Integrated Analysis Plan

Study Number:	MS202359_0025
Clinical Study Protocol Title:	A Single Arm, Open label, Phase 1b Study of Xevinapant in Combination With Weekly Cisplatin and Intensity-modulated Radiotherapy to Assess Safety and Tolerability in Participants With Locally Advanced Squamous Cell Carcinoma of the Head and Neck, Suitable for Definitive Chemoradiotherapy
Study Phase:	Phase 1b
Merck Compound:	Not applicable
Protocol Version:	27 November 2023/Version 2.0
Integrated Analysis Plan Author:	Function: [redacted] Author(s) / Data Analyst(s): [redacted]
Integrated Analysis Plan Date and Version:	14 March 2025 / Version 2.0
Integrated Analysis Plan Reviewers:	Function / Name: [redacted]

[redacted]

Approval Page

Integrated Analysis Plan: MS202359_0025

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

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

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

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CR	Complete Response
(e)CRF	(electronic) Case Report Form
CRR	Complete Response Rate
CSR	Clinical Study Report
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDMS	Electronic Document Management System
EEA	European Economic Area
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FU	Follow-up
HR	Hazard Ratio / Heart Rate
HRQOL	Health Related Quality of Life
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease or Protocol Deviation / Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response

SAE	Serious Adverse Event
SCR	Screening analysis set
SD	Stable Disease / Standard Deviation
SDTM	Study Data Tabulation Model
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	22Apr2024		NA
2.0	14Mar2025		Add Section 7.1 Overview of Planned Analyses after discontinuation of Xevinapant trials

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the analysis of data collected for protocol MS202359_0025. Results of the analyses described in this IAP will be included in the CSR, except when otherwise stated. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

[redacted]

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

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

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

5 Objectives and Estimands

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

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

6 Overview of Planned Analyses

The following analyses are planned for this trial:

- Safety Monitoring Committee (SMC) analyses

- Primary analysis
- Follow-up analyses to report further efficacy and safety data

6.1 Analyses for SMC meetings

The Safety Monitoring Committee (SMC) will recommend on the continuation, modification or stop of the study based on safety data and available PK and available PD data (only when PK data is reviewed). Once all planned number of participants have been treated for at least 5 weeks (DLT-like assessment period) or have experienced a DLT-like event, a data snapshot will be taken for provision of SMC outputs. There will be no data cut-off applied.

Details of analyses for SMC meetings will be specified in Appendix 1.

6.2 Primary Analysis

This analysis will be the main analysis. All planned analyses identified in the Clinical Study Protocol and in this IAP will be performed and the database is locked for the analysis.

The cut-off for the primary analysis will be when CCI [redacted] meet at least 1 of the following criteria:

- Experience at least 1 DLT-like event, regardless of the administered amount of study intervention/completion in the DLT-like assessment period.
- CCI [redacted] of xevinapant and cisplatin during the DLT-like assessment period and either complete the DLT-like assessment period or discontinue study.

6.3 Follow-up Analysis

An extract of the primary analyses as specified in the TLF table of contents will be done in the follow-up analysis when the End of Study has been reached.

7 Changes to the Planned Analyses in the Clinical Study Protocol

7.1 Overview of Planned Analyses after discontinuation of Xevinapant trials

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

Consequently, the scope of analyses for this study (MS202359_0025) has been reduced. The analyses outlined in Section 6 will not be conducted as originally planned. However, following analyses will be performed instead:

- an analysis for the first SMC with 6 patients,

- an analysis using the primary analysis DBL date of 20-SEP-2024 for a synoptic CSR.

The analyses considered relevant for a synoptic CSR are listed below:

- Study Subject Data:
  - Participant disposition
    - Subject Disposition Status
    - Analysis Sets
  - Enrollment details
  - Demographic Characteristics
  - Medical History
  - Other Baseline characteristics
    - Disease History
  - Previous and Concomitant Medications, Procedures, Follow-up Treatments
    - Previous Medication
    - Concomitant Medication
    - Concurrent Procedures
  - Treatment Compliance and Exposure
    - Duration of Therapy
    - Cumulative Dose, Dose Intensity, Relative Dose Intensity
    - Dose Reductions
    - Therapy Delays
- Safety Data:
  - Display of Adverse Events
    - Overview of Treatment Emergent Adverse Events (TEAEs)
    - Overview of TEAEs Leading to Discontinuation / Dose Reduction of Treatment
    - TEAEs by Primary System Organ Class (SOC) and Preferred Term (PT)
    - Study Intervention Related TEAEs by SOC and PT
    - Serious TEAEs by SOC and PT
    - Non-serious TEAEs by SOC and PT at a Frequency Threshold of 5%
    - TEAEs by Worst Grade, SOC and PT
    - Study Intervention Related TEAEs by Worst Grade, SOC and PT
  - Deaths, Other Serious and Significant Adverse Events

        - Deaths by Primary Reason
        - Listing of Deaths
        - Listing of Serious TEAEs
    - Clinical Laboratory Evaluations
        - Hematology - Summary Statistics over Time
        - Hematology - Shift in Toxicity Grading from Baseline to Highest Grade
        - Biochemistry - Summary Statistics over Time
        - Biochemistry - Shift in Toxicity Grading from Baseline to Highest Grade
    - Other Safety Evaluations
        - Vital Signs Results Summary Statistics Over Time
        - ECG Results - Summary Statistics Over Time
- Subject Data Listings:
    - Discontinued Subjects
    - Protocol Deviations
    - Demographic Data
    - Treatment Compliance and Exposure
    - Efficacy Results Data
    - Listing of TEAEs
    - Individual Laboratory Measurements

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

The Screening analysis set includes all participants who signed the informed consent.

