Protocol Number: APX005M-006

Official Title: A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers

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A Phase 2 Study of APX005M in Combination with Concurrent Chemoradiation as Neoadjuvant Therapy for Resectable Esophageal and Gastroesophageal Junction Cancers

Statistical Analysis Plan

Final Analysis

Version: 3.0

Date: 8 March 2023

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1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the final statistical analysis of APX005M-006 study. APX005M-006 study underwent 10 amendments and details are described in the protocol amendments.

The statistical analysis plan is based on the following study protocol APX005M-006:

- Version 1 dated 05 July 2016
- Version 2 dated 21 March 2017
- Version 3 dated 25 May 2017
- Version 4 dated 05 February 2018
- Version 5 dated 05 March 2018
- Version 6 dated 24 July 2018
- Version 7 dated 15 April 2019
- Version 8 dated 28 October 2019
- Version 9 dated 16 March 2020
- Version 10 dated 30 December 2020
- Version 11 dated 12 August 2021.

1.2 Background

There are an estimated 17,000 incident cases of esophageal cancer in the United States annually, with a yearly mortality rate that almost approximates the incidence rate. This number may in fact underestimate the true number of cases, depending on how GE junction adenocarcinomas (which can be categorized as either esophageal or gastric) are classified. Trends for histologic subtypes have been shifting, with the incidence of adenocarcinomas steadily climbing over the past several decades in Western countries, with a concomitant decline in squamous cell carcinomas (which still comprise the majority of cases globally).

Immunotherapeutic approaches have demonstrated clear evidence of therapeutic activity in a subset of patients with advanced gastroesophageal cancers. CD40 agonistic antibodies represent an attractive and novel form of immunotherapy that stimulate an immune response by activating antigen processing and presentation, recruiting immune effectors such as natural killer cells and macrophages, and additionally have direct cytotoxic effects on tumor cells. However, the activity of this class of agents in esophageal/GE junction cancers is unknown and will be evaluated in the context of this study by combining it with standard chemoradiation in the neoadjuvant setting, with serial collection of tissue and blood along the way for correlative purposes to monitor on-target treatment and pharmacodynamics effects. This study represents the first of its kind to evaluate the safety and preliminary efficacy of combining a CD40 agonist antibody with standard chemoradiation in patients with resectable disease.

1.3 Timing of statistical analyses

The following statistical analyses are planned for this study:

- Safety analyses: yearly safety analyses for development safety update report (DSUR)
- Final efficacy and safety analysis, split into two parts:

- The data base freeze analysis after the primary and secondary endpoints are available for all patients and the database is frozen.
- The final analysis after study termination and the database is locked.

This statistical analysis plan (SAP) is related to the final analyses.

2 Modification History

2.1 Changes to the study protocol

The statistical analyses specified in this SAP are consistent with the statistical analyses contained in the study protocols except for the following points:

1. In this study, it was planned to observe patients for long-term follow-up and survival. However, during the course of the study the treatment landscape changed with the approval of new adjuvant therapies. Only approximately one third of patients chose to go into long-term follow-up, and it was determined that the long-term data as originally planned would not be meaningful with the reduced number of patients. Therefore, overall survival analyses were removed accordingly. Since this study examines neoadjuvant therapy, disease-free survival will be analyzed in the efficacy population.

2. All concomitant medications received within 28 days before the first dose of APX005M and to 90 days (30 days as specified in protocol) after the last dose of APX005M should be recorded.

3. For the final analysis, the primary and secondary efficacy populations were removed and the efficacy population will be used for the primary and secondary endpoints. The definition of efficacy population will include those patients that had planned surgery or had it aborted due to progressive disease (same patients as primary efficacy population). In the prior version of the SAP, the secondary efficacy population did not include patients who had aborted planned surgery due to progressive disease. It was decided to remove this population for the final analysis in order to include those patients. Therefore the primary and secondary endpoints will be based on the newly defined efficacy population.

2.2 Changes to previous SAP versions

The following changes were made compared to the first version of the SAP:

Version	Date	Change number	Change description
2	14-Jul-2022	1	No additional analysis will be performed on the Per Protocol Population, the change is included under section Per Protocol Population
2	14-Jul-2022	2	Per client request, the Primary Efficacy Population definition is updated under section Efficacy Population
2	14-Jul-2022	3	Steroids Subgroup definition is updated under section Subgroups
2	14-Jul-2022	4	Surgery Subgroup definition is updated under section Primary efficacy analysis

2	14-Jul-2022	5	Observation and analysis times is corrected due to the wrong update of track changes in the signed first version.
3	28-Feb-2023	6	Due to the CSR requirements for the final analysis, the following additional analysis: SAC, DSUR and ASCO were explained in the previous version of the SAP V2.0 and removed in this version. This part is updated under section Timing of statistical analysis and the sections: SAC Analysis, DSUR Analysis and ASCO Analysis will be removed from this version of the SAP.
3	28-Feb-2023	7	For the final analysis, the primary and secondary efficacy populations were removed and the efficacy population will be used for the primary and secondary endpoints. The definition of efficacy population will include those patients that had planned surgery or had it aborted due to progressive disease (same patients as primary efficacy population). In the prior version of the SAP, the secondary efficacy population did not include patients who had aborted planned surgery due to progressive disease. It was decided to remove this population for the final analysis in order to include those patients. Therefore the primary and secondary endpoints will be based on the newly define efficacy population. This part is updated under section Analysis Population.
3	28-Feb-2023	8	Observation and analysis times are updated to match the protocols. This section is updated under observation and analysis times.
3	28-Feb-2023	9	Disease-Free Survival is added to the final analysis. This part is updated under section disease free survival.
3	28-Feb-2023	10	Overall Survival analysis is updated due to insufficient follow-up time and a small number of deaths among efficacy patients. No analysis will be attempted and Overall Survival data will only be provided in listings. This part is updated under section overall survival.
3	28-Feb-2023	11	The Appendices were removed as none of them were needed for the statistical analysis.
3	28-Feb-2023	12	Progression-Free Survival analyses have been removed.

3 Study Design

Indication	Patients with resectable (T1-3Nx, excluding T1N0) cancers of the esophagus and gastroesophageal (GE) junction, including both squamous cell and adenocarcinomas.
Design	non-comparative open-label multi-site single-arm study

Phase	Phase 2
Primary Objective	To assess the efficacy of this novel combination (APX005M with standard of-care (SOC) chemoradiation (external beam radiation in daily fractions, with concurrent weekly low-dose carboplatin/paclitaxel)), measured by the pathologic complete response (pCR) rate.
Secondary Objective	(1) To further characterize the safety and feasibility of combining APX005M with standard of-care (SOC) chemoradiation (external beam radiation in daily fractions, with concurrent weekly low-dose carboplatin/paclitaxel) in the neoadjuvant setting for patients with resectable esophageal and GE junction cancers (2) To assess the efficacy as measured by rates of R0 resection; pathologic stage at time of surgery; and radiographic/metabolic response to neoadjuvant treatment on computed tomography-positron emission tomography (CT-PET).
Exploratory Objective	(1) To identify possible predictive molecular or immune-based efficacy biomarkers for this novel combination (2) To characterize and assess overall survival and Disease Free Survival
Study treatment	APX005M, a CD40 agonist antibody
[redacted]	[redacted]
Interim analysis	Not planned

3.1 Protocol synopsis

Please refer to the Protocol Version 11, 12 August 2021 (and its Appendices).

3.2 Sample size estimation

The primary objective of this study is to assess the efficacy of combining APX005M with SOC chemoradiation (carboplatin/paclitaxel/radiation therapy), as measured by the pCR (pathological Complete Response) rate.

[redacted] evaluable patients will be enrolled to this phase 2 study. The null hypothesis that the true pCR is 29% will be tested against a 1-side alternative of 53% using Exact Binomial Test with type I error rate of 0.05 and power of 81%. A minimum number of [redacted] evaluable patients with adenocarcinoma history will allow to test the null hypothesis that the true pCR is 23% against a 1-sided alternative of 53% with a type I error rate of 0.05 and power of 77%.

3.3 Randomisation, blinding and unblinding procedures

This study is not randomized.

4 Analysis Populations

4.1 Screening Population

The screening analysis population includes all patients screened and who provide informed consent. Analysis of the disposition of the patients will be presented on the screening population.

4.2 Safety Population

All patients who receive at least one dose of APX005M will be analysed for safety.

Analysis of demographics, background characteristics, study drug exposure, adverse events, laboratory data, ECOG performance status, and vital signs will be presented on the Safety population. The appropriate listings will be presented on the screened or safety population.

4.3 Per Protocol Population

All patients who receive at least one dose of APX005M without any major protocol violation that would impact the assessment of the primary and secondary endpoints. Several analyses would be repeated by Per Protocol Population if the difference between Per Protocol and Safety population is greater than 10%. During the Data Review Meeting, the Final Per Protocol Population was defined and no additional analysis would be repeated by Per Protocol Population.

4.4 Efficacy Population

All patients who are eligible, received neoadjuvant APX005M chemoradiation therapy followed by surgery, or had their planned surgery aborted due to the discovery of progressive disease, are included in the efficacy population. Data is specified in the investigator's assessment of pathologic response (SRRESP).

Analyses	Screened	Safety	Efficacy	Per Protocol
Disposition	X			
Demographics and background characteristics		X		X*
Exposure		X		
Previous and concomitant therapies		X		
Primary Efficacy Endpoint			X	X*
Secondary Efficacy Endpoints			X	X*
Disease free survival			X	
Safety		X		

*As previously noted, during the Data Review Meeting, the Final Per Protocol Population was defined and no additional analyses would be repeated by Per Protocol Population.

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented for the different analysis sets as defined in section 4 Analysis Populations.

In general, continuous variables will be summarised using descriptive statistics, i.e. generally displaying number of patients in the respective analysis population, number of patients with missing values, number of patients with data, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum.

Categorical variables will be summarised by using frequency counts and percentages. In addition, the number of patients with missing values will be displayed. Percentages relate to the number of patients with data.

Means and medians will be presented by 1 additional decimal place and standard deviation will be presented by 2 additional decimal places than the standard presentation level of the respective patient data. Minimum and maximum values will be presented using the same number of decimal places as the patient data.

Percentages will be presented to 1 decimal place if not otherwise stated. In case of 100 % only the integer 100 wil be presented. If the number of patients in a category is 0, then percentage will not be displayed, and only a count of 0 will be shown.

In cases where variables are derived and have floating point values (no fixed number of decimal places), an appropriate level of precision will be determined based on the context.

P-values will be reported to 4 decimal places at least. Values less than 0.0001 will be displayed as <0.0001. Values above 0.9999 will be displayed as >0.9999.

In listings, data will be sorted by site, and patient, and when appropriate by visit or other identifiers for sequence or type of observation.

If not otherwise specified, all statistical tests will be two-sided with alpha level of 0.05.

The analysis will be exploratory in nature and will primarily involve descriptive statistical methods. In addition, exploratory statistical testing will be used to highlight interesting aspects of the data and to investigate differences between baseline and post-baseline assessments.

Study sites, countries and regions

8-12 study sites in the US were planned to participate in the study. No efficacy or safety analyses by site will be performed. 10 sites were activated; 9 sites enrolled patients.

5.2 Covariates and strata

There are no covariates or strata.

5.3 Subgroups

Below, the subgroup analysis will be defined.

- Histological subgroup
  - Squamous Cell Carcinoma

  - Adenocarcinoma
  - Other
- Tumor location subgroup:
  - GE Juction
  - Non-GE Juction (Upper Third of Esophagus, Middle Third of Esophagus, Lower Third of Esophagus)
- Steroids use:
  - Sterioids use Yes: patients with any steroid (ATC2 class CORTICOSTEROIDS FOR SYSTEMIC USE) from within 30 days of the first dose of APX005M to up to 7 days after the first dose
  - Steroids use No: patients not fulfilling previous requirements
- Tumor staging classification, the information from Tumor Staging assessment page from eCRF will be used to define the following:
  - cTNM(before treatment)/ yCTNM (after chemo-radiation; before surgery)
  - ypTNM (afterchemo-radiation; after surgery)

5.4 Missing data

In general, missing data will not be imputed and the data will be analysed as they are recorded. Exceptions are partial and missing dates, see below.

Partial or missing dates and times

Where the start date of an event or medical condition or medication is missing or partially missing, the event will be assumed to be started after the start of study medication, unless there is clear evidence (through comparison of partial dates/times) to suggest otherwise.

In case of a partial or missing end date the medical condition will be assumed to be ongoing after start of study medication except if the partial date indicates that the condition stopped prior to start of study medication.

5.5 Observation and analysis times

The study consists of 3 periods after screening period.

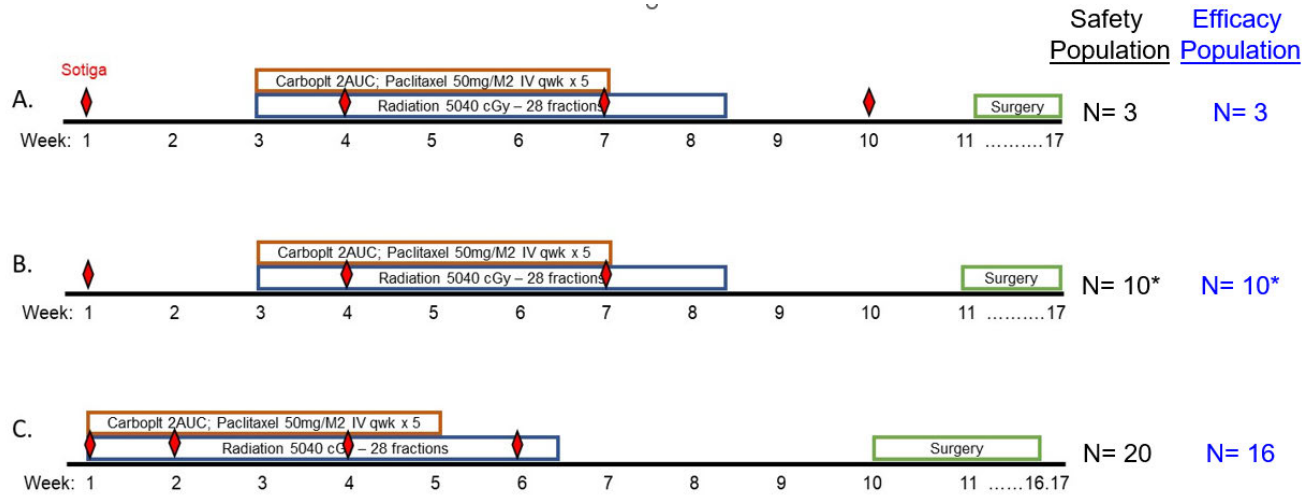
1. Neoadjuvant treatment period with APX005M plus carboplatin plus paclitaxel with tumor targeted curative intent radiation to Esophagus and/or GEJ region.
2. Followed by curative intent surgical resection.
3. Followed by period of observation for disease recurrence and last period of survival follow up.

As the study protocol underwent multiple amendments, the study treatment schedules relative to curative intent surgery changed. Versions 1-8 of the protocol were under an Investigator Sponsor Trial (IST); Versions 9-11 were under Company Sponsor Trial (CST).

The figure below describes the different study treatment schedules for each of protocol versions and how many study participants enrolled under each different Study Treatment Schedules.

In this neoadjuvant study, the primary and secondary endpoints include rates of pathologic response and R0 resection, which are determined by surgical resection and pathologic evaluation. Disease-free survival, defined as the time from curative intent surgery to disease recurrence or death, is clinically meaningful and will be analyzed as an exploratory endpoint.

Study Treatment Schedules:



*1 pt was enrolled on Schedule A but reconsented to Schedule B and did not receive a 4th dose of sotiga.

*APX005M is also known as sotigalimab (sotiga).

Schedule: A – Protocol versions 1 to 5; B – versions 6 to 9; C – versions 10 to 11

All patients regardless of protocol version were to receive 5040 cGY over 28 fractions (Note: In version 3, the treatment schedule figure was inconsistent with the protocol's schedule of events, and one patient received 25 fractions instead of 28. This was documented as a deviation). For protocol versions 1-9, surgery was to be performed between weeks 11-17; in protocol versions 10 and 11, the surgery window was 10-16 weeks.

The assessment of OS was added in version 11.

Since patients are treated according to different Protocol versions different treatment schedules will be taken into account for exposure analysis.

For data analysis the 5 periods are defined as follows:

- Screening period
  - For all patients the screening period is defined as screening measurements performed from 28 days up to treatment start
- Treatment period
  - For all patients the treatment period is defined as the treatment start (the first treatment administered (Carboplatin/ Paclitaxel /APX005M/Radiotherapy) to treatment end (to the last treatment administered Carboplatin/ Paclitaxel /APX005M /Radiotherapy)
- Post Treatment period
  - For all patients, the post treatment period is defined from the day after treatment end to the Surgery, Weeks 10-16 or 11-17, as indicated in the protocol version.
- Follow up period
  - For all patients the follow-up period is defined from the day after surgery to the 6 months post operative visit.

- Survival evaluation period
    - For the efficacy population, disease-free survival analysis will be performed. Due to insufficient follow-up time and a small number of deaths among efficacy patients, no overall survival analysis will be attempted, and Overall Survival data will only be provided in listings.

Definition of baseline values

For all patients treated, the baseline value is defined to be last value assessed before the first infusion of Carboplatin/Paclitaxel/ APX005M/Radiotherapy.

Definition of analysis timepoints

The variables will be evaluated for the time points as indicated for them in the schedule of assessments from the study protocol.

For the data base freeze analysis after the primary and secondary endpoints are available for all patients and the database is frozen, all the study periods beside the Survival Follow-up were used. Also, all the analyses described in the SAP beside the 11.6 Overall Survival and 11.7 Disease Free Survival (DFS) were performed.

For the final analysis after the study has ended and the database is locked, the disease-free analyses, Overall Survival listing and secondary analysis (CT-PET analysis and all data collected after database freeze) and some data base freeze analyses will be performed.

6 Subject Accounting and Disposition

6.1 Subject accounting

An overview of screened patients will be presented in the table showing the number of patients and the percentages based on the screening population. Also the number of not eligible patients will be presented with the inclusion/ exclusion criteria that are not met.

The number and relative frequencies of patients in each analysis populations as defined in section 4. This study is not randomized.

Analysis Populations will be presented overall and by site.

A listing including disposition information will be also created. A separate listing will be created with patients excluded from efficacy analysis.

6.2 Disposition and withdrawals

The number and relative frequency will be presented for patients who completed the study including follow–up and who prematurely discontinued the study with reason for discontinuation. The following reasons for premature study discontinuation will be presented:

- Adverse event
- Confirmed radiographic disease progression
- Death
- Lost to follow-up
- Non-compliance with study treatment or procedure requirements
- Physician decision, other than Adverse event (AE)
- Pregnancy

- Site terminated by sponsor
- Study terminated by sponsor
- The subject or legal representative withdraws consent
- Intercurrent Illness that Prevents Further Administration of Treatment
- Administrative Reasons
- Withdrawal due to COVID-19
- Other

6.3 Protocol deviations

Protocol deviations will be summarized by frequency tables and all patients with protocol deviations will be listed. The protocol deviations will be defined by Protocol Deviation Plan version 3.0 dated 23 August 2022 and will be provided in an excel spreadsheet.

7 Demographics and Background Characteristics

Demographic and baseline characteristics as specified in detail below will be presented descriptively based on safety population.

7.1 Demographics

The following demographic characteristics will be presented

- Age (years)
- Sex (male/female)
- Woman of childbearing potential (no/yes)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Other)
- Weight (kg)
- Height (cm)

7.2 Baseline characteristics

The results from the following investigations at baseline will be presented:

Tumor staging assessment:

- Histology (Squamous cell carcinoma, Adenocarcinoma, Other)
- Tumor location (Upper Third of Esophagus, Middle Third of Esophagus, Lower Third of Esophagus, GE Junction)
- Grade (Grade X, Grade 1, Grade 2, Grade 3)
- T Stage (TX, T0, T1, T1a, T1b, T2, T3, T4, T4a, T4b)
- N Stage (NX, N0, N1, N2, N3)
- M Stage (M0, M1)
- Stage group (Missing, 0, I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, IVB)

- CT-PET scan performed
    - Is the primary tumor measurable? (no, yes)
    - Type of scan recorded (CT scan, CT-PET scan)
    - SUV Mean of Primary Tumor
    - SUV Max of Primary Tumor
    - SUR-Liver
    - SUR-Blood pool
    - Are enlarged lymph nodes present? (no, yes)

7.3 Medical history

The diseases are coded according to Medical Dictionary for Regulatory Activities (MedDRA® version 23.0 or later). Medical history includes history of any pre-existing conditions and/or any malignancy that is not cancer under investigation in this trial. They will be classified as follows

- Previous medical conditions, i.e. medical conditions that stopped prior to first infusion of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy)
- Ongoing (concomitant) medical conditions, i.e. medical conditions still present after first infusion of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy)

All ongoing events at study entry have also to be classified by the CTCAE severity grade 1 to 5.

The frequency of diseases recorded from medical history will be presented for safety population after classification into previous and concomitant conditions

- by system organ class (SOC)
- by preferred terms (PT) within each SOC
- by CTCAE grade within each preferred term

If patients have more than one disease within an SOC or PT or CTCAE Grade they will be counted only once for the respective SOC or PT or CTCAE Grade.

For the summaries, Primary System Organ Classes (SOCs) will be ordered alphabetically and Preferred Terms (PTs) will be ordered by descending count or alphabetically for PTs with the same count.

8 Previous and Concomitant Therapies

Previous and concomitant medications are coded according to the World Health Organization drug dictionary (WHO-Drug version 2021Q2, 21, March or later) and stored with ATC codes/decodes and generic names.

All medications received within 28 days before the first dose of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy) and 90 days after the last dose of (Carboplatin/Paclitaxel/APX005M/Radiotherapy) are to be recorded.

Therapies are classified as previous if the stop date is before the first dose study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy). All other medications are defined as concomitant. Missing or partly missing stop dates will be imputed using the rules defined in Section 5.4.

The number and frequency of previous and concomitant medications will be given per Anatomical Therapeutic Chemical (ATC) categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup).

If a patient has received more than 1 drug within an ATC class, he/she will be counted only once for this ATC class.

9 Exposure

Treatments will be labelled as follows:

- APX005M
- Carboplatin
- Paclitaxel
- Radiotherapy

Descriptive statistics for the characteristics of the non-radiotherapies are presented by timepoint for the safety population. The following items are analysed:

Item	Outcome	APX005M	Carboplatin	Paclitaxel
Treatment received	no yes	X	X	X
Reason APX005M not administered	Adverse event Other	X		
Preinfusion medication taken	no yes	X	X	X
Infusion interrupted	no yes	X		
Reason Infusion interrupted	Adverse event Other	X		
Infusion completed	no yes	X	X	X
Prescribed Dose		[redacted] [redacted] 0.3 other (mg/kg)	1 1.5 2 other (AUC)	30 40 50 other (mg/m2)

Total dose administered (mg)	Amount in mg	X	X	X
Total volume administered (mL)	Amount in mL	X	X	X

For radiotherapy, descriptive statistics of the daily dose (cGy) will be presented by day.

Listings of all APX005M, Carboplatin, Paclitaxel, and radiotherapy exposures will be provided.

10 Efficacy

10.1 Primary efficacy analysis

The primary efficacy measure is the proportion of patients who achieve a pathological complete response (pCR rate) as assessed by the investigator. This efficacy analysis will be performed in the Efficacy Population. The pathological complete response will be defined as ypTNM (after chemo-radiation; after surgery) with T0, N0 stages.

An exact Clopper-Pearson lower 95% confidence limit will be used to test the null hypothesis that the pCR rate is ≤30%. If the lower 95% confidence limit is above 30%, the null hypothesis will be rejected and it will be concluded that the pCR rate is higher than 30%.

These data will be reported for each histologic, tumor location and steroids-use subgroups. The pathologic complete response will also be presented by the following subgroup:

- Patients who have surgery before or at 16/17 weeks
    - Defined as start of study treatment to Surgery date from the surgical resection form, less than or equal to 17 weeks (119 days = 17 weeks * 7 days)
    - Patients who were scheduled to have surgery but had their procedure aborted due to progressive disease at the time of the procedure or immediately before and did not have surgery because of metastasis
- Patients who have surgery after week 17
    - Defined as from start date of study treatment to Surgery date from Surgical Resection eCRF is after the week 17 (119 days = 17 weeks * 7 days).

The pathologic complete response will also be presented in a table by post-treatment response.

10.2 Secondary efficacy analyses

The following tumor staging assessment endpoints are assessed after treatment/before surgery and after treatment/after surgery:

- Histology (Squamous cell carcinoma, Adenocarcinoma, Other)
- Tumor location (Upper Third of Esophagus, Middle Third of Esophagus, Lower Third of Esophagus, GE Junction)
- Grade (Grade X, Grade 1, Grade 2, Grade 3)
- T Stage (TX, T0, T1, T1a, T1b, T2, T3, T4, T4a, T4b)
- N Stage (NX, N0, N1, N2, N3)

- M Stage (M0, M1)
- Stage group (Missing, 0, I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, IVB)

These data will be summarized for the Efficacy population by time point and presented for each histologic and tumor location subgroup

CT-PET scan performed will be presented by timepoints. The following endpoints are reported:

- Is the primary tumor measurable? (no, yes)
- Type of scan recorded (CT scan, PET-CT scan)
- SUV Mean of Primary Tumor
- SUV Max of Primary Tumor
- SUR-Liver
- SUR-Blood pool
- Are enlarged lymph nodes present? (no, yes)
- Is there evidence of response relative to baseline? (responding, stable/unchanged, progressing, not evaluable)

These data will be summarized for the efficacy population and the last variable also by histological and tumor location subgroups.

The surgical resection will be presented in the table showing the number of patients and the percentages based on the efficacy population. The number of patients with surgical resection performed, R0 resection achieved, investigators assessment of pathologic response, major pathologic response will be presented for each histologic, tumor location and tumor staging classification. The surgical resection will be also presented by histologic subgroup separately by each of the tumor time staging classification where the information will be presented by each stage group.

The lesion/RECIST form was added in the updated eCRF.

For target lesion overall, the number of patients with lesions in organs, measurements of longest diameter (mm) or measurements of short axis (mm), method will be presented with the percentages based on the efficacy population by visit. Also this table would be repeated by each of the lesion/organ. The change from baseline will be presented by each timepoint. For non-target lesion overall, the number of patients with lesions in organs, method and status of non-target lesion will be presented with the percentages based on the efficacy population by visit. Also this table would be repeated by each of the lesion/organ.

The summary table of response assessment will be presented showing the number of patients and the percentages based on the efficacy population. The number of patients with RECIST 1.1 Target lesion response, RECIST 1.1 Non-target Lesion response, Overall RECIST 1.1 Response and new lesion will be presented by visit.

All results from efficacy analyses will also be listed by patient.

10.3 Exploratory Objective

The exploratory analysis related to the identification of possible predictive molecular or immune-based efficacy biomarkers for this novel combination is not going to be described in this SAP.

Considering this is a neoadjuvant study, disease-free survival will be a clinically relevant exploratory end point. Overall survival (OS) will be in listings, however no formal statistical analysis is planned as not all study patients consented for OS follow up.

11 Safety

11.1 Adverse events

Adverse events will be coded using MedDRA version 23.0 or later, and analysed for the safety population.

The analysis will focus on the treatment-emergent AEs (TEAE), i.e., AEs which started on or after the first infusion of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy) until 100 days after receiving the last dose of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy), death, or initiation of new anticancer therapy (from Overall Survival Form), whichever occurs first.

Number and frequencies of patients with at least one adverse event of the following types of TEAEs will be summarized:

- At least one TEAEs
- Serious TEAEs
- Serious TEAEs (includes number of events)
- TEAEs with outcome of death
- TEAEs leading to treatment discontinuation
- TEAEs leading to discontinuation of APX005M
- TEAEs leading to discontinuation of Carboplatin
- TEAEs leading to discontinuation of Paclitaxel
- TEAEs leading to discontinuation of Radiotherapy
- TEAEs at least possibly related to APX005M
- TEAEs at least possibly related to Carboplatin
- TEAEs at least possibly related to Paclitaxel
- TEAEs at least possibly related to radiotherapy
- TEAEs at least possibly related to surgery
- >= Grade 3 TEAEs
- >= Grade 3 TEAEs at least possibly related to APX005M
- >= Grade 3 TEAEs at least possibly related to Carboplatin
- >= Grade 3 TEAEs at least possibly related to Paclitaxel
- >= Grade 3 TEAEs at least possibly related to radiotherapy
- >= Grade 3 TEAEs at least possibly related to surgery
- Non-serious AEs
- Non-serious AEs (includes number of events)
- Related TEAEs by treatment (excluding surgery) and overall related

The number of TEAEs will also be presented by decreasing frequency within each primary System Organ Class (SOC), Preferred Term (PT). SOCs will be ordered alphabetically.

Additionally, the number of TEAEs will be presented by decreasing frequency within each primary System Organ Class (SOC), Preferred Term (PT) and maximum CTCAE toxicity grade.

A patient listing will be provided including all adverse events with reported term, preferred term, adverse event start and end date, seriousness, relationship to treatments, action taken with

treatments, relationship to study surgery, NCI CTCAE toxicity grade and outcome as well as duration of adverse event and onset after first infusion of study treatment (Carboplatin/Paclitaxel/APX005M/Radiotherapy).

An additional listing will be created for patients with serious adverse events showing the seriousness criteria and for patients with adverse events leading to treatment discontinuation.

All information associated with deaths is collected on death eCRF page. Number and frequencies of all cause death will be presented in a table and also listed.

11.2 Vital signs

The following variable will be described descriptively by time point for the safety population:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (bpm)
- Body weight (kg)
- Body height (cm)
- Oxygen saturation (%)
- Body temperature (°F)

The actual values and change from baseline in vital signs will be summarized by time point with n, mean, standard deviation, and 25th percentile, median, 75th percentile, min, and max. All data will also be listed by patient.

11.3 Clinical safety laboratory

Hematology, clinical chemistry and coagulation

The following variables will be analysed descriptively by time point for the safety population:

- Hematology:
  - Hemoglobin
  - Hematocrit
  - Red Blood Cell Count (RBC)
  - White Blood Cell Count (WBC)
  - Platelet Count
  - Absolute Neutrophil Count (ANC)
  - Lymphocytes (absolute)
  - Monocytes (absolute)
  - Eosinophils (absolute)
  - Basophils (absolute)
  - Mean Corpuscular Hemoglobin Concentration (MCHC)
  - Mean Corpuscular Volume (MCV)
- Clinical Chemistry:
  - ALT/ SGPT
  - Albumin

  - AST/ SGOT
  - Alkaline Phosphatase
  - Total Bilirubin
  - Bicarbonate
  - Blood Urea Nitrogen
  - Calcium
  - Chloride
  - Creatinine
  - Creatinine Clearance
  - Glucose
  - Potassium
  - Total Protein
  - Sodium
- Coagulation:
  - Prothrombin Time (PT)
  - Activated Partial Thromboplastin Time (aPTT)
  - International Normalized Ratio (INR)

In addition, summary tables will be provided for elevated AST, ALT, Total Bilirubin and Alkaline Phosphate, and also for abnormal neutrophils, white blood cells, platelets and lymphocytes.

The actual values and change from baseline in laboratory variables will be summarized by time point with n, mean, standard deviation, and 25th percentile, median, 75th percentile, min, and max. All data will also be listed by patient.

Additionally, the number of laboratory values that fall outside of pre-determined ranges are displayed by timepoint for the safety population.

Laboratory values that are outside the pre-determined range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

Selected laboratory variables will be classified According to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and frequencies of the respective variables will be tabulated by CTCAE Grade.

Urinalysis

Data from Urinalysis are only collected at screening and are not analysed.

Immune-based correlates

Data from Immine-based correlates can be collected and will not be analysed.

Blood samples collection

Data from Blood samples collection can be collected and will not be analysed.

11.4 ECG

Data from ECG are only to be collected at screening and are not analysed, only listed.

11.5 Physical examination

Data from physical examination are only to be collected at screening and are not analysed.

11.6 Overall Survival

An exploratory assessment of overall survival was planned for 18 months after the 6 months follow-up visit or End of Study visit. Due to insufficient follow-up time and a small number of deaths among efficacy patients, no analysis will be attempted, and OS data will only be provided in listings.
The subject status, disease progression and subsequent anti-cancer therapy will be assessed every 3 months.

11.7 Disease Free Survival (DFS)

Disease Free Survival is defined as the time from date of surgery until progession or death, and will be analyzed for the Efficacy Population using Kaplan-Meier methodology when the study is terminated and the database is locked. For patients who aborted planned surgery due to progressive disease, the date of progression will be recorded as day 0 and duration of disease-free survival will be 0.

11.8 ECOG performance status

The ECOG performance status will be described descriptively with frequency and percentage by outcome (0, 1, 2, 3, 4, 5) for each time point for the safety population.

12 Interim Analyses

An interim analysis is not planned for this study.

13 Software

If not stated otherwise, the data will be analysed using SAS Version 9.4 or higher.

14 Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-PET	Computed Tomography-Positron Emission Tomography
CTR	Clinical Trial Registry
DFS	Disease Free Survival
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GE	Gastroesophageal
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse events
OS	Overall Survival
pCR	Pathological complete response
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUV	Standardized Uptake Value
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures

15 References

1. ICH guideline E2F, Note for guidance on development safety update reports, EMA/CHMP/ICH/309348/2008, September 2010

2. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Guidance for Industry, U.S. Department of Health and Human Services,Food and Drug Administration,Oncology Center of Excellence, December 2018