Statistical Analysis Plan

Clinical Trial Protocol Identification No.	EMR062202-060
Title:	A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil alone for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck
Trial Phase	Phase III
Investigational Medicinal Product(s)	Cetuximab
Clinical Trial Protocol Version	26 February 2018 / Final 3.0
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	16 April 2018 / Final 2
Statistical Analysis Plan Reviewers	PPD [redacted]

1 Signature Page

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A multicenter, randomized, open-label, Phase III trial to assess efficacy and safety of cetuximab when given in combination with cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil alone for the first-line treatment of Chinese subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck

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3 List of Abbreviations and Definition of Terms

AE	Adverse Event
AUC	Area under Curve
BOR	Best overall response
BP	Blood Pressure
BSA	Body surface area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTR	Clinical Trial Report
CTX	Chemotherapy
DBP	Diastolic Blood Pressure
DCR	Disease control rate
DI	Dose Intensity
DOR	Duration of Response
EAIR	Exposure Adjusted Incidence Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOEA	End of efficacy assessment
EoS	End of Study
5-FU	5-fluorouracil
GFR	Glomerular Filtration Rate
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICH	International Conference of Harmonization
Inv	Investigator
IRC	Independent Review Committee

IRR	Infusion-related reaction
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MN	Miettinen & Nurminen
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not evaluable
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PP	Per Protocol
PR	Partial response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCCHN	Squamous cell carcinoma of the head and neck
SCR	Screening
SD	Stable Disease
Sd	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TCM	Traditional Chinese Medicine
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
TNM	Tumor-Nodes-Metastases
WHO-DD	WHO Drug Dictionary

4 Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
Final 1.0	10NOV2016	Marie Hennequi	First version
Version 2.0	19FEB2018	Cheryl Lee	Add 3-tier approach Add analysis for clintrial.gov Add Chinese origin/citizenship Remove lab parameters analysis over each visit Remove repeated baseline TLFs on each subgroup Remove hypothesis test according to protocol Remove each chemotherapy drug related AE and replace it with chemotherapy related AEs Remove subgroup Type of primary tumor; HPV Update protocol deviation list and the definition of Per Protocol analysis set Update the definition of PFS according to the most recent draft protocol Update the shift category for vital signs
	16APR2018	Natalia Traissard	Update the list of analyses of Adverse Events Update actual dose definition for Carboplatin Add definitions of the CTCAE v4.03 Grades for Laboratory Parameters Clarify Concomitant Medication and Procedures and delete Prior Non Anti-Cancer Medications section Add Line of treatment to Anti-cancer treatment after discontinuation Add RDI for carboplatin Update Protocol Deviations list Add a new sensitivity analysis to the primary endpoint Several updates of wording for consistency with protocol amendment and clarification

5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the main and final analyses of data collected for protocol EMR062202-060.

Results of the analyses described in this SAP will be included in the Clinical Trial Report (CTR) and in the CTR addendum (for results based on all data collected until OS cut off - e.g., at least 180 deaths [e.g., 75% of randomized subjects] have been reported, or up to 12 months after the last subject is randomized, whichever is earlier). Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective SAP will be clearly identified in the CTR.

The SAP is based upon Section 8 (Statistics) of the trial protocol and protocol amendments (last version dated 26 February 2018) and is prepared in compliance with International Conference on Harmonization (ICH) E9.

6 Summary of Clinical Trial Features

Objectives:

Primary objective: The primary objective of this trial is to evaluate whether progression-free survival (PFS) time, as assessed by an Independent Review Committee (IRC), in subjects receiving cetuximab in combination with cisplatin plus 5-fluorouracil (5-FU) is longer than that in subjects receiving cisplatin plus 5-FU alone in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).

Secondary objectives: The secondary objectives are to compare the 2 treatment arms in the following:

- PFS time, as assessed by the Investigator
- Overall survival (OS) time
- Best overall response (BOR) rate
- Disease control rate (DCR)
- Duration of response
- Safety

Methodology:

This is an open-label, randomized, parallel-group trial. At the end of a 28-day screening period, all eligible subjects will be randomly assigned into treatment Arm A or B in a 2:1 ratio. Subjects in Arm A will receive a maximum of 6 cycles of chemotherapy (cisplatin plus 5-FU) and cetuximab weekly in the absence of progressive disease (PD), as assessed by the Investigator, and unacceptable toxicity. After 6 cycles of treatment, subjects who derive clinical benefit will continue treatment with cetuximab as monotherapy until either PD or unacceptable toxicity. Subjects in Arm B will receive the same chemotherapy regimen as Arm A alone for a maximum of 6 cycles in the absence of PD and unacceptable toxicity.

Tumor assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The baseline tumor assessment is to be performed during the screening period within 28 days before the start of trial treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) with contrast enhancement is recommended for tumor assessment. Subsequent tumor response evaluations will be assessed every 6 weeks (± 3 days) starting from the randomization day until occurrence of PD regardless of any cycle delay. If treatment is discontinued for reasons other than PD, subjects will continue to have tumor assessments until either PD, the start of a new antitumor treatment, death, the termination of the trial, or loss of follow up, whichever comes first. If symptoms are suggestive of PD, subjects will be evaluated by imaging studies thereafter for documentation and confirmation of the tumor responses.

All subjects in Arm A and B will be followed up continuously for safety evaluations according to schedule of assessments in Table 1.1 of the protocol, **Error! Reference source not found.** starting from date of first signature of informed consent. A Safety Follow-up visit will be performed 30 days (± 3 days) after the last dose of trial treatment or immediately before starting any new antitumor treatment. During the treatment period, additional safety evaluations will be on a weekly basis (Arm A only) for physical examination, vital signs, documentation of adverse events and concomitant medications, and also at the start of each cycle (for both arms) Eastern Cooperative Oncology Group (ECOG) performance status, electrocardiogram (ECG), hematology, biochemistry and urinalysis. Survival data will be collected every 3 months after the end of efficacy assessment (EOEA) visit until either death, loss of follow up, or the termination of the trial, whichever comes first.

The trial will be terminated when the last subject has discontinued the trial treatment or OS cut-off, whichever is later. After OS cut-off and before the trial termination, only SAEs during treatment and at the EOEA visit will be reported, following the usual reporting procedure. Information collected in the EOEA forms will be limited to data on date of trial treatment completion, date of last treatment, subject status at end of trial, reason for discontinuation, disease progression (yes/no). From alive, but trial-treatment-discontinued subjects, no tumor response data, anti-cancer treatment and survival information will be collected.

Planned number of subjects: 240 subjects.

Primary endpoint: The primary endpoint is PFS time, as assessed by an IRC.

Secondary endpoints: The secondary endpoints include PFS time, as assessed by the Investigator, OS time, BOR rate, DCR, duration of response, and safety.

Pharmacokinetics: Not applicable.

Other assessments: Not applicable.

Diagnosis and key inclusion and exclusion criteria:

Trial population: Subjects who have recurrent and/or metastatic SCCHN excluding nasopharyngeal carcinoma and who have not received chemotherapy for recurrent and/or metastatic SCCHN.

Key inclusion criteria:

- ≥18 years of age.
- Histologically and/or cytologically confirmed diagnosis of SCCHN.
- Recurrent and/or metastatic SCCHN, not suitable for local-regional treatment. Subjects with recurrent disease only (no metastases) must have received prior radiotherapy (as adjuvant treatment after surgery or as treatment for locally advanced SCCHN) as part of "loco-regional treatment", and the radiotherapy and the radiotherapy must have been completed more than 6 months before screening imaging.

- Presence of at least 1 measurable lesion according to RECIST version 1.1.
- Signed written informed consent before any trial-related activities are carried out.
- ECOG performance status of 0 or 1.

Key exclusion criteria:

- Prior systemic chemotherapy, except if given as part of multimodal treatment, for locally advanced SCCHN that was completed more than 6 months before randomization.
- Surgery (excluding prior biopsy for diagnosis) or irradiation within 4 weeks before randomization.
- Previous treatment with monoclonal antibody or signal transduction inhibitors targeting epidermal growth factor receptor.
- Nasopharyngeal carcinoma.
- Known central nervous system metastasis and/or leptomeningeal disease.
- Medical or psychological condition that would not permit the subject to complete the trial or sign informed consent.
- Legal incapacity or limited legal capacity.

Investigational Medicinal Product: dose/mode of administration/ dosing schedule:

Cetuximab, supplied in ready-to-use 20 mL vials containing 5 mg/mL solution, will be administered on a weekly basis to subjects in Arm A. The initial dose will be 400 mg/m^2 as an intravenous infusion up to a maximum speed of 5 mg/minute. The subsequent weekly dose will be 250 mg/m^2 as an intravenous infusion up to a maximum speed of 10 mg/minute.

Reference therapy: dose/mode of administration/dosing schedule:

Subjects in both arms will receive a maximum of 6 cycles of chemotherapy of 75 mg/m^2 cisplatin as intravenous infusion (refer to China package insert) on Day 1 of each 21-day treatment cycle, and then 750 mg/m^2/day of 5-FU as a continuous intravenous infusion over 24 hours ± 6 hours a day from Day 1 to Day 5 of each 21-day treatment cycle.

In the case of cisplatin-related nonhematologic toxicity, cisplatin may be replaced by carboplatin at a dose of target area under the serum concentration time curve of 5 in the subsequent cycles. The decision needs to be made in discussion with the Medical Monitor on a case-by-case basis. Carboplatin will be administered using an intravenous infusion of 15 minutes or longer, and in accordance with the China package insert on Day 1 of each 21-day treatment cycle.

Planned treatment duration per subject:

The treatment duration per subject may vary. Subjects will be treated with a maximum of 6 cycles of chemotherapy and/or cetuximab weekly in the absence of PD, as assessed by the Investigator, and unacceptable toxicity. Subjects (in Arm A) who demonstrate at least a tumor

response of stable disease (RECIST version 1.1) after 6 cycles of trial treatment will continue monotherapy with cetuximab until either PD or occurrence of unacceptable toxicity. Subjects who stop treatment before reaching PD will continue to have tumor assessments (CT or MRI) every 6 weeks until either PD, the start of a new antitumor treatment, death, or termination of the trial, or loss of follow up, whichever comes first. Upon occurrence of PD, all trial treatments should be discontinued.

Statistical methods:

Sample Size Calculation: CCI [redacted]

Randomization: Randomization will be performed centrally using an interactive web response system (IWRS). A central stratified permuted block randomization procedure will be used to balance between treatment arms. The stratification factors are ECOG performance status (0 versus 1) and the primary tumor site (oral cavity versus hypopharynx versus others).

Statistical Analyses:

The hazard ratio between the treatment arms in PFS time (based on imaging as assessed by an IRC) will be estimated by Cox's proportional hazards model stratified by randomization strata to assess the stratified hazard ratio. The 95% confidence interval (CI) will also be provided to characterize the variability of the point estimate. In discussion with Chinese Health Authority, this bridging trial would be regarded as positive from regulatory point of view if the point estimation for stratified hazard ratio less than or equal to 0.77. All secondary analyses of the primary variable will be performed to support the results of the primary confirmatory analysis and regarded as purely exploratory.

