, IRT, imaging, and CDMO.

Drug supply and distribution are handled via CDMO including regional depots.

Details of structures and associated procedures will be defined in a separate Operations Manual.

External Data Monitoring Committee

An external DMC will be formed in this study before the randomization of the first participant and will assess the safety, PK and efficacy during the study (see Section 8.2.5 for details). The external DMC will consist of expert members who are independent of the Sponsor. The members will be appointed by the Sponsor based on their expertise in clinical studies, biostatistics, clinical pharmacology, and oncology. Members will not be investigators in the study, nor will they have any conflict of interest with the Sponsor.

The responsibilities of the external DMC include:

- Performing a safety review after 12 participants have been randomized, treated, and followed up until the end of the combination therapy period and hereafter every 4 months during recruitment and twice a year after recruitment has been completed if not otherwise requested earlier by the Sponsor or the external DMC.
- Minimizing the exposure of participants to an unsafe therapy or dose.
- Making recommendations for changes in study processes where appropriate.
- Advising on the need for dose adjustments because of safety issues.
- Endorsing continuation of the study.

- Review available PK exposure and safety data in participants ineligible for high-dose cisplatin, including participants with moderate renal impairment.

At any time during the study when the external DMC recommends major changes, these recommendations will be presented to the SSC. Further details on the objectives, roles and responsibilities, operational procedures, data outputs and data review are described in a separate external DMC Charter.

RT-QA Review Center

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

- Reviewing and approving IMRT plan(s) before starting the first fraction administration to ensure IMRT requirements compliance
- Approving the dosimetry planning before IMRT start
- Confirming IMRT treatment delivery as per the approved planning and evaluate any critical/major deviations from the submitted plan

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.

Independent Review Committee

The IRC will perform a blinded central review of histopathology and radiological imaging of all participants. Details of structures and associated procedures will be defined in a separate Imaging Charter, Independent Review Charter and histopathology guidelines.

Study Steering Committee

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

In particular, the SSC will be mainly responsible for:

- Periodic review of the progress of the study.
- Determining if amendments to the protocol or changes to study conduct are required.
- Monitoring the overall conduct of the study, ensuring that it follows the standards set out in the GCP guidelines.
- Reviewing the recommendations of the external DMC and/or other study committees and suggesting appropriate action to the Sponsor.

- Monitoring the progress of study and deciding on appropriate action in order to maximize the chances of completing it within the agreed timelines.

Additional responsibilities include but are not limited to:

- Approving proposed protocol amendments.

Details on the membership and responsibilities of the SSC are described in the SSC Charter.

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

  For studies with Japanese sites, the Japanese ministerial ordinance on GCP

  Applicable laws and regulations

- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- For studies with Japanese sites, the Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.
- 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 his or her 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 and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participant. The Sponsor takes out insurance to fulfill the responsibility.

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 for DFS, 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 for OS will be reported in a CSR addendum, if applicable.
- Posting of data on ClinicalTrials.gov, EudraCT, 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 eCRFs 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 eCRF. Details for managing eCRFs are in the Operations Manual.
- For PRO data (e.g. QOL and pain assessments), ePRO will be used.
- The Investigator will maintain accurate documentation (source data) that supports the information in the eCRF.
- 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.
- QTLs will be predefined and documented in the Integrated Project Management 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 (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 Monitoring 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 eCRF 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, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

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 eCRFs.
- Data recorded on eCRFs 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 or a record retainer designated by the Head of the study site ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the Clinical Monitoring Plan.

Study and Site Start and Closure

The study start date is when the first participant signs the ICF.

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.

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 7 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Applied to Adjuvant Studies of Squamous Cell Carcinoma of the Head and Neck

The following text was derived from Eisenhauer (2009) and Schwartz (2016). It has been adapted to apply to surgically excised head and neck cancer where no macroscopic residual disease is expected at Screening.

DEFINITIONS

Relapse in resected SCCHN may be local, regional, or as distant metastasis or a combination of these. The term relapse is used below to cover both possibilities, although sites will need to differentiate between locoregional relapse "new lesions local" or "new regional nodes" and distant metastasis "new lesions distant" on the eCRF.