Dose Limiting Toxicity Analysis Set (DLT)

All participants who were administered any dose of any study intervention and meet at least 1 of the following criteria:

- Experienced at least one DLT like event confirmed by the SMC during the DLT like assessment period or for whom the composite ICE strategy led to a DLT like event, regardless of the administered number of doses of study intervention/completion in the DLT like assessment period. ICE strategy is defined as

- Discontinuation/interruption/delay of xevinapant/cisplatin treatment CCI [redacted] in DLT-like assessment period) due to reasons other than treatment-related AE (composite strategy: to be considered as DLT-like event)
- CCI [redacted] during the DLT-like assessment period due to reasons other than treatment-related AE (composite strategy: to be considered a DLT-like event)

- CCI [redacted] of xevinapant and cisplatin during the DLT-like assessment period, regardless of the completion in the DLT-like assessment period.

Full Analysis Set (FAS)/Safety Analysis Set (SAF)

All participants who were administered any dose of any study intervention.

PK Analysis Set (PK)

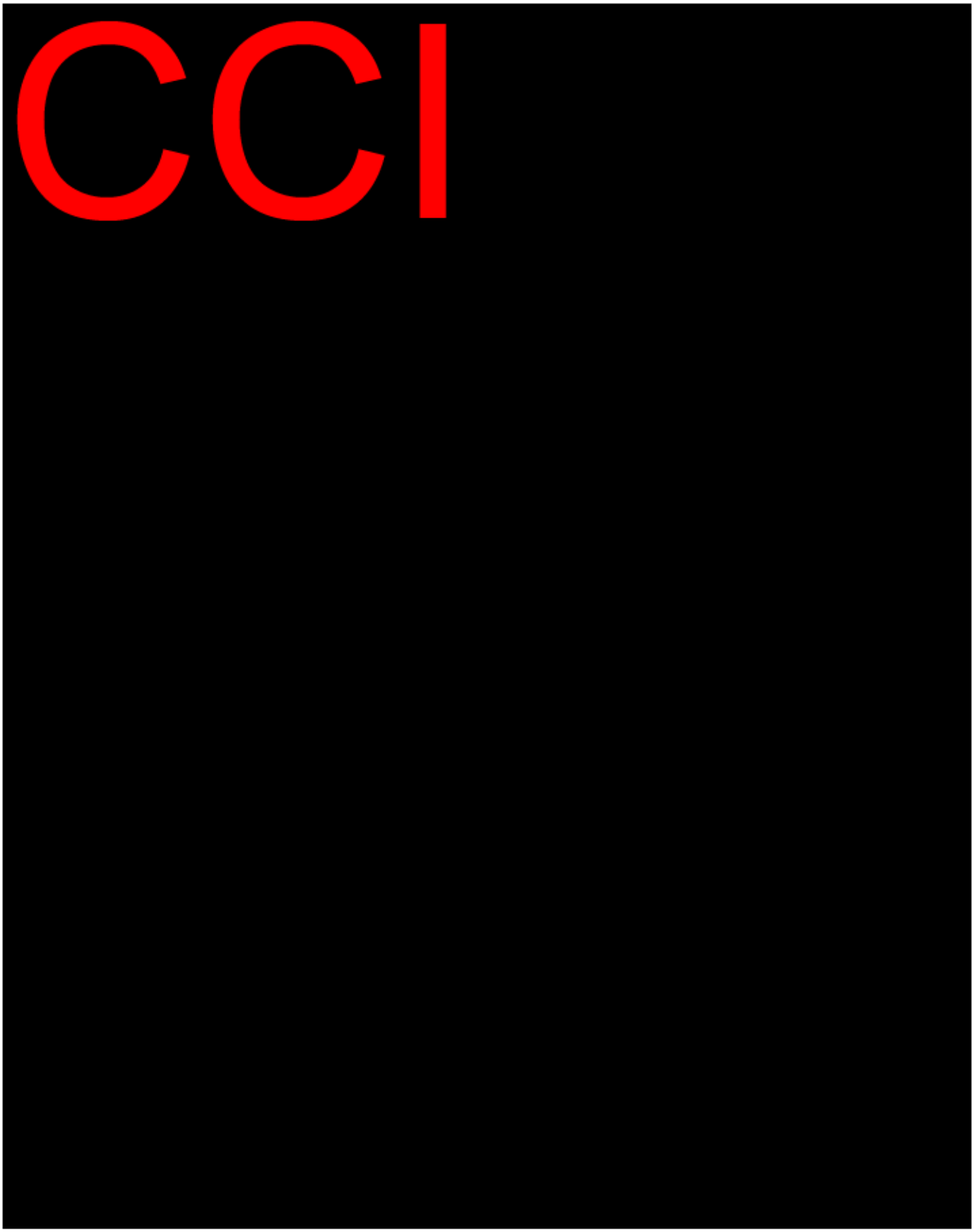
All participants, who receive at least one dose of study intervention, have no relevant protocol deviations or important events affecting PK, and provide at least 1 measurable postdose concentration.