The time-to-event endpoints will follow standard methodology by employing Kaplan-Meier estimates, Cox's proportional hazard model to estimate stratified hazard ratios and corresponding 95% CI.

The counts and percentages will be summarized for dichotomous data.

The main statistical analysis of data is event driven and is expected to be approximately 22 months after trial initiation (i.e., after the 144 PFS events with respect to the primary endpoint have occurred). The final analysis of OS (OS cut-off date should be at least 180 deaths [e.g., 75% of randomized subjects] have been reported, or up to 12 months after the last subject is randomized, whichever is earlier), will be presented in a clinical trial report addendum. Safety data collected after the OS cut-off will be reported through patient profile. No additional statistical analyses will be conducted.

7 Sample Size/Randomization

7.1 Sample Size

CCI

CCI

CCI

CCI

7.2 Randomization

Subjects will be randomized to one of the 2 treatment arms, cetuximab plus chemotherapy (CTX) versus CTX alone, at a 2:1 ratio stratified by the following:

- ECOG performance status: 0 versus 1.
- Primary tumor site: oral cavity versus hypopharynx versus others.

A central stratified permuted block randomization procedure will be employed via IWRS to balance prognostic factors between treatment arms.

8 Overview of Planned Analyses

The main statistical analysis of data is event driven and is expected to be approximately 22 months after trial initiation (i.e., after the 144 independently-assessed PFS events with respect to the primary endpoint have occurred).

The final analysis of OS (OS cut-off date should be after at least 180 deaths [e.g., 75% of randomized subjects] have been reported, or up to 12 months after the last subject is randomized, whichever is earlier), will be presented in a clinical trial report addendum. Safety data collected after the OS cut-off will be reported using patient profiles. No additional statistical analyses will be conducted.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

Not Applicable.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

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

The following deviations will be identified and confirmed prior to or at the last Data Review Meeting.

- Important protocol deviations include
  - Deviations from the inclusion and exclusion criteria
  - Deviations post inclusion
- A subset of these important protocol deviations is defined as being clinically important if leading to the exclusion of the subject from the PP set (see section 10.2).

Details on the important protocol deviations are provided in the Appendix 1.

All the important protocol deviations should be documented in CDISC datasets whether identified through site monitoring, medical review or programming. Important Protocol Deviations as well as all clinically Important Protocol Deviations will be listed.

More details about important protocol deviations identification are provided in Appendix 1.

10.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set

The Screening (SCR) analysis set includes all subjects who signed the informed consent.

Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set includes all subjects who were randomized to trial treatment. Analyses performed on the ITT analysis set will take into account subjects' allocation to treatment groups as randomized

Safety Analysis Set

The safety (SAF) analysis set includes all subjects who received at least one dose of any trial treatment (cetuximab, cisplatin/carboplatin, or 5-FU). Analyses performed on the safety analysis set will consider subjects as treated. As soon as a subject received at least one dose of cetuximab, treatment group corresponding to cetuximab in combination with cisplatin plus 5-FU will be considered as the treatment group for this subject. If a subject receives no dose of cetuximab, then the treatment group corresponding to cisplatin plus 5-FU alone will be considered as the treatment group for this subject.

The safety analysis set will be used for safety analyses.

Per Protocol Analysis Set

The per protocol (PP) analysis set includes all ITT subjects who does not meet one or more of the following criteria:

- Deviations from the inclusion and exclusion criteria:
    - Inclusion criteria not fulfilled (#02): No histologically and/or cytologically confirmed diagnosis of SCCHN
    - Inclusion criteria not fulfilled (#03): No recurrent and/or metastatic SCCHN not suitable for local therapy
    - Inclusion criteria not fulfilled (#06): ECOG performance status of 0 or 1
    - Exclusion criteria fulfilled (ex#01): Prior systemic chemotherapy, except if given as part of multimodal treatment for locally advanced disease which was completed within 6 months before trial entry. (as per Protocol Amendment)
    - Exclusion criteria fulfilled (ex#03): Previous treatment with monoclonal antibody or signal transduction inhibitors targeting EGFR.
    - Exclusion criteria fulfilled (ex#04): Nasopharyngeal carcinoma.
- Randomization error:
    - Incorrect treatment group allocation, different to assignment at randomization
    - Subject randomized but did not receive any trial treatment
- Use of prohibited medication:
    - Additional concurrent chronic systemic immune treatment, chemotherapy, radiotherapy (with exceptions), hormone treatment for treatment of cancer (with exceptions), traditional Chinese medication with approval for use as anticancer treatment or any other investigational agent

- Availability of measurement of the primary endpoint:
  - No evaluable post-baseline tumor assessment (as per IRC) is available

If the Per Protocol analysis set includes at least 90% of subjects in the ITT analysis set, additional efficacy analyses on the Per Protocol analysis set and baseline analysis (including demographics) on PP/safety set will be omitted as the differences in the results based upon these two analysis sets are expected to be negligible.

Analyses	Intent-to-Treat Analysis Set	Per Protocol Analysis Set	Safety Analysis Set
Demographics	✓	✓	✓
Baseline Assessments	✓	✓	
Past and Concomitant Therapies	✓		
Compliance and Exposure			✓
Efficacy: Primary	✓	✓	
Efficacy: Secondary	✓		
Safety and Tolerability			✓

Specific subgroups

The following subgroups are considered of interest to comparatively explore the treatment effect for the definition of subgroups, data as documented in the eCRF will be taken.

- Age: <65 years versus ≥ 65 years
- Sex: Male versus Female
- Baseline ECOG performance status: 0 versus 1
- Primary tumor site: oral cavity versus oropharynx versus hypopharynx versus larynx versus others. The location of the tumor as reported on the "Disease history" eCRF page according to the International Classification of Diseases for Oncology (ICD-O) and the locations are grouped using guidance of the medical advisor.
- Time from initial SCCHN diagnosis: < median versus ≥ median
- Histology: well/moderately versus poorly differentiated
- Extent of disease at trial entry: nonmetastatic recurrent (date of first occurrence of recurrent disease is available and date of first occurrence of metastatic disease is Not applicable) versus nonrecurrent metastatic (date of first occurrence of recurrent disease is Not applicable and date of first occurrence of metastatic disease is available) versus metastatic including recurrent (both dates of recurrent disease and date of first occurrence of metastatic disease are available)
- Prior antitumor therapy:
  - Any: yes versus no;
  - Prior neoadjuvant/induction: yes versus no;

- Prior radiotherapy: yes versus no;
- Prior radiochemotherapy: yes versus no;
- Prior surgery (excluding biopsy): yes versus no;
- Prior platinum-containing treatment for SCCHN: yes versus no.

A summary for the number of subjects in each subgroup will be produced. The analysis of individual subgroups will be done in a case there are enough observations in each subgroup (i.e. more than 10 subjects in any treatment group). If there are more than 2 options within a subgroup and less than 10 subjects in one of the options this option may be pooled with the closest option. The final decision on the pooling of the subgroups will be taken during the data review meeting prior to the database lock for the main analysis.

11 General Specifications for Statistical Analyses

This is a bridging trial. The hypothesis test will not be done and P-values will not be provided, unless otherwise specified. If CIs are to be calculated, these will be 2-sided with a confidence probability of 95%, unless otherwise specified.

Data handling after cut-off date:

Data after cut-off do not undergo the cleaning process. The only exception is the date of death on "Death" eCRF page.

Generally, data obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g., laboratory values of samples taken after data cut-off, AE with onset date after data cutoff, etc. will not be included in any analysis or listing.

The cut-off will be implemented at SDTM level.

Pooling of centers

In order to provide overall estimates of the treatment effect, data will be pooled across centers. The factor center will not be considered in statistical models or for subgroup analyses.

Presentation of continuous and qualitative variables:

Continuous variables will be summarized using descriptive statistics, i.e.

- number of subjects (N), number of subjects with non-missing values
- mean, standard deviation (Sd)
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum and maximum,

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects in the analysis set of interest. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

Definition of Baseline:

The last non-missing measurement prior to the randomization date will be used as the baseline measurement. Definition of baseline will be used for all efficacy analysis.

Definition of pre-treatment value:

The last non-missing measurement prior to the first trial drug administration will be used as the pre-treatment baseline measurement. Definition of pre-treatment value will be used as baseline for all safety analysis.

Definition of duration:

Duration (in days) will be calculated by the difference between start and stop date + 1, unless otherwise specified.

Conversion factors:

The following conversion factors will be used to convert days into weeks or months or years, or vice versa:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Handling of missing data:

Unless otherwise specified (Sections 13.1, 13.3, 14.2, 16.1.1, 17.1), missing data will not be replaced.

In all subject data listings imputed values will be presented. In all listings imputed information will be flagged.

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

Software:

All statistical analyses will be performed using SAS® software version 9.2 or higher.

12 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/trial discontinuations. Additionally, procedures for reporting protocol deviations are provided.

12.1 Disposition of Subjects and Discontinuations

Descriptive statistics will be used to summarize subject disposition and reason for discontinuation, based on the electronic case report form (eCRF) data.

The following information will be reported:

- Number of subjects screened.
- Number of subjects who discontinued from the study prior to randomization, overall and grouped by reason (i.e. Subject did not meet all eligibility criteria, Withdrew informed consent, Progressive disease, Adverse event, Lost to follow-up, Death, Other as reported on the "Study Entry" eCRF page).
- Number of randomized subjects in each treatment arm
- Number of randomized subjects who received no treatment in each treatment arm
- Number of randomized subjects ongoing on treatment in each treatment arm (subject initiated one or more treatment as reported on the "Cetuximab Administration", "Cisplatin Administration", "Carboplatin Administration" and "5-FU Administration" eCRF page and at least one of initiated treatments is not discontinued as reported on the "Cetuximab Termination", "Cisplatin Termination", "Carboplatin Termination" and "5-FU Termination" eCRF pages)
- Number of randomized subjects who are off treatment in each treatment arm and reason for treatment discontinuation. To be accounted as off all treatments a subject must discontinue all the initiated treatments (as reported on the "Cetuximab Termination", "Cisplatin Termination", "Carboplatin Termination" and "5-FU Termination" eCRF pages). If the treatments are discontinued for different reasons, the reason for discontinuation of the last treatment will be taken into account.
- Number of randomized subjects who discontinued the treatment after randomization, grouped by treatment arm and main reason separately for each treatment component (as reported on the "Cetuximab Termination", "Cisplatin Termination", "Carboplatin Termination" and "5-FU Termination" eCRF pages). For cisplatin, the number of randomized subjects who definitely discontinue cisplatin and number of those who switched to carboplatin will also be displayed.
- Number of randomized subjects who stopped assessments grouped by treatment arm and main reason (as reported on "End of Assessment Visit" eCRF page)
- Number of randomized subjects who continued only in survival follow-up after randomization, grouped by treatment arm (subjects who discontinued/completed all treatments and have no evidence of study discontinuation as reported on "Study Termination" eCRF page)

- Number of randomized subjects who discontinued the trial after randomization, grouped by treatment arm and main reason (as reported on "Study Termination" eCRF page)
- The results of the randomization algorithm (according to IWRS) will be summarized as follows:
  - Number of randomized subjects by randomization strata (IWRS)
  - Number of randomized subjects by randomization strata (eCRF)
  - Cross tabulation: stratum by IWRS vs. stratum by CRF
  - Cross tabulation: subjects randomized (A/B/no) vs. treated (A/B/no)

In addition, a summary table will be provided displaying the number and percentage of subjects by site for each analysis set.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Frequency table per reason of important protocol deviations
- Listing of important protocol deviations

Relevant protocol deviations post-inclusion will be determined by either medical review processes or by programming (See Appendix 1 for detailed specifications).