Relapse will be evaluated in this study using an approach for relapse adapted from the international criteria of the RECIST Committee (Version 1.1). As absence of macroscopic residual disease is an inclusion criterion for such studies, participants will not have measurable disease at study entry; there will be no target or non-target lesions at baseline, and the only features to be measured will be normal lymph nodes, which need only to be measured retrospectively if enlargement is suspected. Therefore, many of the usual components of RECIST assessment will not apply in this study.

Lymph nodes: Lymph nodes do merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Lymph nodes are measured in short axis diameter (SAD) which is the longest measurement perpendicular to the longest diameter of the node, and only the SAD of lymph nodes will be considered. The SAD of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). Nodes that have a SAD < 10 mm are considered nonpathological and should be reviewed and measured retrospectively only if they subsequently become enlarged (≥ 10.0 mm SAD but see relapse criteria below).

IMAGING MODALITIES FOR ASSESSMENT OF RELAPSE

For all suspected disease relapse that is detected clinically (by endoscopy), but is not visible on radiographic imaging, an objective evidence supporting disease relapse must be collected and submitted to IRC. Tissue (biopsy) confirmation of disease is required for all local and regional suspected relapse of disease unless medically contraindicated. Photographs and reports from endoscopy procedure should be collected by the site (if available) and both should be submitted to IRC for central review, including those performed during screening. If biopsy has been performed during screening to exclude presence of residual disease, upon IRC request biopsy reports may be presented to the IRC. Please refer to the Imaging Charter for detailed information.

In addition, the most recent pre-surgery diagnostic/staging CT and/or MRI scans done as a part of SoC should be submitted to the IRC vendor, if available, as well as any recent pre-surgery or baseline PET-CT scan if acquired, to facilitate IRC assessment of any potential macroscopic residual disease at baseline.

- **CT, MRI**

  CT is the best currently available and reproducible method to measure lesions selected for imaging assessment. The same method of assessment and the same technique should be used at baseline and during Follow-up. Imaging based evaluation and/or biopsy should always be done unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination and biopsy.

- **Cytology, histology**

  These techniques can be used to differentiate between relapse, nonmalignant lesions and second (other) primary tumor.

- **FDG-PET scans**

  It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of relapse in the absence of biopsy. Relapse on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Earlier negative FDG-PET, with a later positive FDG-PET sign of PD based on a relapse.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is relapse. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly relapse occurring at that site (if so, the date of relapse will be the date of the initial abnormal FDG-PET scan).

Ultrasound, laparoscopy, and bone scan are modalities that are not allowed to be used to assess relapse in the current study. Lesions detected using these modalities must be confirmed by CT/MRI/PET (However, plain radiography and ultrasound scans may be submitted for biopsy localization only).

RELAPSE CRITERIA

- **New Lesions (non-nodal)**

  The appearance of new malignant lesions denotes disease relapse unless known to be non-squamous. There are no specific criteria for the identification of new radiographic lesions; however, 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.

  Any lesion identified on a follow-up image in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate relapse. If a new lesion is equivocal, for example because of its small size, and biopsy is not possible because it is medically contraindicated or the medical risk of biopsy is assessed as too high, continued observation and

follow-up evaluation will clarify if it represents truly new disease. If the equivocal lesion persists on the follow-up scan and has qualitatively/quantitatively increased in size and/or a second new lesion has developed, this then definitely reflects relapse. If repeat scans confirm there is a new lesion, then relapse should be declared using the date of the initial scan.

- **New nodal lesions**

  For diagnosis of relapse, either biopsy confirmation OR, in the absence of biopsy, at least one node that is ≥ 10 mm in SAD AND has increased by ≥ 5 mm over baseline, is required. Thus, a node that was previously 9 mm in SAD must increase to 14 mm in SAD to be considered diagnostic of relapse in the absence of a positive biopsy. This methodology allows for the 5.0 mm variance in measurement used elsewhere in RECIST.