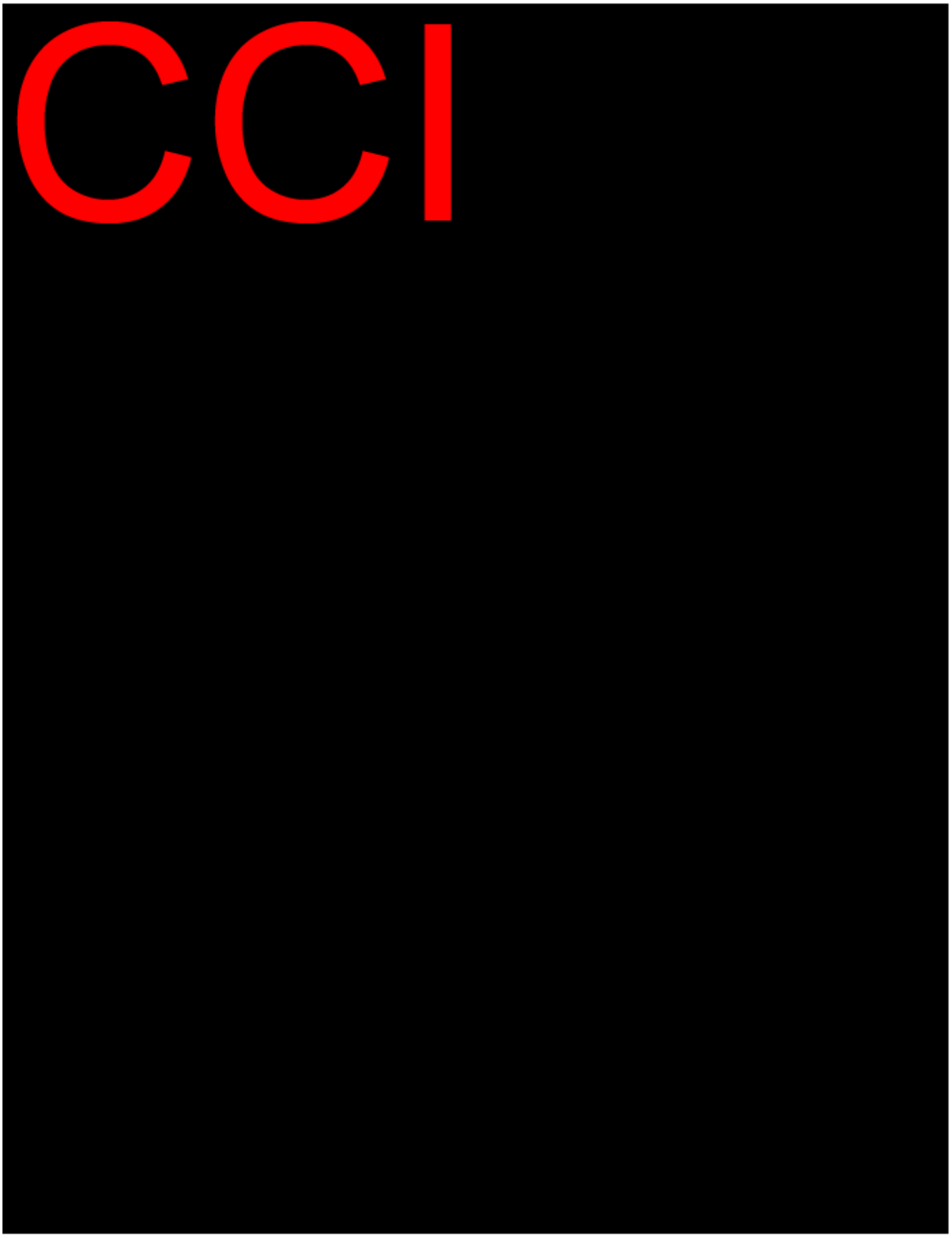
Analyses per Analysis Set

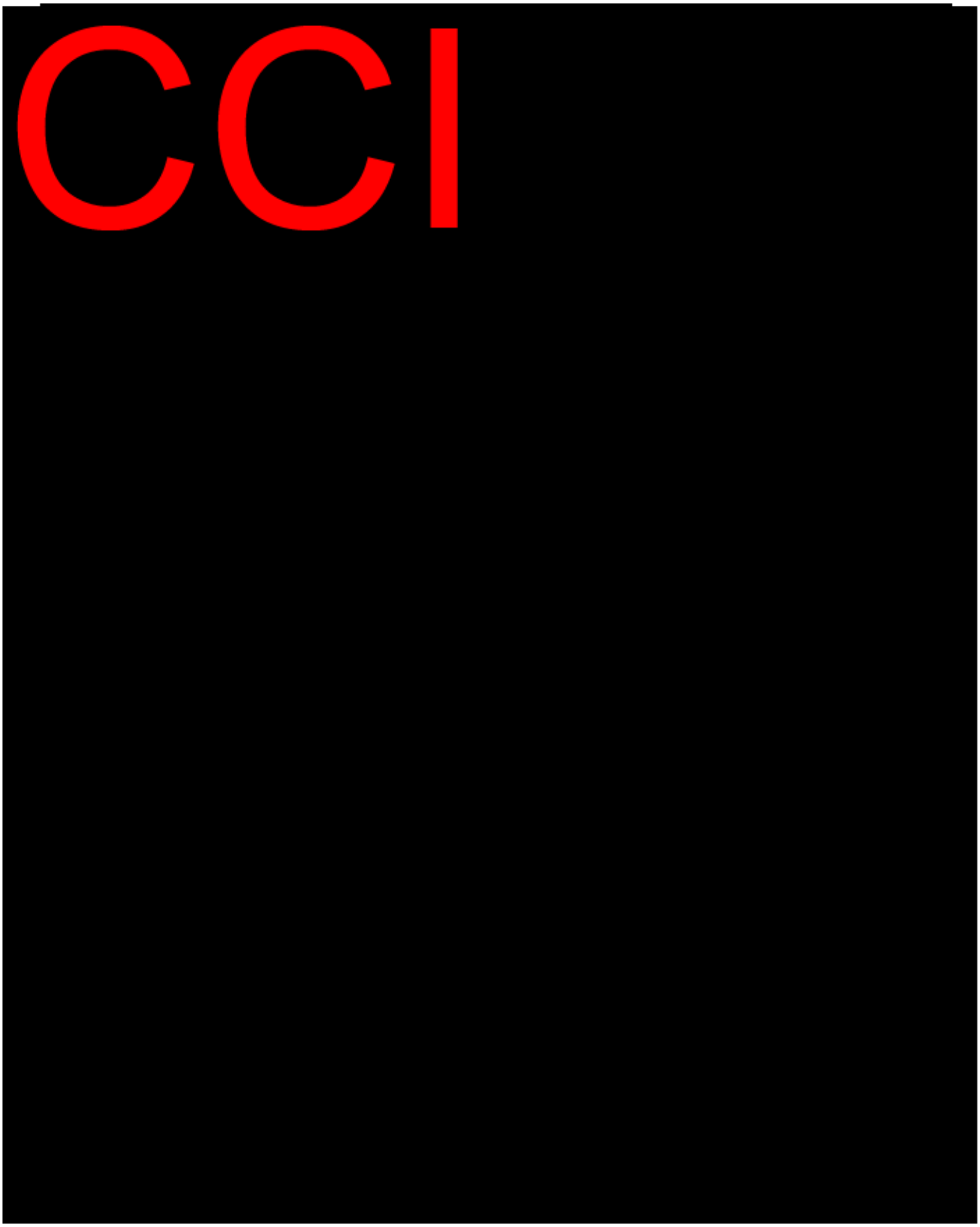
The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set		
Analyses	**FAS/SAF**	**DLT**	**PK**
DLT (tolerability)		✓	
Baseline Characteristics	✓		
Previous and Concomitant Therapies	✓		
Compliance and Exposure	✓		
Efficacy	✓		
Safety	✓		