12.2.2 Reasons Leading to the Exclusion from an Analysis Set

Subjects who meet at least one criteria described in section 10.2will be excluded from the PP. For these subjects, each criteria will be summarized and listed;

- Frequency table per criteria

Listing of each criteria.

13 Demographics and Other Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics, based on the eCRF data. Summaries will be performed on the ITT analysis set.

13.1 Demographics

Demographic characteristics will be based on the ITT analysis set and repeated on the PP and Safety analysis sets only if the PP set is less than 90% of ITT.

Demographic characteristics will be summarized as follows:

- Sex: Male, Female.
- Race: Asian, Other.
- Subject is Chinese: Yes, No
- Subject is Chinese citizen: Yes, No
- Age (years): summary statistics.
- Age categories: < 65 years, ≥ 65 years (further break-down: 65 - < 75 years, 75 - < 85 years, ≥ 85 years).
- Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline: 0, 1, >=2.
- Height (cm) at baseline: summary statistics.
- Nicotine consumption: summary statistics
- Alcohol consumption: summary statistics
- HPV status: positive/negative/unknown

Specifications for computation:

- Age (years): (date of given informed consent – date of birth + 1) / 365.25. The integer part of the calculated age will be used for reporting.
  - In case of missing day for at least one date, but month and year available for both dates:

    For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing month for at least one date, but year available for both dates:

    For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used

A supportive listing will be provided.

13.2 Medical History

The summary tables for past and ongoing Medical History will also be provided detailing the number and percentage of subjects by Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class (SOC) (ordered alphabetically) and Preferred Term (PT) (ordered alphabetically); each subject will be counted only once within each PT or SOC. The summaries will be based on ITT analysis set.

The related listing will also be provided.

13.3 Other Baseline Characteristics

Information on **disease characteristics** collected on the "Disease History" eCRF page will be summarized on ITT analysis set as follows:

- Site of primary tumor. The location of the tumor as reported on the "Disease history" eCRF page according to the International Classification of Diseases for Oncology (ICD-O) and the decoded term will be presented.
- Tumor histopathologic / cytologic type: Squamous cell carcinoma Well differentiated, Squamous cell carcinoma Moderately differentiated, Squamous cell carcinoma Poorly differentiated, Squamous cell carcinoma None.
- T stage at initial diagnosis: T0, T1, T2, T3, T4, TIS, TX.
- N stage at initial diagnosis: N0, N1, N2, N3, NX.
- M stage at initial diagnosis: M0, M1, MX.
- T stage at study entry: T0, T1, T2, T3, T4, TIS, TX.
- N stage at study entry: N0, N1, N2, N3, NX.
- M stage at study entry: M0, M1, MX.
- Time since initial cancer diagnosis (months), defined as (date of randomization – date of initial cancer diagnosis) / 30.4375: summary statistics.
    - Time since first occurrence of recurrent disease (months), defined as (date of randomization – date of first occurrence of recurrent disease) / 30.4375: summary statistics.
- Time since first occurrence of metastatic disease (months), defined as (date of randomization – date of first occurrence of metastatic disease) / 30.4375: summary statistics.
- Metastatic sites.

Handling of missing/incomplete dates for initial cancer diagnosis, documented, locally advanced, inoperable or metastatic disease diagnosis and for first occurrence of metastatic disease:

If only the day is missing, the date will correspond to the last day of the given month. If day and month are missing, the date will be set to the last day of the given year. The imputed date should not be later than the screening date.

A listing will support this table.

Echocardiogram

The left ventricular ejection fraction (LVEF) will be measured at screening by echocardiogram.

The data will only be listed: LVEF (%) and the test result as recorded in "Echocardiogram" eCRF page will be provided.

ECG and Vital Signs

The table summarizing ECG and vital signs at baseline will be produced based on ITT analysis set.

The ECG overall assessment as reported by the investigator on the "Electrocardiogram" eCRF page will be summarized at baseline as follows:

- Number and percentage of subjects with result of ECG reported as Normal.
- Number and percentage of subjects with Abnormal result of ECG.

For vital signs, systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate, weight measurements and body surface area (BSA) at baseline will be summarized.

Laboratory parameters

Hematology and biochemistry parameters measured at baseline will also be presented by descriptive statistics. Refer to the section 17.3 for further details.

14 Previous or Concomitant Medications/Procedures

The summaries in this section will be based on the ITT analysis set.

14.1 Prior Anti-Cancer Treatment and Procedures

The prior anti-cancer treatments and procedures are collected under the "Prior anti-cancer drug therapies", "Prior anti-cancer radiotherapy", "Prior anti-cancer surgeries", eCRF pages.

The overall summary of presence of prior anti-cancer treatments/procedures tables will include:

- Number of subjects with at least one prior anti-cancer drug therapy
  - Type of therapy: Cytotoxic therapy / Endocrine therapy / Monoclonal antibodies therapy / Small molecules / Immunotherapy / Other
  - Intent of therapy: Neoadjuvant / Adjuvant / Metastatic or Locally advanced
  - Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non CR/Non PD) / Not assessable / Unknown
- Number of subjects with at least one prior radiotherapy
  - Disease progression in the given previously-irradiated region: yes/no
  - Was the radiotherapy combined with chemotherapy: yes/no
- Number of subjects with at least one prior anti-cancer surgery
  - Curative intent for surgery: yes/no
  - Outcome of surgery: No residual tumor after resection (R0) / Tumor/metastases not resected completely with microscopic residual lesions (R1) / Tumor/metastases not resected completely with macroscopic residual lesions (R2) / Metastases not resected (NR) / Other

An additional table will display a summary of the prior anti-cancer drugs. This summary table will present Anatomical Therapeutic Chemical Classification System (ATC) 2nd level and preferred term of drug name as given from the World Health Organization Drug Dictionary (WHO-DD) current version (by decreasing frequency) based on the incidence in the "Overall" column. In case of equal frequency regarding PT, alphabetical order will be used. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting. A subject will be counted only once within a given drug name, even if he/she received the same medication at different times.

The following listings of prior anti-cancer treatments and procedures will also be provided:

- Listing of prior anti-cancer drug therapies,
- Listing of prior surgeries,
- Listing of prior radiotherapy.

These will include the subject identification number, treatment arm and all the relevant collected data-fields on the corresponding eCRF pages.

14.2 Concomitant Medication and Procedures

Medications

Concomitant medications are collected on the "Concomitant medications details" eCRF page and coded using WHO-DD current version.

Traditional Chinese Medicines (TCMs) are a subset of concomitant medications and identified by presence of "TCM" in the medication name as reported by investigator.

According to the concomitant medication start and stop dates, they will be classified as follows:

- Concomitant medications - prior to first treatment: medications stopped before the first dose of trial treatment
- Concomitant medications – on study: medications taken on or after the first dose of trial treatment and within 30 days after last dose of trial treatment. Any medication with start and end dates missing will be considered as on study concomitant medication as well.

Concomitant medications will be summarized as number of subjects with any concomitant medication and also within each ATC-2nd level and preferred term separately for medications prior to first treatment and on study. The summary will be presented by treatment arm and overall based on ITT analysis set.

For TCMs the total number of subjects with any TCM and each TCM (as reported by investigator) will be produced separately for medications prior to first treatment and on study. The summary will be presented by treatment arm and overall based on ITT analysis set.

Concomitant medications will be listed. The listing will include: subject identification number, treatment arm and all corresponding collected data-field on the corresponding eCRF pages, as well as a flag to identify each medication as prior to first treatment or on study.

Premedication, as recorded in "Premedication detail" eCRF page, will be summarized and listed separately. The total number of subjects with any premedication and each premedication (as reported by investigator) will be produced.

Procedures

Concurrent procedures are reported on the "Concomitant procedures details" eCRF page, will be coded using the most recent MedDRA version.

According to the procedure start and stop dates, they will be classified as follows:

- Concurrent procedures - prior to first treatment: procedures stopped before the first dose of trial treatment
- Concurrent procedures - on study: procedures taken on or after the first dose of trial treatment and within 30 days after last dose of trial treatment. Any procedure with start and end dates missing will be considered as on study concurrent procedure as well.

The concurrent procedures will be summarized based on ITT population per treatment arm and overall separately for procedures prior to first treatment and on study. The number and percentage of subjects within each MedDRA SOC (ordered alphabetically) and PT (ordered alphabetically) will be displayed. The reason for procedures will be summarized.

Concurrent procedures will also be listed including: subject identification number, treatment arm and all corresponding collected data-field on the corresponding eCRF page and also coding information. A flag will be added to identify each procedure as prior to first treatment and on study.

14.3 Anti-Cancer Treatment after Discontinuation

The data collected from the "Anti-cancer treatment after discontinuation" eCRF page will be listed.

The anti-cancer treatments after discontinuation will also be summarized in terms of:

Number of subjects with at least one anti-cancer drug therapy after discontinuation

- Type of therapy: Cytotoxic therapy / Endocrine therapy / Monoclonal antibodies therapy / Small molecules / Immunotherapy / Other
- Intent of therapy: Neoadjuvant / Adjuvant / Metastatic or Locally advanced
- For the Metastatic or Locally Advanced Intent, the number of subjects with each Line of treatment will be presented
- Best response: Complete Response (CR) / Partial Response (PR) / Stable Disease (SD) / Progressive Disease (PD) / Non-Complete Response/Non-Progressive Disease (Non CR/Non PD) / Not assessable / Unknown

15 Treatment Compliance and Exposure

The extent of exposure for cetuximab, cisplatin, carboplatin, and 5-FU will be characterized by duration (weeks), number of initiated cycles, cumulative dose, dose intensity, relative dose intensity, number of dose reductions and dose delays, drug discontinuation.Descriptive statistics will be used to summarize treatment exposure, based on the eCRF data. Summaries will be performed on the safety analysis set.

All dosing calculations and summaries will be based on "cetuximab Initial Administration", "Cetuximab Administration", "Cisplatin Administration", "Carboplatin Administration", and "5-FU Administration" eCRF pages.

15.1 Cetuximab Exposure

.Analysis of cetuximab exposure will be based on the calculated actual dose levels (total dose administered (mg) / BSA (body surface area in m^2). For total dose administered, the actual dose administered as entered in the eCRF pages will be used. For BSA, BSA value collected on the "BSA Determination" eCRF page will be used. The last available BSA of the subject on or prior to the day of cetuximab dosing will be used. The duration of cetuximab treatment (in weeks) during the study is defined as:

$$\text{duration of cetuximab} = \left(\frac{(\text{date of last dose of cetuximab - date of first dose of cetuximab}) + 7}{7}\right)$$

The total number of cetuximab infusions per subject is the count of the infusions with non-zero dose of cetuximab that the subject received.

The cumulative actual treatment dose (mg/m^2) of cetuximab per subject is the sum of the calculated actual dose levels of cetuximab that the subject received.

The dose intensity of cetuximab (mg/m^2/week) per subject from the second infusion is defined as:

$$\left(\frac{\text{Cumulative dose of cetuximab from 1st infusion} - \text{initial dose of cetuximab}}{((\text{date of last dose of cetuximab} - \text{date of second dose of cetuximab}) + 7) / 7}\right)$$

The relative dose intensity of cetuximab (%) starting from the second infusion is defined as the dose intensity of cetuximab defined in the preceding formula divided by 250 mg/m^2/week (the planned weekly dose as assigned in the protocol) and multiply by 100. Therefore the dose intensity and the relative dose intensity are only calculated for subjects who received at least 2 dosages of cetuximab.

Dose reductions

The minimum doses of trial drugs will be derived per subject and clustered according to the proportions of the planned dose. The minimum dose levels will be categorized as follows:

Minimum relative dose	Cetuximab* (mg/m^2)	Cisplatin (mg/m^2)	5-FU (mg/ m^2/day)	Carboplatin

100 % (planned dose)	250	75	750	AUC 5
⩾ 90%	⩾225	⩾67.5	⩾675	Based on
⩾70 - <90%	175 - <225	52.5 - <67.5	525 - <675	planned dose
⩾50 - <70%	125 - <175	37.5 - <52.5	375 - <525	given in the
<50%	<125	<37.5	<375	CRF

*Initial dose will be omitted

Delays

Cetuximab should be administered, if possible, on the same day of each week with no more than 3 days deviation. From there, a delay will be defined as a period of more than 10 days between 2 subsequent infusions (from the second infusion). The number of days delay will be calculated as follows:

[date of infusion (i) – date of infusion (i-1)] – 10 days, where i=2,3,..I

If the value above is >0 days, then this will be classed as a delay. A subject may have more than one treatment delay throughout the course of treatment.

The summary of cetuximab treatment exposure table will include the following information:

- Duration of cetuximab therapy (weeks): summary statistics.
- Number of initiated cycles for cetuximab: summary statistics
- Total number of cetuximab infusions received: number of subjects with 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, >10 infusions
- Cumulative actual treatment dose of cetuximab (mg/m^2): summary statistics.
- Dose intensity of cetuximab (mg/m^2/week) excluding initial dose: summary statistics.
- Relative dose intensity of cetuximab (%) excluding initial dose: < 60%, 60% - < 80%, 80% - < 90%, 90% - 110%, > 110%.
- Number of subjects per minimum relative dose category (as defined Section 15.1)
- Number of subjects with at least one delayed cetuximab infusion, and maximum length of delay (no delay including 1-2 days delay, 3-8 days, 9-15 days, ≥16 days) – worst case

A listing will detail cetuximab exposure for each subject based on “Cetuximab administration” eCRF page.

In addition, batch numbers data, as recorded in “Accountability Group A” eCRF page will be listed.

15.2 Cisplatin Exposure

Analysis of cisplatin exposure will be based on the calculated actual dose levels (total dose administered (mg) / BSA (body surface area in m^2). For total dose administered, the actual dose administered as entered in the eCRF pages will be used. For BSA, BSA value collected on the

"BSA Determination" eCRF page will be used. The last available BSA of the subject on or prior to the day of dosing will be used.

The number of initiated cycles for cisplatin:

A cycle is considered initiated if at least one non-null dose of cisplatin was administered during this cycle.

The duration of cisplatin treatment (in weeks) during the study is defined as:

$$\text{duration of cisplatin} = \left(\frac{(\text{date of last dose of cisplatin} - \text{date of first dose of cisplatin}) + 21}{7}\right)$$

The total number of cisplatin infusions per subject is the count of the infusions with non-zero dose of cisplatin that the subject received.

The cumulative actual treatment dose (mg/m^2) of cisplatin per subject is the sum of the calculated actual dose levels of cisplatin that the subject received.

The dose intensity (mg/m^2/3 weeks) of cisplatin and the relative dose intensity (%) of cisplatin will be calculated for a 3-weekly cycle:

$$\text{dose intensity of cisplatin} = \left(\frac{\text{Cumulative dose of cisplatin from 1st infusion}}{\text{duration of cisplatin in weeks} / 3}\right)$$

The relative dose intensity (%) of cisplatin is defined as the dose intensity of cisplatin divided by 75 mg/m^2/3 weeks (the planned dose per cycle for cisplatin as assigned in the protocol).

Delays

Cisplatin should be administered, if possible, on the same day of each cycle with no more than 3 days deviation. From there, a delay will be defined as a period of more than 24 days between 2 subsequent infusions (from the second infusion). The number of days delay will be calculated as follows:

$$[\text{date of infusion (i)} - \text{date of infusion (i-1)}] - 24 \text{ days, where i=2,3,..I}$$

If the value above is >0 days, then this will be classed as a delay. A subject may have more than one treatment delay throughout the course of treatment.

Dose intensity by cycle

Each cycle is defined by a 3-week period. The dose intensity per cycle is defined by the sum of the total dose levels that the subject received within that time period, i.e. treatment(s) within the last 3 days of each cycle (e.g., day 19-21) are linked to the subsequent cycle as these administrations are regarded as premature start of the next cycle.

Cycle 1 (week 1-3)	Cumulative dose from day 1 to day 18

Cycle 2 (week 4-6)	Cumulative dose from day 19 to day 39
Cycle 3 (week 7-9)	Cumulative dose from day 40 to day 60
Cycle 4 (week 10-12)	Cumulative dose from day 61 to day 81
…	…
Cycle x (week (x-1)*3+1-x*3)	Cumulative dose from day (x-1)*21-2 to day x*21-3

The summary of cisplatin treatment exposure and compliance table will include the following information:

- Duration of cisplatin therapy (weeks): summary statistics.
- Number of initiated cycles for cisplatin: summary statistics
- Total number of cisplatin infusions received: number of subjects with infusions: 0, 1, 2, 3, 4, 5, 6, others, missing
- Cumulative actual treatment dose of cisplatin (mg/m^2): summary statistics.
- Dose intensity of cisplatin (mg/m^2/3 weeks) overall and by cycle: summary statistics.
- Relative dose intensity of cisplatin (%): < 60%, 60% - < 80%, 80% - < 90%, 90% - 110%, > 110%.
- Number of subjects per minimum relative dose category (as defined Section 15.1)
- Number of subjects with delayed cisplatin infusions, and maximum length of delay (no delay including 1-2 days delay, 3-8 days, 9-15 days, ≥16 days)

In addition, a listing will provide detail on cisplatin exposure for each subject based on "Cisplatin administration" eCRF page.

15.3 Carboplatin Exposure

Analysis of carboplatin exposure will be based on the total actual dose administered. For total dose administered, the actual dose administered as entered in the eCRF pages will be used.

Number of subjects received carboplatin in each arm will be summarized.

The number of initiated cycles for carboplatin:

A cycle is considered initiated if at least one non-null dose of carboplatin was administered during this cycle.

The duration of carboplatin treatment (in weeks) during the study is defined as:

$$\text{duration of carboplatin} = \left(\frac{(\text{date of last dose of carboplatin - date of first dose of carboplatin}) + 21}{7}\right)$$

The total number of carboplatin infusions per subject is the count of the infusions with non-zero dose of carboplatin that the subject received.

The dose intensity (mg/3 weeks) of carboplatin:

$$\text{dose intensity of carboplatin} = \left(\frac{\text{Cumulative dose of carboplatin from 1st infusion}}{\text{duration of carboplatin in weeks / 3}}\right)$$

The planned dose (mg/3weeks) of carboplatin at each cycle is defined based on the Area under curve (AUC) = 5 and the Glomerular filtration rate (GFR) as collected on the "Carboplatin administration" eCRF page

$$\text{planned dose of carboplatin} = \text{AUC [mg/ml x min]} \times (\text{GFR [ml/min]} + 25\text{[ml/min]})$$

The relative dose intensity (%) of carboplatin is defined as the dose intensity of carboplatin divided by the mean of planned doses at each cycle.

Delays

Carboplatin should be administered, if possible, on the same day of each cycle with no more than 3 days deviation. From there, a delay will be defined as a period of more than 24 days between 2 subsequent infusions (from the second infusion). The number of days delay will be calculated as follows:

[date of infusion (i) – date of infusion (i-1)] – 24 days, where i=2,3,..I

If the value above is >0 days, then this will be classed as a delay. A subject may have more than one treatment delay throughout the course of treatment.

The summary of carboplatin treatment exposure and compliance table will include the following information:

- Duration of carboplatin therapy (weeks): summary statistics.
- Number of initiated cycles for carboplatin: summary statistics
- Total number of carboplatin infusions received: number of subjects with infusions: 0, 1, 2, 3, 4, 5, 6, others, missing
- Cumulative actual treatment dose of carboplatin (mg): summary statistics.
- Dose intensity of carboplatin (mg/ 3 weeks) overall and by cycle: summary statistics.
- Relative dose intensity of carboplatin (%): < 60%, 60% - < 80%, 80% - < 90%, 90% - 110%, > 110%.

- Number of subjects with delayed carboplatin infusions, and maximum length of delay (no delay including 1-2 days delay, 3-8 days, 9-15 days, ≥16 days)

An additional table will provide the following statistics:

- Overall duration of cisplatin and carboplatin treatment (weeks) defined as:

$$\text{overall duration} = \left(\frac{(\text{date of last dose} - \text{date of first dose}) + 21}{7}\right)$$

where date of last dose is the latest date between last dose of cisplatin and last dose of carboplatin, and date of first dose is the first dosing date of cisplatin.

- Overall number of cycles from the date of first dose of cisplatin until the latest date between last dose of cisplatin and last dose of carboplatin
- Number of subjects with cisplatin treatment by cycle
- Number of subjects with carboplatin treatment by cycle

In addition, a listing will provide detail on carboplatin exposure for each subject based on "Carboplatin administration" eCRF page.

15.4 5-FU Exposure

Analysis of 5-FU exposure will be based on the calculated actual dose levels (total dose administered (mg) / BSA (body surface area in m^2). For total dose administered, the actual dose administered as entered in the eCRF pages will be used. For BSA, BSA value collected on the "BSA Determination" eCRF page will be used. The last available BSA of the subject on or prior to the day of dosing will be used.

The number of initiated cycles for 5-FU:

A cycle is considered initiated if at least one non-null dose of 5-FU was administered during this cycle.

The duration of 5-FU treatment (in weeks) during the study is defined as:

$$\text{duration of 5-FU} = \left(\frac{(\text{stop date of last dose of 5-FU} - \text{start date of first dose of 5-FU}) + 16}{7}\right)$$

The total number of 5-FU infusions per subject is the count of the infusions with non-zero dose of 5-FU that the subject received.

The cumulative actual treatment dose (mg/m^2) of 5-FU per subject is the sum of the calculated actual dose levels of 5-FU that the subject received.

The dose intensity (mg/m^2/3 weeks) of 5-FU and the relative dose intensity (%) of 5-FU will be calculated for a 3-weekly cycle:

$$\text{dose intensity of 5-FU} = \left(\frac{\text{Cumulative dose of 5-FU from 1st infusion}}{\text{duration of 5-FU in weeks / 3}}\right)$$

The relative dose intensity (%) of 5-FU is defined as the dose intensity of 5-FU divided by 750*5 mg/m^2/3 weeks (the planned dose per cycle for 5-FU as assigned in the protocol).

The summary of 5-FU treatment exposure and compliance table will include the following information:

- Duration of 5-FU therapy (weeks): summary statistics.
- Number of initiated cycles for 5-FU: summary statistics
- Total number of 5-FU infusions received: number of subjects with infusions: 0, 1, 2, 3, 4, 5, 6, others, missing
- Cumulative actual treatment dose of 5-FU (mg/m^2): summary statistics.
- Dose intensity of 5-FU (mg/m^2/3 weeks) overall and by cycle: summary statistics.
- Relative dose intensity of 5-FU (%): < 60%, 60% - < 80%, 80% - < 90%, 90% - 110%, > 110%.
- Number of subjects per minimum relative dose category (as defined Section 15.1)
- Number of subjects with delayed 5-FU infusions, and maximum length of delay (no delay including 1-2 days delay, 3-8 days, 9-15 days, ≥16 days)

In addition, a listing will provide detail on 5-FU exposure for each subject based on "5-FU administration" eCRF page.

16 Endpoint Evaluation

The ITT analysis set will be used for endpoint evaluation. Efficacy analysis will be repeated on the PP analysis set only if the PP set represents less than 90% of the ITT analysis set.

16.1 Primary Endpoint Analyses

16.1.1 Primary Analysis of Progression Free Survival (PFS)

Analysis Set

- ITT, PP (as sensitivity analysis if less than 90% of ITT)

The primary endpoint of this trial is PFS time as assessed by independent radiology read. IRC will perform *radiology* and *clinical* reviews as described in the IRC Charter. The results of the *radiology* review will be used for the primary analysis.

The PFS time by IRC is defined as the duration (in months) from the date of randomization until first observation of PD (based on imaging as assessed by IRC), or death due to any cause when death occurs within 60 days after the last tumor assessment or the randomization (whichever is later).

Any subject with neither assessment of tumor progression, nor death date within 60 days after last tumor assessment or randomization will be censored on the date of last tumor assessment or randomization. A subject who has not received trial treatment and for whom no date of progression or death is known will be censored on the date of randomization (Day 1) or date of last tumor assessment, whichever comes later. The following censoring rules will be applied.

Censoring Rules

Situation		Date of event / censoring	Censoring
Radiological PD (RECIST 1.1)		Date of PD	No
No radiological PD (RECIST 1.1)	If death within 60 days after last tumor response assessment or the randomization (whichever is later)	Date of death (CRF)	No
	If death not within 60 days after last tumor response assessment / No death	Date of last tumor response assessment within trial	Yes

Special cases which overrule general rules:

No tumor assessment at baseline	Death within 60 days after date of randomization	Date of death	No
	Death not within 60 days after date of randomization / No death	Date of randomization	Yes
No tumor assessment after start of treatment and no radiological PD (RECIST 1.1)	Death within 60 days after date of randomization	Date of death	No
	Death not within 60 days after date of randomization / No death	Date of randomization	Yes

The last tumor assessment date is defined as the last available and evaluable tumor assessment performed prior to the cut-off date (or prior to EoS, i.e. subjects lost to follow-up or who withdraw consent). If no evaluable tumor assessment is available, this date will be the randomization date.

Imputation methods for estimating missing data:

- For imputing missing parts of dates for the efficacy analyses (except OS) the missing day in a date will be imputed as the 15th of the month, if month and year is documented. If the imputation is earlier than the date of randomization, the day of randomization is taken. In all other cases missing or incomplete dates will not be imputed.

- For imputing missing day of death date, if month and year is available, the day will be imputed by 15, unless this results in a date not later as a date the subject is known to be alive. In that case the date of death will be imputed by the last date known to be alive + 1.

The treatment effect expressed as hazard ratio of cetuximab plus CTX to CTX alone including 95% CI on PFS time will be primarily evaluated using a stratified Cox proportional hazard model, including treatment and the randomization strata (as specified in the IWRS, see Section 7.2): ECOG performance status (0 versus 1) and primary tumor site (oral cavity versus hypopharynx versus others).Each strata will define separate baseline hazard functions (using the 'STRATA' - statement in SAS Proc PHREG), i.e. for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the treatment arm (0=CTX only, 1=CTX + cetuximab) and β the unknown regression parameter.

Ties will be handled by replacing the proportional hazards model by the discrete logistic model (Ties=Discrete option in SAS Proc PHREG). This is a bridging trial; in discussion with Chinese Health Authority, this trial would be regarded as positive if the point estimation of the stratified hazard ratio is less than or equal to 0.77 (retaining at least 50% of the estimated treatment effect of EXTREME trial).

The PFS time of the 2 treatment arms will be described by means of Kaplan-Meier survival curves (product-limit estimates) and associated summary statistics (median PFS time, corresponding two-sided 95% confidence intervals, minimum, maximum, Q1, Q3). Survival estimates at certain time points (3-, 6-, 12-, 18-, 24 months and every 6 months thereafter as applicable), and number of subjects under risk will also be provided. The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and confidence intervals for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980)[2] (conftype=loglog default option in SAS Proc LIFETEST).

The number of events (PD/death) will also be presented within the same table.

An additional table will provide frequencies for events and censoring status by treatment arm according to the following categories:

- Events: Radiological PD based on existing lesions (progressive disease reported for target and/or non-target lesions) / Radiological PD based on new lesions (new lesion(s) is/are reported) /Radiological PD based on existing and new lesions (both progressive disease reported for target and/or non-target lesions and new lesion(s) are reported) / Death within 60 days
- Censoring: Death not within 60 days / Censored at randomization / Lost to follow-up or withdraw consent / Due to data cut-off

Subjects will be considered as “censored at randomization” in case they have no tumor assessment at baseline and no tumor assessment after start of treatment and no radiological PD or death.

They will be considered as censored due to “Lost to follow-up/withdraw consent” in case they have no PD or death before they are lost to follow-up/withdraw consent.

They will be considered as censored "due to cut-off" in case they have no PD or death before the trial data cut-off.

A listing will display information on event and censoring including the following:

- Subject identification number,
- Treatment arm
- Randomization Date
- Last tumor assessment date before cut-off date
- Death date
- Progression date (IRC)
- PFS (IRC): Censoring Flag (Yes/No)/ Description of the Event/Censoring/ PFS (months)

A scatter plot will be produced to compare planned (y-axis) and actual (x-axis) relative day of tumor assessments by treatment arm (2 colors will be used to clearly identify treatment groups). The planned day for EOEA visit will be assigned as the planned day for the last available efficacy assessment visit.

16.1.2 PFS Sensitivity Analyses

To assess the robustness of the primary analysis, the following analyses can be conducted:

- Per-protocol analysis: the same analysis as described above Section 16.1.1 will be repeated on PP analysis set only if PP analysis set includes less than 90% of the ITT analysis set.
- The same analysis as described above Section 16.1.1 will be repeated using results of the *clinical* review from IRC, corresponding listing will also be produced.
- The same analysis as described above Section 16.1.1 will be repeated considering all death as event.
- The same analysis as described above Section 16.1.1 will be repeated considering all death and start of new anti-cancer treatment as event.
- To address the bias due to different times of assessment of disease progression caused by different treatment schedules, the same analysis as described above Section 16.1.1 will be repeated considering date of planned imaging visits instead of date of actual imaging visits. If an event is observed between two planned visits, it will be assigned to the previous one. The planned day for EOEA visit will be assigned as the planned day for the last available efficacy assessment visit.
- The same analysis as described above Section 16.1.1 will be repeated excluding subjects who met the inclusion criteria 3 as defined in protocol version 1.0 (17 November 2014) but who do not meet the updated inclusion criteria 3 as defined in protocol version 2.0 (20 April 2016). Please refer to Appendix 2 for the details for inclusion criteria 3.
- The same analysis as described above Section 16.1.1 will be repeated based on the stratification factors based on eCRF data instead of IWRS data.

Results of PFS primary and sensitivity analyses (hazard ratio and 95%CI) will be displayed using a forest plot.

16.1.3 PFS Subgroup Analyses

Subgroup analyses will comprise univariable unstratified analyses considering the subgroups as defined in Section 10**Error! Reference source not found.**. To assess the heterogeneity of treatment effects across the subgroups levels Cox proportional hazards model will be performed for PFS time as dependent variable and with subgroup type, the treatment arm assignment and with and without the treatment by subgroup type interaction as explanatory variables. P-values for the interaction test will be provided together with the hazard ratios (CTX+Cetuximab over CTX) and 95% CIs.

A forest plot of hazard ratio by subgroups will be provided for illustration. It will include, for each subgroup, the number of subjects per subgroups and treatment group, the number of events with related median (in month) by treatment group and hazard ratio (CTX+Cetuximab over CTX) with the corresponding 95% CIs.

16.1.4 PFS Exploratory Analysis

To explore the treatment effect when adjusted for exploratory variables of potential prognostic values, a **multivariable Cox regression** analysis will be performed. (The potential baseline prognostic factors variables used for this analysis will be the subgroup variables as defined in Section 10.2)

A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata (as documented in the eCRF) which will be included in all models during the selection procedure. The Cox proportional hazard model is defined as: $h(t) = h(0;t) \exp(X\beta)$, where $h(0;t)$ defines the baseline hazard function and X defines the vectors of explanatory variables and β the unknown vector of regression parameters. Variables are entered into and removed from the model in such a way that each forward selection step can be followed by one or more backward elimination steps. The stepwise selection process terminates if no further variable can be added to the model or if the variable just entered into the model is the only variable removed in the subsequent backward elimination. The level of significance for an explanatory variable to enter the model is set to 0.15 and the significance level for removing is set to 0.40. This analysis will be performed using the stepwise selection method available in SAS (Proc PHREG). Once this procedure stops, the factor 'treatment group' will be added to the final model in order to evaluate the effect of treatment on PFS when adjusted for the selected explanatory variables. The hazard ratios of all selected explanatory variables and of the treatment effect will be reported including two-sided 95% confidence intervals. If there is a treatment by covariate interaction present for any of the covariates including in the model (as tested in subgroup analyses, see section 16.1.3), the corresponding parameter will not be considered for the stepwise analysis.

To include baseline variables into Cox's proportional hazards model, in case of low numbers of subjects within a category (< 10 subjects), categories will be pooled as described in the section 10.

16.2 Secondary Endpoint Analyses

The secondary endpoints include PFS time, as assessed by the Investigator, OS time, BOR, DCR, and duration of response (DOR). The following analyses will be performed on the ITT analysis set.

The following secondary endpoints will be analyzed using both IRC radiological assessments and investigator assessments:

- BOR
- DCR
- DOR

16.2.1 PFS Time by Investigator Assessment

PFS time, as assessed by the Investigator, is defined as the duration (in months) from randomization until first observation of radiologically confirmed PD (by the Investigator), or death due to any cause when death occurs within 60 days after the last tumor assessment or randomization (whichever is later). The same censoring rule as with the PFS time assessed by IRC is applied.

The date of first PD radiologically confirmed will be based on the earliest imaging date for the tumor assessment visit where overall assessment visit is PD.

In case there are several dates of scans within the same tumor assessment visit, the earliest date will be used as the date of first confirmed PD.

The same analyses as described Section 16.1.1 will be conducted, the corresponding listing will be produced.

Subgroup analyses will be performed for predefined baseline factors (see Section 15.1.3).

The PFS time, as assessed by the investigator, will be described by means of Kaplan-Meier survival curves (product-limit estimates) for each treatment arm.

The concordance between the IRC radiology assessment and the investigator assessment will be tabulated by treatment group including the following information:

- PFS event by source (Investigator only / IRC only / IRC and Investigator / no PFS event)
- Difference in days (PFS date assessed by IRC – PFS date assessed by investigator)
  - ≤ -30 days
  - >-30 days to < 30 days
  - ≥ 30 days
- Overall concordance of PFS

- Agreement
- Disagreement
- Both no PFS event

- Summary of difference (days)

16.2.2 Overall Survival Time

OS time is defined as the time (in months) from randomization to the date of death. If a subject is alive at the time of analysis, survival time will be censored at the last date when the subject is known to be alive. If this date is after data cut-off, subjects will be censored at the date of data cut-off.

The latest of the following dates will used to determine the last date known to be alive:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after trial treatment discontinuation.
- AE start and end dates
- Last date of contact collected on the 'Survival information' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study drug start and end dates
- Randomization date

The same analyses as described Section 16.1.1 will be conducted.

Subgroup analyses will be performed for predefined baseline factors (see Section 15.1.3 and use OS instead of PFS).

The OS time will be described by means of Kaplan-Meier survival curves (product-limit estimates) for each treatment group and a forest plot will also be provided as described for PFS

An additional table will provide frequencies for events and censoring status by treatment group according to the following categories:

- Events: Death
- Censoring: At data cut-off (administrative censoring) / Before data cut-off (non-administrative censoring)

Subjects last known to be alive before data cut-off, subjects who withdrew consent or subjects lost to FU before end of trial will be considered as censored before data cut-off.

A listing will display information on event and censoring including the following:

- Subject Id

- Treatment Arm
- Randomization Date
- Death date
- Last date known to be alive
- Date of first cetuximab administration given as Anti-cancer Drug Therapy after Discontinuation of the trial treatment
- OS: Censoring Flag (Yes/No)/ OS (months)

16.2.3 Best Overall Response, Disease Control Rate and Duration of Response

The parameters described in this section will be based on both IRC (radiologist) and investigator assessment as recorded in the "Assessment of Disease Based on Imaging" eCRF page. The BOR summary will also be produced based on the IRC clinical assessment.

The **BOR** for each subject is defined as the best result obtained among all tumor assessments from the randomization until documented disease progression. The overall response will be based on imaging, classified according to RECIST version 1.1 criteria (unconfirmed response).

The best possible overall response can be CR, PR, SD and PD, non-CR/non-PD, NE. If a subject has a missing baseline tumor assessment and/or no tumor assessment on-treatment, BOR will be Not Evaluable (NE). In the case the single response is SD, SD must have been assessed no less than 6 weeks (at least 42 days) after randomization, otherwise the best response will be NE.

The BOR rate (also referred as Objective Response Rate) is defined as the number of subjects, whom BOR was either Complete Response (CR) or Partial Response (PR), relative to the number of subjects belonging to the trial set of interest.

The **DCR** will also be based on imaging and classified according to RECIST version 1.1 criteria. The DCR is defined as the number of subjects whose BOR is either CR, PR or SD, divided by the number of subjects belonging to the trial set of interest.

The DOR will be determined for subjects whose BOR was either CR or PR. It is defined as the time from the first assessment of CR or PR until the event defining PFS time (see section 16.1.1) and expressed in weeks. The subjects with no event will be censored to the last tumor assessment data available before cut-off date or randomization date whatever comes later.

The following information will be summarized, by treatment group and overall:

- BOR per type of BOR (CR, PR, SD, PD, non-CR/non-PD and NE),
- BOR rate,
- DOR,
- DCR.

BOR rate and DCR will be presented with the corresponding two-sided 95% exact confidence interval based on the Clopper-Pearson method.

The odds ratio adjusted by randomization strata with associated 95% confidence interval will also be presented.

Subgroup analyses will comprise univariable unstratified analyses considering the subgroups as defined in Section 10. For each subgroup, odds ratio and p-value for the interaction test will be provided. In addition, the response rate with 95% exact confidence intervals using the Clopper-Pearson method will be computed.

To explore the treatment effect on the BOR when adjusted for exploratory variables of potential prognostic values, a multivariable analysis will also be conducted (the potential baseline prognostic factors variables used for this analysis will be the subgroup variables as defined in Section 10.2). A stepwise selection procedure will serve to identify explanatory variables of potential prognostic values additional to the randomization strata (as documented in the eCRF) which will be included in all models during the selection procedure. The level of significance for an explanatory variable to enter the model will be set to 0.15 and the significance level for removing will be set to 0.40. If there is a treatment by covariate interaction present in any of the covariates including in the model, the corresponding parameter will not be considered for the stepwise analysis.

For each covariate kept in the model, the p-value, the odds-ratio and the corresponding 95% CI will be provided. An odds-ratio > 1 will indicate increased chance of response when a binary covariate takes the value 1, and increased chance of response for higher values of continuous covariates.

The listing of tumor assessments per time points (including e.g., type of lesion, imaging date, lesion description (site, type, size/status, assessment method), sum of diameter of TLs and overall response per timepoint) will also be provided based on data recorded on the “Tumor assessment - Target Lesions”, “Tumor assessment – Non-Target Lesions”, “Tumor assessment - New Lesions” and “Sum of diameters” eCRF pages.

16.3 Other Endpoint Analyses

Follow-up Duration (in months) is calculated in the same way as PFS duration as assessed by investigator (see section 16.2.1), but the censoring rules (described in the section 16.1.1) are inverted: subjects accounted as experiencing an event for PFS are censored and those who are censored for PFS are accounted as events.

17 Safety Evaluation

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

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

17.1 Adverse Events

Treatment emergent adverse events (TEAEs) are those events that emerge during treatment having been absent pre-treatment, or worsen relative to the pre-treatment state and with onset dates occurring within the first dosing day of trial treatment (cetuximab, cisplatin, carboplatin, or 5-FU) until 30 days after the last dose of trial treatment.

All analyses described in Section 17.1 will be based on TEAEs if not otherwise specified.

Incomplete AE-related dates will be handled as follows:

- Incomplete or missing start date:
  - In case the onset date is completely missing or the onset is in the same year (if the onset year is available only) or the onset is in the same month and year (if the day is missing) as start of trial treatment, then the onset date will be replaced by the minimum of start of trial treatment date and AE resolution date (imputed, if incomplete).
  - In all other cases the missing onset day or onset month will be replaced by 1.
- Incomplete or missing stop date:
  - Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case the date of death will be used to impute the incomplete stop date.
  - In all other cases, the incomplete stop date will not be imputed.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

The severity of AEs will be graded by the investigator using the NCI-CTCAE version 4.03.

Related Adverse Events are those AEs with relationship to any trial treatment (cetuximab, cisplatin, carboplatin, or 5-FU) reported by the investigator as related or those of unknown relationship (i.e. no answer to all the questions “Relationship with Cetuximab”, “Relationship with Cisplatin”, “Relationship with Carboplatin” and “Relationship with 5-FU”). If relationship is missing the adverse event will be set to “Related” if the subject received at least one dose of given drug and the start date of adverse event is on or after the date of the first dose of this drug.

Cetuximab related Adverse Events are those AEs with relationship to cetuximab reported by the investigator as related or those of unknown relationship to cetuximab (i.e. no answer to the question “Relationship with Cetuximab”). If relationship is missing then the worst-case scenario is applied and the adverse event will be set to “Cetuximab Related”.

Chemotherapy related Adverse Events are those AEs with relationship to cisplatin or carboplatin or 5-FU reported by the investigator as related or those of unknown relationship to cisplatin (i.e. no answer to the question “Relationship with Cisplatin” or “Relationship with

Carboplatin" or "Relationship with 5-FU"). If relationship is missing then the worst-case scenario is applied and the adverse event will be set to "Chemotherapy Related".

Serious Adverse Events (SAEs) are those events reported on the "Adverse Event Details" eCRF page with the "Serious Adverse Event" field ticked "Yes".

Adverse Events leading to cetuximab discontinuation are those AEs with action taken regarding cetuximab reported by the investigator as "Drug withdrawn".

Adverse Events leading to chemotherapy discontinuation are those AEs with action taken regarding cisplatin, carboplatin or 5-FU reported by the investigator as "Drug withdrawn".

Adverse Events leading to cetuximab and chemotherapy discontinuation are those AEs with action taken regarding all the ongoing drugs (received at least one dose and not discontinued before the AE start date) reported by the investigator as "Drug withdrawn".

Adverse Events leading to cetuximab interruption are those AEs with action taken regarding cetuximab reported by the investigator as "Drug interrupted".

Adverse Events leading to chemotherapy interruption are those AEs with action taken regarding cisplatin, carboplatin or 5-FU reported by the investigator as "Drug interrupted".

Adverse Events leading to cetuximab dose reduction are those AEs with action taken regarding cetuximab reported by the investigator as "Dose reduced".

Adverse Events leading to chemotherapy dose reduction are those AEs with action taken regarding cisplatin, carboplatin or 5-FU reported by the investigator as "Dose reduced".

Adverse Events leading to hospitalization/prolongation are those AEs with "Requires/prolongs hospitalization" ticked by the investigator.

Adverse Events leading to death are those AEs with outcome reported by the investigator as "Fatal" and/or AEs with a toxicity grade reported by the investigator as "Grade 5".

17.1.1 All Adverse Events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per subject, using MedDRA (latest version) PT as event category and MedDRA (latest version) SOC body term as Body System category.

Adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

If an adverse event is reported for a given subject more than once during treatment, the worst severity and the worst relationship to trial treatment will be tabulated.

In case a subject had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed.

An overview table of TEAEs will be provided detailing the number and percentage of subjects with:

- Any TEAE
- Any trial treatment related TEAE
- Any cetuximab related TEAE
- Any chemotherapy related TEAE
- Any serious TEAE
- Any non-serious TEAE
- Any trial treatment related serious TEAE
- Any cetuximab related serious TEAE
- Any chemotherapy related serious TEAE
- Any TEAE by worst NCI-CTCAE severity grade
- Trial treatment related TEAE by worst NCI-CTCAE severity grade
- Cetuximab related TEAE by worst NCI-CTCAE severity grade
- Chemotherapy related TEAE by worst NCI-CTCAE severity grade
- Any TEAE leading to death
- Any trial treatment related TEAE leading to death
- Any cetuximab related TEAE leading to death
- Any chemotherapy related TEAE leading to death

Tables for TEAEs frequency corresponding to each category in the overview table above will be provided for actions by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically), each subject will be counted only once within each PT or SOC.

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- Summary tables for non- serious adverse events excluding SAEs applying frequency threshold of 5% will be provided.

Besides this, the following tables will also be generated:

- TEAEs with ⩾10% difference between treatment groups
- TEAEs Grade ⩾3 with ⩾5% difference between treatment groups

  SAEs with ⩾5% difference between treatment groups

All TEAEs will be listed to support these tables.

A listing of TEAEs leading to death will also be provided including all relevant information.

17.1.2 Adverse Events Actions

An overview table will be provided for TEAEs actions as following:

- Adverse Events leading to any trial treatment discontinuation
- Adverse Events leading to cetuximab discontinuation
- Adverse Events leading to chemotherapy discontinuation
- Adverse Events leading to both cetuximab and chemotherapy discontinuation
- Adverse Events leading to trial treatment interruption.
- Adverse Events leading to cetuximab interruption.
- Adverse Events leading to chemotherapy interruption
- Adverse Events leading to trial treatment dose reduction
- Adverse Events leading to cetuximab dose reduction
- Adverse Events leading to chemotherapy dose reduction
- Adverse Events leading to hospitalization/prolongation.

Tables for TEAEs frequency corresponding to each category in the overview table above will be provided for actions by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically), each subject will be counted only once within each PT or SOC.

A listing of TEAEs actions including all relevant information will also be provided.

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

17.2.1 Deaths

All deaths, deaths within 30 days after last dose of trial treatment (cetuximab, cisplatin, carboplatin, or 5-FU), deaths within 60 days after first dose of trial treatment as well as the primary reason for death, will be tabulated based on information from the "Report on Death" eCRF page:

- Any subject who died and primary reason for death
  - Progressive disease and/or disease related condition
  - Related to trial treatment(s)
    - Cetuximab
    - Cisplatin
    - Carboplatin
    - 5-FU
  - Event unrelated to trial treatment

    - Unknown
- Subjects who died within 30 days after last dose of treatment and primary reason for death
    - Progressive disease and/or disease related condition
    - Related to trial treatment(s)
        - Cetuximab
        - Cisplatin
        - Carboplatin
        - 5-FU
    - Event unrelated to trial treatment
    - Unknown
- Subjects who died within 60 days after first dose of treatment and primary reason for death
    - Progressive disease and/or disease related condition
    - Related to trial treatment(s)
        - Cetuximab
        - Cisplatin
        - Carboplatin
        - 5-FU
    - Event unrelated to trial treatment
    - Unknown

In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information (date of first / last administration, separately for cetuximab, cisplatin, carboplatin, and 5-FU).

This listing will also include:

- Data from "Report on Death" eCRF page
- Flag for death within 30 days after last dose of trial treatment
- Flag for death within 60 days after first dose of trial treatment

17.2.2 Serious Adverse Events

The following summary tables will be provided for serious TEAEs detailing the number and percentage of subjects by MedDRA primary SOC (ordered alphabetically) and PT (ordered alphabetically); each subject will be counted only once within each PT or SOC:

- Serious TEAEs.

- Trial treatment related serious TEAEs.
- Cetuximab related serious TEAEs
- Chemotherapy related serious TEAEs

A listing of serious TEAEs will also be provided including all relevant information.

17.2.3 Special Adverse Events Categories

Special safety summaries will be performed for special adverse event categories (SPAEC):

- Acne-like rash
- Skin reaction
- Infusion related reaction
- Neurotoxicity associated AEs
- Mucositis
- Septic events
- Cardiac events

The latest special AE list provided by drug safety will also be referred. If there are any difference, the special AE list provided by drug safety has higher priority.

The SPAEC "Infusion related reaction" is further divided into the following medical concepts:

- Allergy/anaphylaxis
- Dyspnea
- Fever
- Other

The SPAEC "Cardiac events" is further divided into the following medical concepts:

- Congestive Heart Failure
- Arrest
- Infarction-ischemia
- Arrhythmia
- Sudden death

The AEs are associated to a category by matching with a list of predefined PT.

The AEs are associated to a category by matching with a list of predefined PT. For the Infusion related reactions, there are 2 categories of events:

- AEs flagged in the definition as "Inclusion of AEs on Day 1 only" = No: any TEAE with the corresponding preferred term will be taken into account
- AEs flagged in the definition as "Inclusion of AEs on Day 1 only" = Yes: AEs with the corresponding preferred term occurred at Cycle 1 Day 1

A listing with all preferred terms for each category and medical concept will be provided.

The following summaries will be produced for all SPAEC:

- Number of subjects with SPAEC events, overall and by medical concept if applicable
- Number of subjects with SPAEC events by NCI-CTCAE grade (any, 1, 2, 3, 4, 5, ⩾3), overall and by medical concept

Special summaries will be prepared separately for events on "skin reactions" and "acne-like rash" (=SPAEC1) only for the patients who received at least one dose of cetuximab as follows:

- Time until first occurrence of any "SPAEC1"
    - 1-7 days,
    - 8-14 days,
    - 15 -21 days,
    - 22-28 days,
    - 29-35 days,
    - 36-42 days,
    - ⩾43 days
- Time until first occurrence of grade 3/4 "SPAEC1" by category:
    - 1-7 days,
    - 8-14 days,
    - 15 -21 days,
    - 22-28 days,
    - 29-35 days,
    - 36-42 days,
    - ⩾43 days
- The resolution status of SPAEC1 after cetuximab discontinuation
    - 0 days (resolved during treatment),
    - resolution within days 1-30,
    - 31-60,
    - 61-90,

- 91-120,
- >120.

- The resolution status of SPAEC1 Grade 3/4 after cetuximab discontinuation
  - 0 days (resolved during treatment),
  - resolution within days 1-30,
  - 31-60,
  - 61-90,
  - 91-120,
  - >120.

The time until first occurrence of any "SPAEC1" (in days) will be calculated as

(first onset date of any "SPAEC1" related event with any grade – first dosing day of cetuximab +1).

The time until first occurrence of grade ⩾ 3 "SPAEC1" will be calculated similarly. These statistics will be categorized for those subjects with any grade ⩾ 3.

The resolution status of SPAEC1 will be prepared for all subjects in the cetuximab treatment arm with SPAEC1. The resolution status will be presented by calculating the duration (in days) of SPAEC1 after last cetuximab infusion as follows:

Duration = resolution date of SPAEC1 – last dosing date of cetuximab +1

For subjects with overlapping events the last resolution date will be taken. Duration of SPAEC1 per subject (any, grade ⩾ 3) will be categorized into intervals of 30 days length up to a sensible limit (e.g., 120 days), >sensible limit, at least one episode ongoing (including outcome death), unknown. Unknown is defined as at least one episode of resolved with SPAEC1 unknown resolution date, but without any further ongoing SPAEC1. Events with a resolution date before the last cetuximab infusion will be assigned a value of 0 days, which represents the subjects with resolution during cetuximab treatment.

Subjects with missing onset or resolution dates of "SPAEC" and subjects with "SPAEC" ongoing at the final visit will be flagged in the individual subject data listings indicating the type of missing variable.

17.2.4 3 Tier Approach

The Crude Rate is calculated as number of subjects with specific AE divided by the total number of subjects at risk expressed as percentage.

The Exposure Adjusted Incidence Rate (EAIR) is defined as the number of subjects with a specific AE divided by the total exposure-time among the subjects in the treatment group at risk of the initial occurrence of the event. If a subject has multiple events, the exposure period of the first

event is used. For a subject with no event, the exposure period is censored at the last follow-up time for the AE summarization period. EAIR will be measured in 1000 subjects within 1 year.

The AEs identified for Tier 1 reporting in this trial are:

- Infusion related reactions
- Skin reactions
- Hypomagnesaemia.

The first two categories are composite and will be based on the list of preferred terms based on the latest MedDRA version and provided by Merck Drug Safety. Hypomagnesaemia includes one preferred term "Hypomagnesaemia".

All the other AEs will be further classified into Tier 2 or Tier 3 based on the Rule-of-4 and Crude Rate threshold. If there are 4 or more subjects with the reported term in any treatment group and Crude Rate is equal or superior to 5%, that term will be included in Tier 2. Otherwise, it will be included in Tier 3.

For the Tier 1 the following summaries will be presented:

- Number of subjects and percentage by category in each treatment group accompanied by Crude Rate difference between treatment groups with 95% CI. CI will be generated using Miettinen & Nurminen (MN) method.
- Forest tree showing Crude Rate and Crude Rate difference with 95% MN CI
- Number of subjects, number of subject-years and EAIR with 95% CI using Poisson method by category in each treatment group. In addition, EAIR difference between treatment groups along with 95% CI will be shown.

For the Tier 2 following summaries will be presented:

- Number of subjects and percentage by SOC and PT and overall in each treatment group accompanied by Crude Rate difference between treatment groups with 95% CI. CI will be generated using MN method.
- Number of subjects, number of subject-years and EAIR with 95% CI using Poisson method by SOC and PT in each treatment group. In addition, EAIR difference between treatment groups along with 95% CI will be shown.

For the Tier 3 following summaries will be presented:

- Number of subjects and percentage by SOC and PT and in each treatment group accompanied by Crude Rate difference between treatment groups.

- Number of subjects, number of subject-years and EAIR by SOC and PT in each treatment group. In addition, EAIR difference between treatment groups will be shown.

No multiplicity adjustment will be applied for Tier 1 and 2 AEs.

17.3 Clinical Laboratory Evaluation

All laboratory assessments are performed at local laboratories and comply with local requirements.

Laboratory values (including corresponding normal ranges) from local laboratories will be converted into the standard units by data management. The results in standard units will be used for the analyses.

Laboratory results will be classified according to the NCI-CTCAE toxicity grading version 4.03. If toxicities for high and low values of a specific parameter are defined, these toxicities will be analyzed separately for the parameter as "Parameter low" and "Parameter high".

Laboratory results that are not part of the NCI-CTCAE will be presented according to the categories: below normal limits, within normal limits and above normal limits (according to the local laboratories normal ranges) by treatment arm.

The hematology differential parameters (Lymphocytes/Leukocytes (%), Neutrophils/Leukocytes (%), Monocytes/Leukocytes (%), Eosinophils/Leukocytes (%), Basophils/Leukocytes (%)) will only be listed.

The definitions for the NCI-CTCAE toxicity grading version 4.03 for each parameter are available in the Appendix 3.

NCI-CTCAE grades available:

The worst on-trial grade, i.e. the highest CTCAE grade after the first dose of trial treatment will be summarized by parameter as follows:

- Number and percentage of subjects with grade >= 0.
- Number and percentage of subjects with grade >= 3.
- Number and percentage of subjects with grade = 4.

Tables will summarize, separately for hematology and biochemistry parameters, the shift from baseline grade to worst on-treatment grade by parameter and treatment group.

NCI-CTCAE grades not available:

The worst on-treatment value for hematology and biochemistry parameters which cannot be graded per NCI-CTCAE will be summarized by parameter according to the local laboratories normal ranges as follows:

- Lowest value after the first dose of trial treatment will be summarized according to Low category (value below normal limits) and Normal category (value within normal limits or above normal limits).
- Highest value after the first dose of trial treatment will be summarized according to Normal category (value within normal limits or below normal limits) and High category (value above normal limits).

Additional tables will summarize, separately for hematology and biochemistry parameters, the shift from baseline to worst on-treatment value by parameters and treatment group. The following categories of values will be used: Low/Normal/High/Missing.

Listings of all hematology and biochemistry values and also abnormal hematology and biochemistry values will also be provided. Abnormal values are defined as values outside of normal ranges. The following information will be included in those listings in addition to the subject ID and treatment arm:

- Selected dosing information: date of first / last administration separately for cetuximab, cisplatin, carboplatin, and 5-FU.
- Laboratory parameter with unit.
- Visit of laboratory parameter measurement
- Collection date of laboratory parameter
- Value of laboratory parameter
- Local laboratories normal ranges for laboratory parameter (lower limit of normal and upper limit of normal).
- Normal range indicator for value of the laboratory parameter (Low, Normal, High).
- Associated grade for value of the laboratory parameter according to NCI-CTCAE.

Urinalysis

All urinalysis results as reported on the "Urinalysis" and "Urinalysis Microscopic Evaluation" eCRF pages will be listed.

Creatinine clearance

Values for Urine creatinine, Serum creatinine and Creatinine clearance as reported on the "Creatinine Clearance" eCRF page will be listed.

Viral Serology

All test results for Hepatitis B Virus (HBV) antigen, HBV antibody, Hepatitis C Virus (HCV) antibody, Human Immunodeficiency Virus (HIV) as collected on the "HBV, HCV, HIV Tests" eCRF page will be listed.

17.4 Vital Signs

Vital signs data will be summarized by treatment group for the Safety analysis set.

Body temperature, blood pressure (BP), heart rate, respiratory rate as well as the weight measurements, will be summarized in shift tables (including number of subjects and percentages) of baseline value versus worst on-treatment change from baseline will be provided for both increase and decrease.

Last assessments prior to first trial drug infusion will be taken into account to define the pre-treatment baseline value.

The following parameter categories will be used for shift tables:

Parameter	Baseline categories	Post-baseline categories
Systolic blood pressure (SBP)	<140 / >=140 mmHg	Absolute change of: =<20 / >20 - =<40 / >40 mmHg
Diastolic blood pressure (DBP)	<90 / >=90 mmHg	Absolute change of: ≤ 20 / >20 - ≤40 / >40 mmHg
Pulse rate	≤100 / >100 bpm	Absolute change of: ≤20 / >20 - ≤40 / >40 bpm
Respiratory rate	≤20 / >20 bpm	Absolute change of: ⩽5/min, >5-⩽10/min, >10/min
Temperature	<37°C / 37°C - <38°C / 38 - <39°C / 39 - <40°C / >=40°C	Absolute change of: <1 / 1 - <2 / 2 - <3 / ⩾3°C
Weight	None (kg)	Absolute change of: <5% / ≥5 - <10% / ≥10 - <20% / ≥20%

The missing and overall categories will also be shown in these tables.

All vital signs data (including body weight), as recorded in the "Vital signs" eCRF page, will be presented in a listing including the value at baseline and the change from baseline.

17.5 Other Safety or Tolerability Evaluations

ECG

The "Result of ECG" parameter will be summarized by treatment arm for the Safety analysis set as follows: shift table from baseline to the worst on-treatment result will be tabulated with the subsequent categories:

- Normal ECG
- Abnormal ECG (includes clinically significant and not clinically significant)
- Missing
- Total

A listing of all ECG parameters results from the "Electrocardiogram" eCRF page will be provided.

Eastern Cooperative Oncology Group performance status

The ECOG data will be summarized by treatment arm for Safety analysis set. Shifts in ECOG performance status from baseline to worst on-treatment performance status will be summarized by treatment group. Missing category will also be included.

A listing will also be provided for ECOG performance status.

18 Benefit Risk Assessment

Not applicable.

19 References

1. Brookmeyer, R. and Crowley, J. (1982), A confidence interval for the median survival time. Biometrics, 38, 29-41.

2. Kalbfleisch, J. D. and Prentice, R. L. (1980), *The Statistical Analysis of Failure Time Data*, New York: John Wiley & Sons.

20 Appendices

Appendix 1 Important Protocol Deviations

Important Protocol Deviations	Clinically Important PD (Y/N)	Can be programmed or not (Y/N)
Inclusion criteria not fulfilled		
Inclusion criteria not fulfilled (#02): No histologically or cytologically confirmed diagnosis of SCCHN	Y	Y
Inclusion criteria not fulfilled (#03): No recurrent and/or metastatic SCCHN not suitable for local therapy	Y	Y
Inclusion criteria not fulfilled (#06): ECOG performance status of 0 or 1	Y	Y
Exclusion criteria fulfilled		
Exclusion criteria fulfilled (ex#01): Prior systemic chemotherapy, except if given as part of multimodal treatment for locally advanced disease that was completed within 6 months before trial entry. (Amendment)	Y	Y
Exclusion criteria fulfilled (ex#03): Previous treatment with monoclonal antibody or signal transduction inhibitors targeting EGFR.	Y	Y
Exclusion criteria fulfilled (ex#04): Nasopharyngeal carcinoma.	Y	Y
All patients who don't fulfill other inclusion criteria or fulfill exclusion criteria.	N	Y
Other Protocol Deviations		
Randomization error: Incorrect treatment group allocation, different to assignment at randomization	Y	Y
Randomization error: Subject randomized but did not receive any study treatment	Y	Y
Randomization error: Stratification error	N	Y
Use of prohibited medication: Additional concurrent chronic systemic immune treatment, chemotherapy, radiotherapy (with exceptions), hormone treatment for treatment of cancer (with exceptions), traditional Chinese medication with approval for use as anticancer treatment or any other investigational agent	Y	N
Tumor assessment: missed one or more locations on tumor assessment	N	N
Tumor evaluation error by investigator according to RECIST version 1.1	N	N
Tumor assessment delay: Out of window visit equal or above 3 weeks	N	Y

Important Protocol Deviations	Clinically Important PD (Y/N)	Can be programmed or not (Y/N)
Continuation on cetuximab treatment when withdrawal criteria met: Occurrence of pregnancy during trial treatment	N	N
Continuation on cetuximab treatment when withdrawal criteria met: Occurrence of PD according to RECIST version 1.1	N	N
Continuation on cetuximab/chemotherapy treatment if occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety and discontinuation is considered necessary by the Investigator and/or Sponsor	N	N
Continuation on cetuximab/chemotherapy treatment if occurrence of AEs and discontinuation of trial treatment is desired or considered necessary by the Investigator and/or the subject	N	N
Continuation on chemotherapy if a delay in chemotherapy treatment of more than 21 days due to toxicity	N	Y
Continuation on cisplatin if occurrence of more than 2 dose reductions of cisplatin	N	N
Continuation on carboplatin if more than 1 dose reduction of carboplatin	N	N
Continuation on 5-FU if occurrence of more than 2 dose reductions of 5-FU	N	N
Continuation on chemotherapy if occurrence of any other criteria requiring discontinuation of chemotherapy.	N	N
Continuation on chemotherapy if occurrence of AEs, if discontinuation of chemotherapy is desired or considered necessary by the subject and/or Investigator.	N	N
Continuation on cetuximab treatment if more than 2 consecutive cetuximab infusions withdrawn due to toxicity	N	N
Continuation on cetuximab treatment if occurrence of any Grade 4 toxicities related to cetuximab	N	N
Continuation on cetuximab treatment if a fourth occurrence of a Grade 3 skin toxicity related to cetuximab despite appropriate dose reduction	N	N
Continuation on cetuximab treatment if occurrence of at least Grade 3 infusion-related reaction (excluding fever) related to cetuximab	N	N
Continuation on cetuximab treatment if a second episode of any cetuximab infusion-related reaction following a 50% reduction in infusion rate	N	N
Continuation on cetuximab treatment if diagnosis of interstitial lung disease during the trial	N	N
Continuation on cetuximab treatment if occurrence of AEs, if discontinuation of cetuximab is desired or considered necessary by the subject and/or Investigator.	N	N
IP/Non-IP compliance: Received less than 3 full consecutive cetuximab infusions as specified in the protocol (a full dose is defined as 90% of planned dose)	N	N
IP/Non-IP compliance: More than 24 days off cetuximab treatment	N	N
IP/Non-IP compliance: Drug overdose – Actual dose is >10% greater than Planned dose	N	Y

Appendix 2 Inclusion Criteria 3

Inclusion criteria 3 in protocol version 1	Inclusion criteria 3 in protocol version 2
Recurrent and/or metastatic SCCHN, not suitable for local-regional treatment.	Recurrent and/or metastatic SCCHN, not suitable for local-regional treatment. Subjects with recurrent disease only (no metastases) must have received prior radiotherapy (as adjuvant treatment after surgery or as treatment for locally advanced SCCHN) as part of “loco-regional treatment”, and the radiotherapy must have been completed more than 6 months before screening imaging.

Appendix 3 NCI-CTCAE v4.03 Grades for Laboratory Parameters

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology							
Erythrocytes (10E12/L)	No						
Hemoglobin (g/L) High	Yes	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Hemoglobin (g/L) Low	Yes	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Leukocytes (10E9/L)	Yes	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Lymphocytes (10E9/L) High	Yes	Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Lymphocytes (10E9/L) Low	Yes	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Neutrophils (10E9/L)	Yes	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Monocytes (10E9/L)	No						
Eosinophils (10E9/L)	No						
Basophils (10E9/L)	No						
Platelet (10E9/L)	Yes	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Biochemistry							
Creatinine (umol/L)	Yes	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Alanine Aminotransferase (U/L)	Yes	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Aspartate Aminotransferase (U/L)	Yes	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Gamma Glutamyl Transferase (U/L)	Yes	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Total Bilirubin (umol/L)	Yes	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Direct Bilirubin (umol/L)	Yes	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Lipase (IU/L)	Yes	Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Amylase (IU/L)	Yes	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Total Protein (G/L)	No						
Albumin (g/L)	Yes	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase (IU/L)	Yes	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Glucose (mmol/L) High	Yes	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Glucose (mmol/L) Low	Yes	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Blood Urea Nitrogen (mmol/L)	No						
Uric Acid (umol/L)	Yes	Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Sodium (mmol/L) High	Yes	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Sodium (mmol/L) Low	Yes	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Potassium (mmol/L) High	Yes	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Potassium (mmol/L) Low	Yes	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Chloride (mmol/L)	No						
Calcium (mmol/L)	No						
Calcium Corrected (mmol/L) High	Yes	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL;>3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

Laboratory Parameter	CTCAE grade is defined based on lab value only	CTCAE v4.03 term	NCICTC Definition				
			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Calcium Corrected (mmol/L) Low	Yes	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Magnesium (mmol/L) High	Yes	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Magnesium (mmol/L) Low	Yes	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death

21 Literature

No literature.

CTP EMR062202-060 Statistical Analysis Plan Main Body Version 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Business Approval	18-Apr-2018 08:15 GMT+02
PPD	Technical Approval	18-Apr-2018 12:49 GMT+02
PPD	Business Approval	22-Apr-2018 09:13 GMT+02
PPD	Technical Approval	24-Apr-2018 14:45 GMT+02