  Measurements of nodes at baseline and on-study must not be recorded unless they subsequently become enlarged beyond 10 mm in SAD: only the SAD will be measured and may be recorded retrospectively. A small increase in the size of a single node (for example from 9 mm to 10 mm) even if above the size threshold for abnormality, is not automatically considered to be relapse since this falls within the limits of measurement error.

  Lymph nodes identified as possible sites of relapse, when they are measured, should always have the actual SAD measurement recorded (measured in the same anatomical plane as the baseline examination) and compared with that of the same nodes at baseline. Biopsy should be performed, if possible, unless it is medically contraindicated or medical risk of biopsy is assessed as too high; alternatively continued follow-up is advised until relapse is unequivocal. The date of relapse will be the date on which the node first met the 10 mm SAD criterion.

  Nodes that are 'too small to measure': While on-study, all nodes that later become enlarged (≥ 10.0 mm SAD) should have their actual measurements recorded, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes may be so faint on CT scan at some timepoints that the radiologist may not feel confident assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the node was not present at Screening, the screening measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false detection of relapse based upon measurement error. However, as mentioned above, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

- **Bone lesions**

  Solitary new bone lesions on bone scan or PET should be confirmed malignant by biopsy if possible, unless biopsy is medically contraindicated or medical risk of biopsy is assessed as too high: at least confirmation by CT/MRI is required. Since there is no residual disease at Screening, new sclerotic bone lesions cannot be considered a treatment healing effect, and hence should considered to be new lesions.

For equivocal findings of relapse (e.g. very small and uncertain new lesions), treatment or observation may continue until the next scheduled assessment or until biopsy confirmation. If at

the next scheduled assessment relapse is confirmed, the date of relapse should be the earlier date when relapse was suspected.

Further details will be in histopathology guidelines and Imaging Charter provided for this study.

Appendix 8 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 (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 are considered clinically significant in the medical and scientific judgment of the Investigator (i.e. not related to progression of underlying disease, but may be leading to study intervention discontinuation). See Appendix 12 for specific requirements in India. • 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 a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a 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. See Appendix 12 for specific requirements in India. • 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 his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3. See Appendix 12 for specific requirements in India.

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).

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 or AESIs.

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 eCRF.
- 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 eCRF 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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a 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 November 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 his or her 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 his/her 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 his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator 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, for reasons not due to disease progression, during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- 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/Sub-Investigator 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 in single center studies in addition to the standard electronic CRF and as a back-up method for an EDC system failure. The 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.

- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- 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 form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the eCRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the eCRF.

Reporting of AESIs

- For a nonserious AESI, the site will complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site will complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

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.


CCI


CCI

Appendix 12 Country-Specific Requirements

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

Japan

5.1 Inclusion Criteria No.9, eGFR calculation

For participants enrolled in Japan, eGFR will be calculated using modified CKD-EPI formula with Japanese Coefficient 0.813 based on national CKD guidelines (Horio 2010). Modified CKD-EPI formula will be used for assessment of ineligibility to cisplatin as well as for safety assessments. See Section 5.1, Inclusion criteria #9 and Table 8.

5.2 Exclusion Criteria No 6, HBV

HBsAb will be tested for participants enrolled in Japan. If HBsAb is positive, quantitate HBV-DNA will be tested. If HBV-DNA is ≥ 20 IU/mL along with HBsAb being positive, the participant will be excluded from the study. See Section 5.2 for Exclusion Criteria.

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

Appendix 4 Contraception and Barrier Requirements

The following highly effective contraception methods are **not** approved in Japan:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation:
  - Injectable

South Korea

5.1 Inclusion criteria No 11, Contraception use – specific requirement in bold and underlined:

WOCBP and male participants using a highly effective contraception method, have to continue using this method until 12 months after the last dose of radiotherapy:

The Investigator confirms that each participant agrees to use appropriate contraception and barriers, if applicable. The contraception, barrier, and pregnancy testing requirements are below.

a. A female participant

- Is not breastfeeding
- Is not pregnant (i.e. has a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention)
- Is not a WOCBP
    - If a WOCBP, 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 4 for the following time periods:

      1. Before the first dose of the study intervention(s), if using hormonal contraception:
          - Has completed at least one 4-week cycle of an oral contraception pill and either had or has begun her 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 study intervention is administered) for at least 12 months, after the last dose of radiotherapy and agree not to donate eggs (ova, oocytes) for reproduction during this period.
      4. Female participants using hormonal contraception must also use a barrier contraception method (preferably male condom) due to potential risk of CYP3A4/5 induction by xevinapant which may reduce hormonal contraception efficacy.

b. A male participant

Agrees to the following during the study intervention period and **for at least 12 months** after the last dose of radiotherapy

- Refrains from donating fresh unwashed semen

PLUS, either

- Abstains from any activity that allows for exposure to ejaculate

OR

Uses a male condom:

- When having sexual intercourse with a WOCBP, who is not currently pregnant, and instructs her to use a highly effective contraceptive method with a failure rate of < 1% per year, as described in Appendix 4 since a condom may break or leak.
- When engaging in any activity that allows for exposure to ejaculate.

France

5.1 Inclusion criteria No 9 - – specific requirement in bold and underlined:

9 Are unfit to receive high-dose cisplatin by meeting one or more of the following criteria:

- eGFR < 60 mL/min /1.73 m^2 (using the CKD-EPI creatinine formula)
- History of hearing impairment, **defined as Grade ≥ 3** audiometric hearing loss or tinnitus **Grade ≥ 3.** An audiogram is not required if one of the other criteria meets unfitness to receive high-dose cisplatin
- Peripheral neuropathy ≥ Grade 2

  If ≥ 70 years, unfit according to G8 questionnaire (Score ≤ 14) or ineligible for cisplatin treatment due to age limit according to national guidelines

India

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

For SAE reporting specific for India, as per the guidance in NDCTR 2019, chapter VI: The Investigator shall report all serious adverse events to the Central Licensing Authority, the sponsor or its representative, who has obtained permission from the Central Licensing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, and the Ethics Committee that accorded approval to the study protocol, according to local regulatory requirements.

Appendix 8 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow- up, and Reporting

All adverse events meeting AE and subsequently SAE definition irrespective of its relatedness/causality need to be reported by the Investigator according to local regulatory requirements.

US

5.1 Inclusion criteria No 9 - – specific requirement in bold and underlined:

9. Are unfit to receive high-dose cisplatin by meeting one or more of the following criteria:

- eGFR < 60 mL/min /1.73 m^2 (using the CKD-EPI creatinine formula).
- History of hearing impairment, defined as Grade ≥ 2 audiometric hearing loss or **tinnitus Grade 3**. An audiogram is not required if one of the other criteria meets unfitness to receive high-dose cisplatin.
- Peripheral neuropathy ≥ Grade 2
- If ≥ 70 years, unfit according to G8 questionnaire (Score ≤ 14) or ineligible for cisplatin treatment due to age limit according to national guidelines.

Appendix 13 Protocol Amendment History

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

Protocol Version 5.0 (25 July 2023)

The main rationale for this protocol amendment is to extend allowed maximum time window between surgery and start of treatment from 8 to 10 weeks, and revise exclusion criterion 13 related to history of prior malignancies.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added text in bold and removed strikethrough text: If biopsy has been performed during screening to exclude presence of residual disease, **upon IRC request** biopsy reports ~~should be also collected and submitted~~ **may be presented** to **the** IRC. Adding text "and except for the urinalysis dipstick tests on CxD1, which will be done locally".	Clarification of IRC process. To clarify who will perform the dipstick tests.
5.1 Inclusion Criteria	To change the allowed window after surgery from 4 – 8 weeks into 4 -10 weeks.	To implement feedback from investigators
5.2 Exclusion Criteria	To update exclusion criterion #13 as follows: 13. History of another malignancy prior to randomization, with the following exceptions: • 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. • Prior malignancy treated with curative intent and no relapse and no anti-cancer treatment within the last 3 years and does not have potential to interfere with the safety or efficacy assessments of the study.	To implement feedback from investigators
6.5.2.2 Treatment	To update text in line with exclusion criterion 13 into and addition of recommendation: Initiation of radiotherapy must start 4 to 10 weeks after surgery on C1D1 of xevinapant / placebo. If possible, it is recommended to start treatment within 8 weeks from surgery.	To implement feedback from investigators
8.2.4 Clinical Safety Laboratory Assessments	For the urinalysis dipstick tests, except for screening and EOT, the following was added as a footnote to Table 16:	To clarify who will perform the dipstick tests.