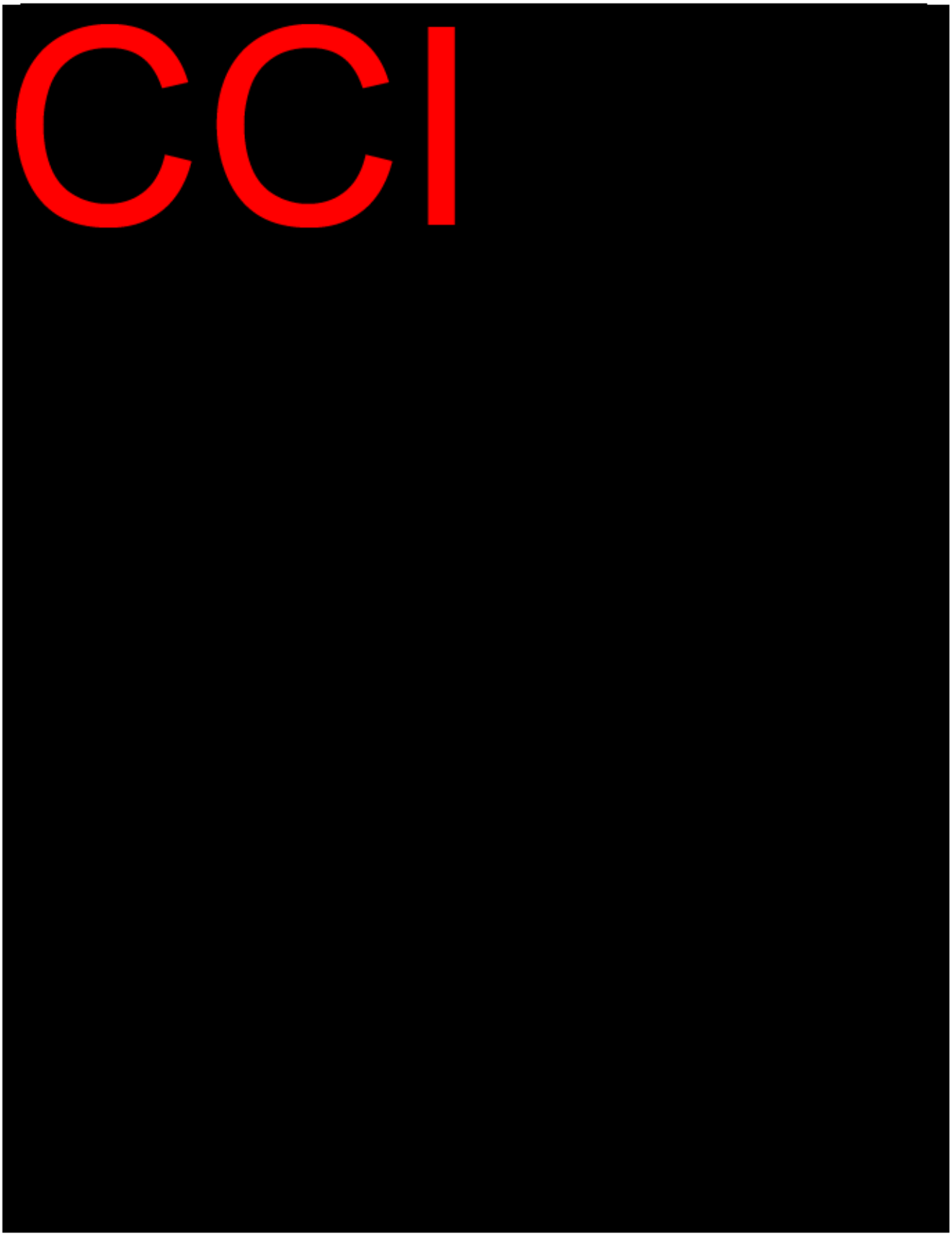
CCI [redacted]