Section # and Name	Description of Change	Brief Rationale
	b: Dipsticks provided by central laboratory; test done locally. In case of abnormal result, microscopic evaluation at central laboratory. For screening and EOT visit, urinalysis (dipstick and microscopic evaluation) done at central laboratory	
PPD	[redacted]	[redacted]

Protocol Version 4.0 (10 May 2023)

The main rationale for this protocol amendment is to integrate the changes from various local amendments into a global amendment, revise the inclusion criterion for ECOG PS to 0-2, harmonize pregnancy testing to a frequency of every 3 weeks, adjust the definition of endpoint and intercurrent event strategy for the secondary objective on HRQOL, recommend dose modifications for eGFR as per TrilynX protocol (Study MS202359_0006 – Phase III study xevinapant and CRT in unresected LA SCCHN) and to resolve some identified discrepancies in the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and Estimands 3 Objectives and Estimands	Adjusted definition of endpoints and intercurrent event strategy of the objective for HRQOL	To align with Health Authority recommendation received and implemented for another study of xevinapant in a similar LA SCCHN setting
1.3 Schedule of Activities	Added text to specify the screening window of 28 days until randomization	For clarity
1.3 Schedule of Activities Appendix 7- Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Applied to Adjuvant Studies of Squamous Cell Carcinoma of the Head and Neck	Added text to clarify that biopsy reports collected during screening, should be submitted to IRC Added text to clarify that endoscopy photographs and reports and biopsy reports collected during screening, should be submitted to IRC	To facilitate IRC assessment of potential macroscopic residual disease at baseline
1.3 Schedule of Activities, Table 1	Deleted the C3D2 visit	To resolve discrepancy
1.3 Schedule of Activities, Table 2	In case of premature treatment discontinuation:	To ensure that all participants are evaluated by the same schedule and for better clarity

Section # and Name	Description of Change	Brief Rationale
	Deleted text “CT/MRI scan to be performed at least 3 months (±2 wks) after ending IMRT”. Added revised text “tumor assessments to be performed according to original schedule (Week 20 for EOT assessment)”	
1.3 Schedule of Activities, Table 4 8.1.1 Radiological Assessment	Deleted text “The DFS FU period starts immediately after EOT visit”. Added revised text “while imaging and clinical tumor assessments will follow original schedule, starting from Month 9" Added text Tumor assessments to be performed according to original schedule regardless of premature treatment discontinuations or treatment delays	
1.3 Schedule of Activities, Table 1 and Table 2, 8.2.4 Clinical Safety Laboratory Assessments, Table 16 Appendix 2	Addition of Pregnancy testing at C2D1, C4D1 and C6D1	To comply with local regulatory requirements for Pregnancy testing the frequency is harmonized and to be conducted every 3 weeks
1.3 Schedule of Activities, Table 4 Text for Survival follow up telephonic visit added at M39 visit	Included Month 39 for telephone follow- up	To ensure consistency across the protocol for 3 monthly follow-up for survival status
1.3 Schedule of Activities, Table 6 Time point for PK sampling to be clarified	Column for Dosing of Xevinapant removed Added time frame for sample collection at C4D1, C5D1 and C6D1	Resolve discrepancy between dosing and PK collection timepoints
4.2-Scientific Rationale for Study Design 5.1-Inclusion Criteria	Deleted text regarding ECOG performance ≥ 2 ECOG status changed from 0-1 to 0-2 and text added to Inclusion criteria #2 “able to tolerate standard of care IMRT treatment according to the Investigator assessment”	To implement a recommendation from regulatory authorities and feedback from investigators
5.1-Inclusion Criteria	Updated Inclusion criteria #9 regarding cisplatin ineligibility criteria: • For Japanese participants, modified CKD-EPI creatinine formula needs to be referred (Appendix 12) • For participants with history of hearing impairment-added text to refer to Appendix 12 for France specific requirements	To align with local requirements

Section # and Name	Description of Change	Brief Rationale
	• For participants ≥ 70 years, unfit according to G8 questionnaire, following text has been added: "or ineligible for cisplatin treatment according to national guidelines"	To align with national guidelines defining participants aged >70 ineligible to cisplatin (i.e. UK)
5.2 Exclusion Criteria	Added the word "Recurrent" in exclusion criteria #4	To clarify the exclusion of participants with recurrent disease in this study
6.5.1.1 Concurrent Administration to IMRT	Deleted text specifying time of drug administration "1 to 4 hours" before IMRT and replaced with text "in the morning"	For operational ease, as specific time of IMRT administration is not being captured
6.5.1.2 Dose Modification, Interruption and Discontinuation of Xevinapant / Placebo Treatment Table 8	Dose modification for eGFR (using the CKD-EPI creatinine formula) after an Adverse Event	To follow updated dose modifications rules from TrilynX (Study MS202359_0006 – Phase III study xevinapant and CRT in unresected LA SCCHN)
6.5.2.2 Treatment	Deletion of text in parenthesis in the sentence "Initiation of radiotherapy must start 4 to 8 weeks after surgery (unless there are healing or logistical concerns) on C1D1 of xevinapant / placebo"	To align with inclusion criteria #3, that participants have received surgery in the past 4 to 8 weeks before start of treatment and to avoid any potential delays
6.8.2 Medications to be Used with Caution with Xevinapant or Placebo Table 11	Added the drug "Lansoprazole"	To add commonly used medication with potential PK interaction with xevinapant
8.2.3 Electrocardiograms	Added text: If QTcF is not automatically measured, it can be calculated separately	For operational ease at sites
Appendix 3-Conduct of the study during COVID-19 Pandemic"	Updated **header and** text in the appendix to make COVID-19 recommendations generic for all countries	Section is applicable to all countries during COVID-19 pandemic
Appendix 7-Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Applied to Adjuvant Studies of Squamous Cell Carcinoma of the Head and Neck	Added text for collection of baseline photographs and reports for endoscopy and biopsy	To facilitate IRC assessment of potential macroscopic residual disease at baseline
Appendix 12-Country-Specific Requirements	Updated to add local requirements from Japan, South Korea, France and India	To align with the various local amendments
	Updated Inclusion Criteria #9 for Japan regarding eGFR	According to local practice guidelines, modified eGFR calculation formula should be used for Japanese participants for more precise evaluation of renal function
	Updated 5.1 Inclusion Criteria #11 for South Korea Contraception requirements	To extend the contraception period to 1 year after radiotherapy treatment as per Korean Health Authority recommendation.

Section # and Name	Description of Change	Brief Rationale
	Updated 5.1 Inclusion Criteria #9 for France History of hearing impairment	As per France Health Authority recommendation
	Updated Regulatory Reporting Requirements for Serious Adverse Events for India	To include the local reporting requirements for serious adverse events as per feedback from the Indian Health Authority.

Protocol Version 3.0 (17 August 2022)

Overall Rationale for the Amendment

The main rationale for this protocol amendment is to provide additional clarification on the cisplatin ineligibility criteria, revised PK sampling, and to remove the ^{18}F-FDG-PET-scan at screening.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Estimands 8.1.3 DFS Events and Definitions	Added clarity regarding date for the primary endpoint: Disease-Free Survival	To clarify that in case of disease recurrence, the earlier date of biopsy collection or imaging is used to confirm a DFS assessment
1.1 Synopsis 3 Objectives and Estimands 9.4.1 Efficacy Analyses (Table 19)	Revised the PRO estimands to focus the evaluation during the on treatment period	To align the PRO objectives with data collection (in particular, to account for missing data expectation)
1.3 Schedule of Activities, Table 1 5.1 Inclusion Criterion #6 5.4 Screen Failures 8.1 Efficacy Assessments and Procedures CCI [redacted]	Removed ^{18}F-FDG-PET scan at screening visit	^{18}F FDG-PET scan soon after major surgery may cause false positive results and causes additional complexity. It is therefore not considered a standard assessment in this setting.