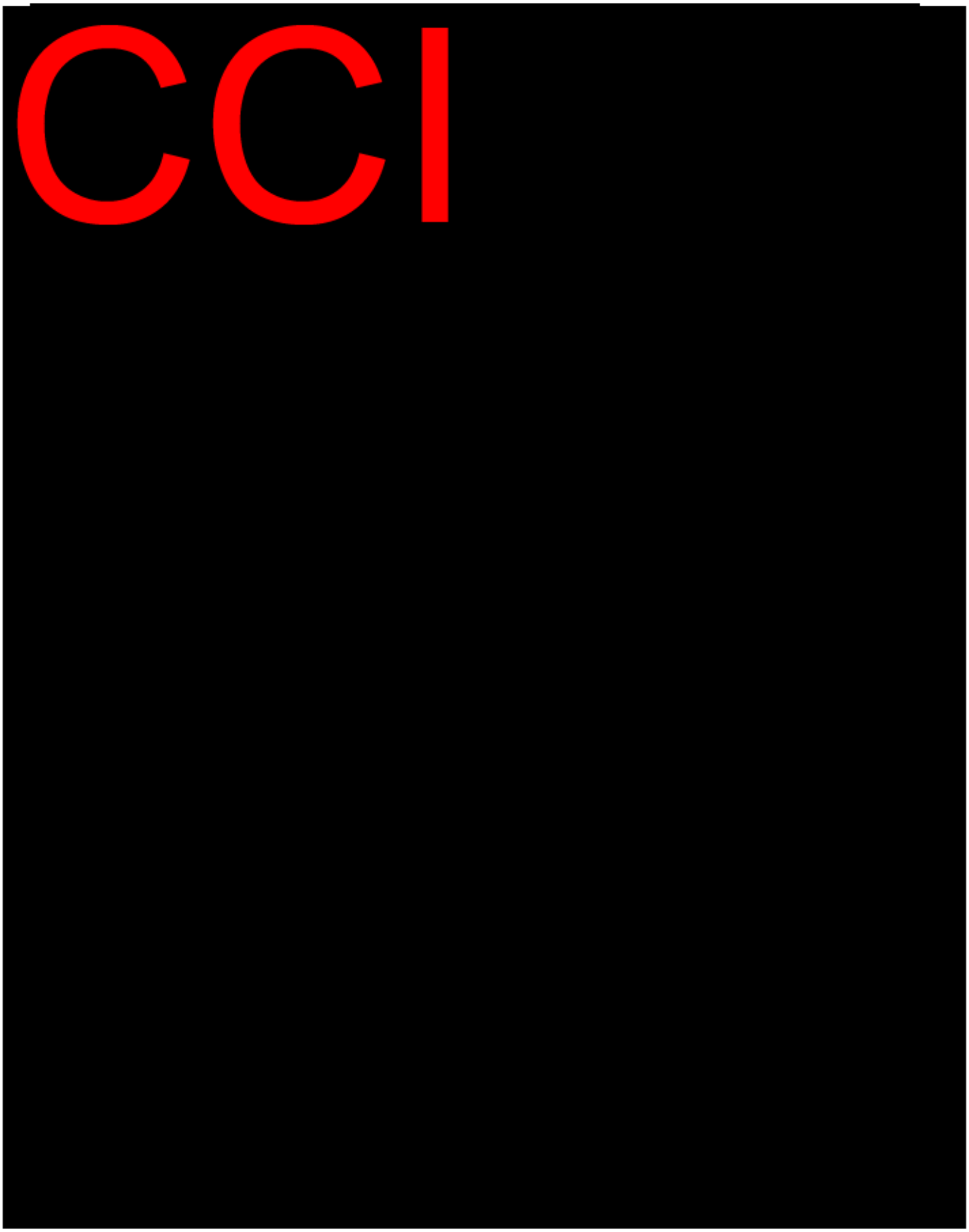

CCI


CCI


CCI


CCI




CCI

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented. Percentages will be presented with respect to the number of treated participants.

Total number of participants screened (i.e. participants who gave informed consent) (overall only)

Number of participants who discontinued from the study prior to study intervention overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdrawal of consent)

Number and percentage of treated participants.

The end of study intervention status will be summarized by:

- Number and percentage of treated participants with ongoing xevinapant
- Number and percentage of treated participants with ongoing cisplatin
- Number and percentage of treated participants with ongoing carboplatin
- Number and percentage of treated participants with ongoing IMRT
- Number and percentage of participants who completed xevinapant
- Number and percentage of participants who completed cisplatin
- Number and percentage of participants who completed carboplatin
- Number and percentage of participants who completed IMRT
- Number and percentage of treated participants who discontinued the xevinapant (overall and by primary reason)

- Number and percentage of treated participants who discontinued the cisplatin (overall and by primary reason)
- Number and percentage of treated participants who discontinued the carboplatin (overall and by primary reason)
- Number and percentage of treated participants who discontinued the IMRT (overall and by primary reason)

The end of study status will be summarized by:

- Number and percentage of treated participants with ongoing any study intervention
- Number and percentage of treated participants off-treatment and in follow-up period
- Number and percentage of treated participants who completed or prematurely discontinued the study after, grouped by main reason

Additionally, the number of participants screened, and enrolled in each analysis set will be provided overall, by region (North America, Western Europe, EEA (required by EudraCT), and Rest of the world), by country within region and by site.

The number of participants treated in each analysis set will be provided.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

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

Important protocol deviations include:

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

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

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

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

- Sample processing errors that may lead to inaccurate bioanalytical results
- Inaccurate dosing or dosing errors (e.g., dose administration delayed, dose change or missed doses), when dosing information is available
- Pre-dose or trough sample collected after the actual dosing
- Concomitant medications and dietary or herbal supplements that are known potent inhibitors or inducers of P-glycoprotein (Table 13 of protocol).

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

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

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

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

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

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the FAS/SAF.

11.1 Demographics

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

The following demographic characteristics will be included:

- Sex:

  - male
  - female
  - undifferentiated
- Race:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian
  - Other Pacific Islander
  - White
  - More than one race
  - Other
  - Not collected at this site
- Ethnicity:
  - Hispanic or Latino
  - Not Hispanic or Latino
- Age (years)
- Age categories:
  - < 65 years,
  - ≥ 65 years
    - 65-74,
    - 75-84,
    - ≥85 years
- Pooled Region:
  - North America
  - Europe
  - Asia
  - Rest of the World
- Geographic Region:
  - North America
  - Latin America
  - Western Europe

- Eastern Europe
- Middle East
- Australia
- Asia

- Weight (kg)
- Height (cm)
- BMI (kg/m^2) at Baseline
- BSA (m^2) at Baseline
- ECOG Performance status (0,1,2,3,4)

Specifications for computation:

$$\text{BSA } [\text{m}^2] = \sqrt{\frac{\text{height[cm]} \times \text{weight[kg]}}{3600}}$$

$$\text{BMI } [\text{kg/m}^2] = \frac{\text{weight [kg]}}{\text{height[cm]}^2} \times 10000$$

Site codes will be used for the determination of the participant's geographic region.

11.2 Medical History

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

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

11.3 Other Baseline Characteristics

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

- Disease History:
  - Site of primary tumor
  - Time since initial cancer diagnosis (months)
  - Histopathological grade
  - Pathological stage (derived from the TNM values) and TNM classification at study entry
- Nicotine usage:
  - Nicotine usage (never smoker, current smoker, former smoker)

- Nicotine usage type (cigarettes, cigars, pipes, chewing tobacco, nicotine gum, e-cigarettes or vapor)
- Nicotine exposure (pack-years)
- Nicotine exposure time (years)
- Years since quitting

- Alcohol consumption:
  - Alcohol consumption (Yes/No)
  - Alcohol consumption (units per week)
- ECOG performance status
- Height, Weight, Body Surface Area, and Body Mass Index
- HPV status at screening

Specifications for nicotine usage computation:

Nicotine usage will be derived using information about the use of nicotine products that can be smoked: cigarettes, cigars, pipes.

The information collected about products that are smoked will be used to derive the smoking status for each participant:

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

Nicotine history computation:

- Chewing tobacco, nicotine gum and e-cigarette are not taken into account for nicotine exposure calculation
- Cigarette equivalents are calculated as follow: 1 cigar is regarded equivalent to 5 cigarettes and 1 pipe is regarded equivalent to 3 cigarettes
- Duration of smoking (years):
  - (end date of smoking – start date of smoking +1)/ 365.25

- Pack-year:
  - Calculate cigarette equivalents per day using the conversion factors given above
  - Convert to packs per day where 20 cigarettes are regarded as 1 pack
  - Pack-year=packs per day*duration of smoking (years)

Specifications for alcohol consumption computation:

- Units per day are calculated as follow: 360ml or 12oz of beer is regarded equivalent to 1 unit, 150ml or 5oz of wine is regarded equivalent to 1 unit and 45ml or 1.5oz of spirits is regarded equivalent to 1 unit
- units per week:
  - Calculate units per day equivalents using the conversion factors given below
  - Convert to units per week *7

12 Previous or Concomitant Therapies/Procedures

The following analyses will be performed based on the SAF.

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

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

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

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

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

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

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

All concomitant procedures will be listed.

Subsequent anti-cancer therapy

Anti-cancer therapy after end of study intervention will be summarized according to the respective CRF page. Treatments will be categorized by means of coding and medical review. The same approach as for concomitant medications will be applied based on ATC level 2 and preferred term.

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

Summary statistics will be created for best response across all post study treatments (as indicated on "Follow up treatment" page). For participants who received more than one anti-cancer drug therapy after discontinuation of study intervention, the best overall response among all anti-cancer drug therapies will be summarized.

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on SAF.

All dosing calculations and summaries will be based on "Study Drug Administration" CRFs pages.

If the total dose is missing, the protocol defined dose of each study intervention will be used.

No imputation of missing start dates of study interventions will be done.

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

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

- the earliest start date of dosing in the Cycle X Day 1 visit eCRF exposure page, if the participant received any study intervention on that visit (i.e., any study intervention with dose>0 at that visit)
- the first day of assessments in the Cycle X Day 1 visit, if the participant did not receive study intervention on that visit (i.e., all study interventions had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs (assuming vital signs are the first assessment of the cycle on Cycle X Day 1 visit.

Actual cycle end date for each participant is:

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

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

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

A dose is regarded to be administered, if the actual dose received is > 0, or the duration of the infusion is > 0, or the start date or end date is not missing.

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

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

Xevinapant Dose intensity (mg/day) is defined as the cumulative dose of xevinapant by the cycle duration in days as:

$$\text{dose intensity} = \left(\frac{\text{cumulative dose}}{\text{(planned dosing days per cycle (14 days))} * \text{exposure duration (cycles)}}\right)$$

Cisplatin/carboplatin Cumulative dose (mg/m^2 or AUC) overall is the sum of the actual doses of study intervention received overall, respectively.

Cisplatin/carboplatin Dose intensity (mg/m^2/day or AUC/day) is defined as the cumulative dose of cisplatin/carboplatin by the exposure duration in days as:

$$\text{dose intensity} = \left(\frac{\text{cumulative dose}}{\text{(planned dosing days per week (1 day))} * \text{exposure duration (weeks)}}\right)$$

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

IMRT Dose intensity (Gy/day) is defined as the cumulative dose of IMRT by the exposure duration in days as:

$$\text{dose intensity} = \left(\frac{\text{cumulative dose}}{\text{(planned dosing days per week (5 days))} * \text{exposure duration (weeks)}}\right)$$

Relative dose intensity (%) is defined as the actual dose intensity divided by the planned dose intensity during the study and expressed in percentage:

$$\text{relative dose intensity} = \left(\frac{\text{dose intensity}}{\text{planned dose}}\right) * 100$$

Where the planned dose is:

- Xevinapant: CCI mg/day
- Cisplatin: CCI mg/m2/day
- Carboplatin: AUC2/day
- IMRT: 70 Gy/day

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

- Total duration of xevinapant, cisplatin, carboplatin and IMRT (weeks) and by categories of ≤ 3 weeks, > 3 – 6 weeks, > 6 – 9 weeks, > 9 -12 weeks, > 12 – 15 weeks, > 15 – 18 weeks
- Number of IMRT Fractions
- Total number of cycles received of xevinapant, cisplatin, carboplatin and IMRT
- Cumulative dose of xevinapant, cisplatin, carboplatin and IMRT
- Dose intensity of xevinapant, cisplatin, carboplatin and IMRT
- Relative dose intensity (%) of xevinapant, cisplatin, carboplatin and IMRT
- Dose reduction of xevinapant, cisplatin, carboplatin and IMRT per time period (overall and by reason)
- Missed doses of xevinapant, cisplatin, carboplatin and IMRT per time period
- Discontinuation of xevinapant, cisplatin, carboplatin and IMRT per time period (overall and by reason)
- A listing will be provided for all administrations of participants for the primary analysis only.

14 Efficacy Analyses

This analyses will not be conducted. See Section 7.1 for the details.

15 Safety Analyses

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

Safety analyses will be done on SAF and according to the as-treated principle unless otherwise stated.

15.1 Occurrence of DLT-like events

Analyses of primary objective will be done on DLT analysis set.

Objective:

To evaluate tolerability of xevinapant when added to weekly cisplatin-based CRT in LA SCCHN.

Endpoints:

Occurrence of DLT-like events.

Population:

Treatment naïve patients with LA SCCHN (Stage III, IVA, or IVB) with histologically confirmed diagnosis in at least 1 of the following sites: oropharynx (HPV-negative), hypopharynx, and larynx, eligible to receive weekly cisplatin-based concurrent CRT.

Treatment:

Xevinapant, weekly cisplatin, and IMRT followed by xevinapant monotherapy.

Intercurrent Event Strategy:

- Discontinuation/interruption/delay of xevinapant/cisplatin treatment (> 40% of planned cumulative dose missed in DLT-like assessment period) due to reasons other than treatment-related AE (composite strategy: to be considered as DLT-like event)
- RT delay > 2 weeks during the DLT-like assessment period due to reasons other than treatment-related AE (composite strategy: to be considered a DLT-like event)

Population-Level Summary:

- DLT-like event rate and associated CI
- Standard summary statistics

Definition of DLT-like events:

DLT-like events were defined in the protocol Section 8.2.5.1.

15.1.1 Population-Level Summary for DLTs

All DLT-like events that occurred in the analysis population during the DLT-like assessment period of each participant will be analyzed.

The number and proportion of participants experiencing DLT-like events in the analysis population will be reported together with the corresponding Clopper-Pearson 95% CI.

15.2 Adverse Events analyses

Treatment-emergent adverse events (TEAE) are those events with onset or worsening (seriousness or severity) dates occurring within the on-treatment periods as defined in Section 9.8.

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

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

All analyses described in Section 15.2 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with the TEAE in the category of interest, as well as the number of events, primary SOC and PT in decreasing frequency. In case of the same incidence, alphabetical order of SOC and PT will be applied.

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

15.2.1 All Adverse Events

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

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

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

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of participants with each of the following:
  - TEAEs
  - TEAEs, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4
  - Serious TEAEs
  - Non-Serious TEAEs
  - TEAEs leading to death (AEs with Grade 5 or outcome "fatal")
  - CCI
  - For xevinapant, cisplatin/carboplatin, IMRT and for any study intervention:
    - [Intervention] related TEAEs
    - [Intervention] related TEAEs, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4
    - TEAEs leading to permanent discontinuation of [intervention]
    - [Intervention] related Serious TEAEs
    - [Intervention] related TEAEs leading to death
    - [Discontinued intervention] related TEAEs leading to permanent discontinuation of [intervention] (This item is not applicable for 'any intervention')

Additional tables will be produced:

- TEAEs by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- TEAEs by SOC and PT for Grade ≥3 TEAEs
- TEAEs excluding SAEs, by SOC and PT.
- For xevinapant, cisplatin/carboplatin, IMRT and for any study intervention:
  - [Intervention] related TEAEs by SOC and PT and worst grade
  - [Intervention] related TEAEs leading to death by SOC and PT

- [Intervention] related TEAEs by SOC and PT for Grade ≥3 TEAEs

Additionally, a listing of all AEs will be provided, sorted by subject ID, and onset of AE.

15.2.2 Adverse Events Leading to Discontinuation of Study Intervention

The frequency (number and percentage) of participants with each of the following will be presented for TEAEs leading to discontinuation of study intervention.

- For xevinapant, cisplatin/carboplatin and IMRT:
  - TEAEs leading to temporary discontinuation of [intervention] by SOC and PT
  - TEAEs leading to permanent discontinuation of [intervention] by SOC and PT
  - TEAEs leading to dose reduction of [intervention] by SOC and PT
  - [Discontinued intervention] related TEAEs leading to temporary discontinuation of [intervention] by SOC and PT
  - [Discontinued intervention] related TEAEs leading to permanent discontinuation of [intervention] by SOC and PT
  - [Discontinued intervention] related TEAEs leading to dose reduction of [intervention] by SOC and PT

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

15.3.1 Deaths

All deaths, deaths within 30 days after last dose of study intervention, death within 60 days after first dose as well as reason for death, will be tabulated based on information from the "Death" page in eCRF:

- Number of Deaths
- Number of Deaths within 30 days after last dose of each study intervention
- Number of Deaths within 30 days after last dose of any study intervention
- Number of Deaths within 60 days after first dose of any study intervention
- Primary Reason of Death:
  - Disease progression
  - AE related to study intervention
  - AE not related to study intervention
  - Other
  - Unknown

In addition, date and cause of death will be provided in individual participant data listing together.

This listing will include:

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

Where AE related/not related to study intervention in Primary Reason of Death is defined as patients with:

- Related = 'What is the primary cause of death?' in "Death" page in eCRF is 'Adverse Event' and at least 1 fatal AE related to any study intervention
- Not related = 'What is the primary cause of death?' in "Death" page in eCRF is 'Adverse Event' and no fatal AE related to any study intervention

15.3.2 Serious Adverse Events

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

- Incidence of serious AEs by SOC and PT
- For xevinapant alone, cisplatin alone, carboplatin alone, IMRT alone and any study intervention:
  - Incidence of [intervention] related serious AEs by SOC and PT

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

15.3.3 Other Significant Adverse Events

CCI [redacted].

15.4 Clinical Laboratory Evaluation

15.4.1 General specifications

All laboratory values will be reported in SI units.

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

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

For the definition of baseline measurement please see section 9.2.

Values below the detection limit will be imputed by half of the detection limit.

In case just a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data will be summarized using descriptive statistics presenting baseline value, maximum on treatment, and minimum on treatment as well as their changes to baseline.

Qualitative data based on reference ranges will be described according to the categories (i.e. Low, Normal, and High).

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

Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available. Laboratory values within normal range but considered grade 1 according to NCI-CTCAE will thus not be graded 1 (grade 0, instead).