1.3 Schedule of Activities, Table 2	Added notes in the row for blood hematology about requirement of local tests for confirming eligibility for treatment	To ensure consistency across protocol
1.3 Schedule of Activities, Table 2 and Table 6 6.5.1 Xevinapant or Placebo Dosing and Administration 8.2.6 Patient Diary	Adjusted row for collection of additional PK samples at C5D1 and C6D1 in Table 2 In Table 6, added new rows for sample collection at the additional timepoints, C5D1 and C6D1.Also, for timepoint C2D8, window period for postdose sample collection added Added clarification, regarding reporting of time of last dosing prior to PK sample, for PK timepoints C3D8, C4D1, C5D1 and C6D1	To collect information for Population-Pharmacokinetics as per regulatory request
4.2 Scientific rationale for Study Design 5.1 Inclusion criteria 10. References	Added clarification on cisplatin ineligibility criteria with regard to renal clearance, hearing impairment, peripheral neuropathy, ECOG Updated with additional references in rationale	To clarify that participants with an eGFR of 50 to 59 ml/min who are deemed ineligible for any cisplatin treatment based on current clinical practice can be included in this study To clarify that participants with a Grade ≥ 2 audiometric hearing loss or tinnitus, or peripheral neuropathy are ineligible for cisplatin To clarify that participants with ECOG ≥ 2 have a high risk factor for toxicities and are therefore excluded To provide justification for rationale
4.2 Scientific rationale for Study Design	Added text for clarification on R1 resection	To clarify that only participants with microscopically close margin ≤ 1 mm or microscopic positive margin (R1) are included in the study
5.1 Inclusion criteria	Added text for lower limit of eGFR (inclusion criteria # 9) and inclusion criterion# 10 was modified to clarify the interpretation of inclusion criterion #9	To clarify that participants with severe renal impairment should not be included in the study, and therefore they should have an eGFR ≥ 30 mL/min/1.73m²
5.2 Exclusion criteria	Added the word “interventional” in exclusion criteria no.21	To clarify that only participants who took part in an interventional clinical study within 28 days prior to screening or during participation in this study must be excluded from this study
8 Study Assessments and Procedures	Updated text for increase in volume of blood from “55 mL” to “60 mL” for 24- hour period and for “120 mL” to “130 mL” for 4-week period	To update the blood volume for the additional PK samples
8.1 Efficacy Assessments and Procedures	Added requirement of sending diagnostic pre-surgery CT/MRI scan and recent pre-surgery or baseline PET-CT scan, if available, to IRC	To facilitate IRC assessment of any potential macroscopic residual disease at baseline

8.1.1. Radiological Assessment	Added text that the Sponsor may discontinue image transfer to vendor once no further analyses by IRC assessment are planned.	To stop sending images to vendor if no further analyses by IRC assessments are planned.
8.1 2 Clinical Assessment and [redacted]	Added requirement of submitting endoscopy photographs to IRC	For all suspected disease relapse that is detected clinically (by endoscopy), objective evidence supporting disease relapse must be collected and submitted to IRC
8.2.3 Electrocardiograms	Added additional clarification on number of traces in case ECG is abnormal	In case of an abnormal ECG trace, in total 3 traces need to be collected, including the original abnormal trace.
9.4.1 Efficacy Analyses Table 19	Estimand naming and order of supplementary and sensitivity analyses have been changed	As per Health Authority comment
Throughout	Minor editorial and document formatting revisions	Administrative revisions implemented for clarity and consistency. Minor, therefore, have not been summarized

Protocol Version 2.0 (28 April 2022)