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

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

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

- Lymphocyte count decreased:
- derived absolute count does not meet Grade 2-4 criteria, and
- % value < % LLN value, and
- derived absolute count ≥ 800/mm^3
- Neutrophil count decreased
- derived absolute count does not meet Grade 2-4 criteria, and
- % value < % LLN value, and
- derived absolute count ≥ 1500/mm^3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows

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

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

The time windows as specified in the schedule of assessments in the protocol will be applied to allocate measurements to timepoints, where Day 1 is the first day of any study intervention. In case multiple blood samples are collected in the same window, the value closest to the target day will be used for analysis, where the target day is the middle of the time window. If there are two values with the same time before and after the target day, the earlier value will be used for analysis.

Since the number of participants will decrease over time, time windows will not be applied for the complete study intervention period. For summaries by timepoint, the last available laboratory measurement will be presented in addition to the timepoints defined above.

15.4.2 Presentation of the Laboratory data

For both hematology and biochemistry, summary statistics over time (using the visit windows) will be tabulated.

Parameters with NCI-CTCAE grades available:

The laboratory toxicities will be **tabulated using descriptive statistics** (number of participants and percentages) during the on-treatment period.

The **shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade**. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary. In addition, the **worst on-treatment value will be tabulated**.

In case of gradings involving baseline measurements (see section 9.14) for the identification of grades during the on-treatment period, the shift table will present baseline normal and abnormal. Normal will include measurements below and within normal range (direction increase), or measurements within and above normal range (direction decrease). In case of missing baseline values, the on-treatment grades will be generated assuming the baseline was normal.

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE (see Appendix 2 for specific parameters).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and row percentage) of participants with:

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

In this study, these apply to the parameters listed in Appendix 2.

Box-and-whisker plots for the absolute change from baseline by dose, by time point will also be provided.

Listings of laboratory results will be provided for all abnormal (above 2ULN or below LLN/2) or ≥ grade 3 laboratory parameters. The listings will be sorted by study intervention, parameters and assessment dates or visits for each participant.

All other parameters collected on the eCRF will be listed in dedicated listings presenting all corresponding collected information on the eCRF.

An evaluation of Drug-Induced Serious Hepatotoxicity **(eDISH)** plot will also be created, by graphically displaying two figures with log-scale transformed axes presented as:

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT =3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST =3×ULN and total bilirubin =2×ULN.

15.5 Vital Signs

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

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) presenting baseline value, maximum on treatment, and minimum on treatment as well as their changes to baseline.

The maximum changes of vital sign measurements screening/baseline to maximum changes after start of 1st study intervention will be grouped as follows:

Body temperature increase	< 1°C , 1-<2°C , 2-<3°C, ≥ 3 °C
Heart rate increase from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from baseline <100 bpm ; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

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

For each participant the worst on-treatment value will be calculated. For the definition of baseline values see Section 9.2. Missing values will define a separate category.

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

- Maximal Shifts (changes in categories)
- Listing of highest change per participant

An additional participant data listing will present all changes from baseline reported in the highest categories.

15.6 Other Safety or Tolerability Evaluations

15.6.1 ECOG

The ECOG data will be listed.

15.6.2 Electrocardiogram (ECG)

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

The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below.

The QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Data will be summarized using QTcF, results will be listed.

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc), during the on-treatment period. Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and QT parameters.

- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of participants with notable ECG values according to the following categories. The denominator to calculate percentages for each category is the number of participants evaluable for the category:
    - QT/QTc increase from baseline >30 ms, >60 ms
    - QT/QTc > 450 ms, > 480 ms, > 500 ms
    - HR $\leq$ 50 bpm and decrease from baseline $\geq$ 20 bpm
    - HR $\geq$ 120 bpm and increase from baseline $\geq$ 20 bpm
    - PR $\geq$ 220 ms and increase from baseline $\geq$ 20 ms
    - QRS $\geq$ 120 ms

Complete ECG profiles will be listed for participants with at least one notable ECG interval value or change. Also, qualitative ECG abnormalities will be listed for each participant and time point and the corresponding notable values and abnormality findings will be included in the listings.

16 Analyses of Other Endpoints/Estimands

This analyses will not be conducted. See Section 7.1 for the details.

17 References

Not applicable.

18 Appendices

Appendix 1 – SMC Analyses

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

The SMC will review available data during study conduct. The data extraction for the SMC reviews will be triggered CCI [redacted] for at least 5 weeks (DLT-like assessment period) or have experienced a DLT-like event. For the SMC review after 18 participants the tolerability of treatment will be assessed using the DLT-like criteria during the initial 5 weeks for each participant (DLT-like assessment period). Additional SMC reviews may be requested by the Sponsor or the SMC.

For each SMC review outputs described in this appendix will be provided along with the participant profiles.

Analysis Sets

SMC analyses will be done on SAF following the same specification described in Section 8.1 unless otherwise stated.

When the analysis is done on DLT analysis set for SMC, the analysis set will be defined based on DLTs as per investigator.

General Specifications for Data Analyses

Same specifications described in Section 9 will be used for SMC analyses.

In addition to the analyses for CSR, line plots of the following lab parameters will be provided by actual time in days for all analyses (with x-axis time, y-axis lab value), using different colors to identify participants:

- eGFR
- Creatinine
- ALT
- AST
- Neutrophils
- Platelets
- Lymphocytes
- Hemoglobin

Where feasible, reference lines for CTCAE grades should be added to graphical displays.

Planned Analysis

[redacted]

[redacted]

Appendix 2 –Laboratory Parameter Grading

Hematology and chemistry evaluations which can be graded per CTCAE:

- Hematology:

Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Cholesterol (cholesterol high), Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia), Triglycerides (hypertriglyceridemia).

Parameters with NCI-CTC grades not available:

- Hematology:

Hematocrit, Red Blood Cell (RBC), Reticulocytes, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC).

- Serum Chemistry:

Chlorine, C-Reactive Protein, Lactate Dehydrogenase (LDH), Total Protein, Total Urea, Uric Acid.

Signature Page for VV-CLIN-359974 v2.0

Approval Task	-2025 05:05:38 GMT+0000

Approval Task	5:04 GMT+0000

Signature Page for VV-CLIN-359974 v2.0