Overall Rationale for the Amendment

The main rationale for this protocol amendment is to clarify how the DFS primary endpoint will be assessed for statistical analysis, and to clarify the collection of AEs and AESIs.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 4	Adjusted row to collect AE up to FU28 visit. Added updated section number.	Adjusted for more clarity Table 4 and Table 5 and Section 8.3.7.
1.3 Schedule of Activities, Table 5	Changed "≤ 3 months" into "at least every 3 months". Adjusted row to collect AESI up to EOS. Added updated section number. Added additional information in the notes for collection of AEs for participants who move to OS FU phase early.	To clarify that visits in the EOS period should occur at least every 3 months. Adjusted for more clarity Table 4 and Table 5 and Section 8.3.7. To allow for monitoring of such events during 28 months after treatment as adequate. No collection of AEs after a participant needs next line anticancer treatment since Sponsor would have limited access to participants and their data (participant may change to another study or another hospital).
4.2 Scientific Rationale for Study Design	'DFS as assessed by IRC will be used in an alpha-controlled supplementary analysis': 'centralized independent review' was deleted from sentence.	Consistency across protocol.
5.2 Exclusion Criteria	Exclusion of participants with major surgery changed from 6 weeks to 4 weeks prior to start of study intervention.	4 weeks is considered sufficient for participants to recover from surgery.
6.3.2 Blinding	Added IRC to list of blinded personnel and deleted corresponding paragraph.	In a double-blind study, IRC is no additional measure of blinding.

Section # and Name	Description of Change	Brief Rationale
8.3.7 Adverse Events of Special Interest	Inserted subheadings for each collection period and aligned AESI to be collected in these periods. Adapted list of late onset AESI	Adjusted for more clarity Table 4 and 5 and Section 8.3.7. Since all AEs are collected up to FU28 visit, no need to specify the AESI in the first months of the DFS FU period.
9.4.1 Efficacy Analyses, Table 19	Replaced 'centralized independent review' by 'IRC'; clarification that OS significance testing is conducted only if both DFS hypotheses are rejected.	Consistency across protocol.
9.4.4 Sequence of Analysis	Figure 6 updated to include assessor of DFS. All levels of the hierarchical (alpha-controlled) testing strategy now listed.	Better traceability of the statistical testing procedure.
CCI [redacted]	[redacted]	[redacted]
Appendix 14	Change in name of Medical Responsible	The Medical Responsible for this study has changed.
Throughout	Minor editorial and document formatting revisions	Administrative revisions implemented for clarity and consistency. Minor; therefore, have not been summarized

Appendix 14 Sponsor Signature Page

Study Title:	A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high risk for relapse and are ineligible for high-dose cisplatin
Regulatory Agency Identifying Numbers:	FDA Center for Drug Evaluation and Research, IND: 156735 EudraCT: 2022-001144-18
Clinical Study Protocol Version:	18 October 2023/Version 6.0

I approve the design of the clinical study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	Merck Healthcare KGaA
Address:	Frankfurter Str. 250 64293 Darmstadt, Germany
General Merck Phone Number:	+ 49 6151 720
General Merck Fax Number:	Not applicable

Appendix 15 Coordinating Investigator Signature Page

Study Title:	A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high risk for relapse and are ineligible for high-dose cisplatin
Regulatory Agency Identifying Numbers:	FDA Center for Drug Evaluation and Research, IND: 156735 EudraCT: 2022-001144-18
Clinical Study Protocol Version:	18 October 2023/Version 6.0
Site Number:	101

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.

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function/Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
Fax number:	PPD
E-mail address:	PPD

Appendix 16 Principal Investigator Signature Page

Study Title:	A randomized, double-blind, placebo-controlled, 2-arm Phase III study to assess efficacy and safety of xevinapant and radiotherapy compared to placebo and radiotherapy for demonstrating improvement of disease-free survival in participants with resected squamous cell carcinoma of the head and neck, who are at high risk for relapse and are ineligible for high-dose cisplatin
Regulatory Agency Identifying Numbers:	FDA Center for Drug Evaluation and Research, IND: 156735 EudraCT: 2022-001144-18
Clinical Study Protocol Version:	18 October 2023/Version 6.0
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: