

STATISTICAL ANALYSIS PLAN

CONFIDENTIAL

Oraxol

KX-ORAX-007

Clinical Phase 1

A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients

Statistical Analysis Plan Date: 17 Sep 2019

Version: Final 1.2

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APPROVAL SIGNATURE(S)

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and safety analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in the revision of SAP.

PROTOCOL TITLE: A Clinical Study to Determine the Pharmacokinetics of Oraxol in Breast Cancer Patients

PROTOCOL NUMBER: KX-ORAX-007

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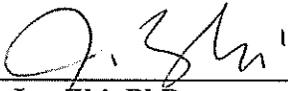
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19 - Sep - 2019

VERSION HISTORY

Version Number	Version Date	Summary and rational of change(s)
Final 1.0	26-Feb-2018	Initial version of SAP according to protocol version amendment 04 v5.0_10 Jul 2017
Final 1.1	17-May-2019	<p>1. To obtain long-term progression-free survival, overall survival and new anti-cancer therapy data according to <u>protocol amendment 05, v6.0</u>, the following section are adjusted accordingly.</p> <ul style="list-style-type: none"> • Section 4.2 (Secondary Objectives) Added progression-free survival [PFS], overall survival [OS]) as activity. • Section 5 (Study Design) Added the frequency of long-term follow-up and new anti-cancer therapy collected after final visit. • Section 5.3 (Follow-up) Added the details for long-term follow-up after final visit. • Section 9.2 (Secondary Endpoints) Added progression-free survival and overall survival. • Section 14.1.2 (Activity Analysis) Tumor data during long-term follow-up should be listed and added details for analysis of progression-free survival and overall survival. <p>2. Add Central Radiology Review Committee to review all radiology images for activity assessment when the patients completed Final Visit according to <u>protocol amendment 06, v7.0</u>, the following section are adjusted accordingly.</p> <ul style="list-style-type: none"> • Section 14.1.2 (Activity Analysis) Added analysis of tumor response is presented for central radiology data. <p>3. Revised text to reflect subjects who do not complete Week 4 PK assessments will be replaced; qualified language about replacement of subjects who discontinue from the study according to <u>protocol amendment 02, v3.0</u>, the following section are adjusted accordingly.</p> <ul style="list-style-type: none"> • Section 8.2 (PK Evaluable Population)

		<p>Revised the definition of PK evaluable population to define subjects should have at least one post-baseline PK results on Week 4.</p> <p>4. Other Changes:</p> <ul style="list-style-type: none">• Section 10 (General Consideration) Added the definition of Baseline when analyzing change from baseline in safety data.• Section 11.4.1 (Prior Medication and Oncology Treatment History) Added details in analyzing oncology treatment history.• Section 11.4.3 (Procedure) Added details of analysis in procedures and therapies collected during study.• Section 13.1.2 (Population Pharmacokinetic Analysis) Added details of Population Pharmacokinetic Analysis.• Section 16 (Deviations from Protocol-Specified Statistical Analysis) Added description to describe deviation from protocol analysis, a new analysis population of Response Evaluable Population which is defined in SAP only but not defined in protocol. Added description to describe deviation from protocol analysis, population pharmacokinetic will be explored with pooling the PK data from other studies and reported separately. Added description for C_{min} should be replaced by C_{trough}, C_{avg} and AUC_{τ} should be deleted.
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Final 1.2	22-Aug-2019	<p>1. Section 14.1.3 (Laboratory Evaluations)</p> <p>Shift table for laboratory results is to be based on CTCAE v4.03 grading.</p> <p>2. Updated PK Evaluable Population definition, the following section are adjusted accordingly:</p> <ul style="list-style-type: none">• Section 8.2 (PK Evaluable Population) <p>Revised the definition of PK evaluable population to include all subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment PK evaluation on Week 4.</p> <ul style="list-style-type: none">• Section 16 (Deviations from Protocol-Specified Statistical Analysis) <p>Added description to describe deviation from protocol analysis, modify the definition of PK evaluable population</p>
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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
BSA	body surface area
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
MedDRA	Medical Dictionary for Regulatory Activities
NE	Inevaluable
PD	progression disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
OS	overall survival
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SOC	System Organ Class
WHO-DRUG	World Health Organization Drug
TEAE	treatment-emergent adverse event

3. INTRODUCTION

This statistical analysis plan (SAP) has been developed after reviewing of the clinical study protocol (protocol amendment 06, v7.0, dated 14 August 2018).

This SAP describes the planned analysis of the safety, tolerability and activity data from this study. The planned TFLs to be presented in the clinical study report (CSR) will be originally copied or modified from the SAP accompanying TFL shells document.

The intent of this document is to provide guidance for the statistical analyses of investigating the pharmacokinetic (PK) data of orally administered paclitaxel. In general, the analyses are based on information from the protocol, unless otherwise specified. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol, where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR.

4. OBJECTIVES

4.1 Primary Objective

The primary objective of the study is to investigate the PK (AUC) of orally administered paclitaxel (as Oraxol) in breast cancer patients.

4.2 Secondary Objectives

The secondary study objectives are to determine the safety and activity (response rate, progression-free survival [PFS], overall survival [OS]) of Oraxol in breast cancer patients.

5. STUDY DESIGN

This is a multicenter, open-label, single-arm PK study in approximately 24 breast cancer patients for whom paclitaxel treatment is indicated. Subjects will receive Oraxol 205mg/m² daily x 3 days weekly for up to 16 weeks. Subjects must have measurable disease as per RECIST v1.1 criteria.

The study will be conducted at approximately 6 sites in Taiwan. The study period will be approximately 8 months (first person first visit to last person last visit [FPFV-LPLV]). The duration of the study for each subject is approximately 21 weeks (**up to 4 weeks for Screening/Baseline, 16 weeks for treatment, and 1 week for follow-up**).

The study contains 3 periods: the Screening / Baseline Period, the 16-week Treatment Period, and the 1-week Follow-up Period. A Final Visit will occur within 7 days of the last dose of study treatment. After completion of Final Visit assessments, subjects will be contacted every 2 months to follow PFS and OS. New anti-cancer therapy will be collected.

Subjects may be treated until disease progression, or unacceptable toxicity requiring more than 2 dose reductions, or a maximum of 16 weeks. If subjects achieve stable disease (SD), complete response (CR), or partial response (PR) at Week 16, they may continue Oraxol treatment in a separate extension study.

Pharmacokinetic parameters will be analyzed and various safety assessments (e.g., AEs, laboratory tests) will be conducted throughout the study, as well as imaging and tumor assessments which will be performed to evaluate tumor response.

For purposes of PK sampling, study weeks will be counted consecutively from Week 1. Week 4 PK sampling may be delayed at the discretion of the Investigator, e.g., to allow the subject to recover from unacceptable toxicity. In the event of a treatment delay, Week 4 PK samples should be obtained as soon as possible once the subject resumes treatment.

An overview of the study design is presented in below [Figure 1](#).

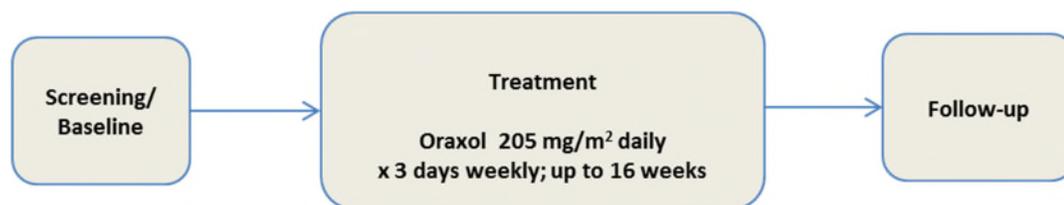


Figure 1 Study Design in KX-ORAX-007

5.1 Treatment Phase

The Treatment Phase consists of continuous treatment with Oraxol for 3 consecutive days per week for 16 weeks. Dosing is presented in [Table 1](#).

Table 1. Dosing in KX-ORAX-007

	Strength	Dose Form / Route of Administration	Number Dispensed and Frequency	Study Days Administered
Investigational Product				
HM30181AK-US	15 mg	Tablet taken orally	1 × 15-mg tablet, on designated treatment mornings, 1 hour before oral paclitaxel	Days 1-3, weekly for 16 weeks
Paclitaxel	30 mg	Capsules taken orally	Number dispensed based on calculated doses (205 mg/m ² once on designated treatment mornings)	Days 1-3, weekly for 16 weeks

5.2 Management of Unacceptability Toxicity

Unacceptable toxicity occurs when any of the following events, graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (or later) criteria, are considered at least possibly related to Oraxol:

- ANC $\leq 0.8 \times 10^9/L$
- Grade 3 or 4 ANC plus fever or Grade 3 or 4 ANC with bacteremia or sepsis
- Grade 3 thrombocytopenia ($<50 \times 10^9/L$ platelets) for more than 7 days, or accompanied by clinically significant bleeding
- Grade 4 thrombocytopenia ($<25 \times 10^9/L$ platelets) regardless of duration or

clinical manifestations

- Grade ≥ 3 nausea, vomiting, or diarrhea persisting for more than 48 hours despite optimal medical management
- Grade ≥ 3 nonhematologic abnormalities not listed above. This does not include:
 - laboratory abnormalities not considered to be SAEs and which resolve back to Grade 1 or baseline within 7 days
 - alopecia
 - anorexia or asthenia which resolves within 7 days
- Nonhematologic toxicities and hematologic toxicities not mentioned above which cause a dose delay of >7 days

Management of Unacceptability Toxicity:

Subjects experiencing unacceptable toxicity who have completed the first week of Oraxol treatment will have their Oraxol treatment delayed until the toxicity improves.

Subjects whose unacceptable toxicity improves to CTCAE Grade 1 or baseline within 2 weeks of their last dose of Oraxol may continue treatment with dose reduction as described below:

Dose Reduction After First Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 165 mg/m² per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Dose Reduction After Second Occurrence of Unacceptable Toxicity

Treatment will resume at an oral paclitaxel dose of 130 mg/m² per day for 3 consecutive days each week. The HM30181 dose of 15 mg will be kept the same.

Once the dose has been reduced, it cannot be increased at a later date.

Discontinuation due to Unacceptability Toxicity:

Oraxol treatment will be permanently discontinued for subjects who are unable to complete the first week of dosing due to unacceptable toxicity.

After 2 dose reductions, subjects whose unacceptable toxicity does not improve to Grade 1 or baseline within 2 weeks of their last dose of Oraxol will have their Oraxol treatment permanently discontinued.

Subjects who continue to experience unacceptable toxicity after 2 dose reductions will be discontinued from the study.

5.3 Follow-up

If a subject completes the study or discontinues the study at any time, a Final Visit will occur within 7 days after the last dose of study treatment. Safety assessments, as detailed in Table 6 of protocol, will be performed at the Final Visit.

Subjects will be requested to participate in long-term follow-up for progression-free survival and overall survival. New anti-cancer therapy will be collected. After completion of this study, subjects or designated family members or physicians may be contacted every 2 months to determine if the patient has had progressive disease or whether the subject remains alive, or if any new anticancer therapy has been taken.

If a subject discontinues the study due to progression of disease, the Final Visit assessments can be performed at the last on-treatment visit. If possible, this visit should be scheduled before the subject receives additional chemotherapy.

6. DETERMINATION OF SAMPLE SIZE

A total of 24 evaluable subjects receiving Oraxol will be analyzed. Subjects who do not have Week 4 PK assessments for any reason will be replaced.

7. PROTOCOL DEVIATIONS

All protocol deviations collected by the study team will be updated during the reviews throughout the study prior to database lock. In general, all protocol deviation details will be presented in a data listing.

8. ANALYSIS POPULATIONS

8.1 Safety/Full Analysis Population

The Safety/Full Analysis Population will include all subjects who receive at least 1 dose of study treatment.

8.2 PK Evaluable Population

The PK evaluable population will include all subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment PK evaluation on Week 4.

According to protocol, Week 4 PK sampling may be delayed at the discretion of the Investigator, eg, to allow the subject to recover from unacceptable toxicity. In the event of a treatment delay, Week 4 PK samples should be obtained as soon as possible once the subject resumes treatment.

8.3 Response Evaluable Population

The response evaluable population will include all subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment tumor response evaluation.

9. STUDY ENDPOINTS

9.1 Primary endpoint

- Evaluation of PK parameters for oral paclitaxel

9.2 Secondary Endpoints

- Safety
 - Incidence of all AEs, including SAEs
 - Laboratory values
 - Other safety assessments including vital signs, physical exams, electrocardiograms (ECGs)
- Activity
 - Tumor response rate, which is defined as the number of subjects with CR or PR at any post-baseline assessments expressed as the proportion of the total number of subjects in the Response Evaluable Population.
 - PFS and OS

10. GENERAL CONSIDERATION

All statistical analyses will be performed after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required.

Statistical analyses will be reported using summary tables, figures and data listings. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. All raw data obtained from the case report form/electronic case report form (CRF/eCRF) as well as any derived data will be included in data listings. Median and SD will be presented to one more decimal place than the standard digits.

The baseline for continuous laboratory, vital sign and ECG parameters is defined as the last assessment performed before first dosing date and time, this baseline will be used for summary of change from baseline for laboratory, vital sign and ECG results.

For tumor response, the baseline tumor should be collected at the screening visit before first dosing date according to protocol.

Missing values in this study will not be imputed.

11. STUDY POPULATION

11.1 Patient Disposition

The number of patients will be tabulated by study sites. Patient disposition (the number of patients treated and discontinued, and reasons for discontinuation) will be summarized. Patients may remain in the study until they are lost to follow-up or withdraw consent. The following will be summarized when applicable:

Summary of Analysis Populations:

- Number of patients in All Patient population (all enrolled patients are included)
- Number of patients in the Safety Analysis Population
- Number of patients in the Response Evaluable Population

Summary of Patient Disposition:

- Number of patients screened
- Number of patients treated with Oraxol
- Number of patients discontinued from the study
- Number of patients completed study
- Primary reason for discontinuation from the study
 - Death
 - Progression of disease
 - Recurrent unacceptable toxicity following 2 dose reductions of Oraxol
 - Adverse event not associated with progression of disease

- Noncompliance
 - Withdrawal of consent
 - Termination of the study by the Sponsor
 - Other
- A listing of patient disposition status, including the patient status (screen failure/completed/discontinuation), date of informed consent, date of first/last medication, date of completion/discontinued, primary and secondary reasons for discontinued from the study.

11.2 Baseline and Demographic characteristics

Demographic characteristics will be summarized by all patients in Safety Analysis Population in Screening phase, using the following information from the Demographics eCRF section.

- Sex: Female
- Race: Asian and Other
- Age (years)
- Age categories: < 65 years, ≥ 65 years
- Height (cm)
- Weight (kg)
- Body surface area (BSA) (m²)
- Eastern Cooperative Oncology Group (ECOG) performance status at screening (0, 1, 2, 3, 4, 5)
- Metastatic Sites (bone, brain, kidney, lungs, lymph nodes, liver, and other)

A summary of metastatic site(s) will be provided by descending order.

11.3 Medical History and Baseline Disease Characteristics

Medical/surgical history will be recorded at Screening/Baseline, and all pertinent medical history will be noted in the eCRF. A complete oncologic medical history will also be recorded. All of the medical conditions are also summarized by SOC and PT terms.

Summary tables and listings of medical/surgical history and current medical conditions will be provided as follows:

- A summary of medical history (non-oncology) by MedDRA SOC and PT will be presented for all patients in Safety Analysis Population.
- A summary of medical history (oncology) by MedDRA SOC and PT will be presented for all patients in Safety Analysis Population.
- A summary of surgical history (non-oncology) will be presented by SOC and PT for all patients in Safety Analysis Population.
- A summary of baseline disease characteristics will be presented for all patients in Safety Analysis Population.
- A by-patient listing of medical history will be presented.
- A by-patient listing of non-oncology surgical history will be presented.

11.4 Prior and Concomitant Medications

11.4.1 *Prior Medication and Oncology Treatment History*

All medications (prescription and nonprescription), treatments, and therapies taken from 28 days before the initiation of the study through the final study visit, will be recorded on the Concomitant Medication eCRF. A complete oncologic treatment history will be recorded on the Oncologic Treatment History eCRF. All the prior medications and oncology treatment history (chemotherapy, endocrinotherapy, biotherapy and other) are coded by the World Health Organization Drug (WHO-DRUG) dictionary. The oncology treatment history for surgery and radiation therapy are coded by MedDRA SOC and PT.

Prior is any medication that was ongoing at screening within 28 days prior to Day 1 and whose stop date is before day 1 is a prior medication.

- Summary table of prior medications will be summarized by ATC class 1 and preferred term for all patient in Safety Analysis Population.
- Summary table of oncology treatment history (chemotherapy, endocrinotherapy, biotherapy and other) will be summarized by ATC class 1 and preferred term for all patient in Safety Analysis Population.
- Summary of oncology treatment history for surgery and radiation therapy by SOC and PT for all patient in Safety Analysis Population.
- A by-patient listing of prior medications will be presented.
- A by-patient listing of oncology treatment history will be presented.

11.4.2 Concomitant Medication

Any medication (including nonprescription remedies) or therapy administered to the subject during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication eCRF. The Investigator will record any AE on the Adverse Events eCRF for which the concomitant medication/therapy was administered. All the medications are coded by the World Health Organization Drug (WHO-DRUG) dictionary.

- Summary table of concomitant medications will be summarized by ATC class 1 and preferred term for all patient in Safety Analysis Population.
- A by-patient listing of concomitant medications will be presented.

11.4.3 Procedure

All procedures and therapies other than medications (eg, radiotherapy, surgery) performed from 28 days before the initiation of the study through the final study visit will be recorded on the Procedure eCRF. All procedures are coded by MedDRA SOC and PT.

- Summary table of concomitant procedures will be summarized by SOC and PT for all patient in Safety Analysis Population.
- A by-patient listing of concomitant procedures will be presented.

12. TREATMENT COMPLIANCE

Overall compliance will be assessed for each patient. Compliance will be computed by determining the number of tablets/capsules taken relative to the number of tablets/capsules that should have been administered. Treatment compliance will be summarized in terms of compliance in treatment phase.

Oraxol Compliance will be calculated based on the following formula for HM30181AK-US tablet and Oral Paclitaxel capsule respectively:

$$\text{Oraxol Compliance during treatment phase (\%)} = \frac{\text{Actual number of tablets/capsules taken during treatment phase}}{\text{Scheduled number of tablets/capsules during treatment phase}} \times 100$$

The scheduled number of administered tablets/capsules for each patient will be calculated based on BSA as [scheduled number of tablets/capsules per day* 3 consecutive days * 16weeks]. For early withdrawal patients, the scheduled number of tablets/capsules should be based on the number of weeks subjects were supposed to be dosed.

The actual number of tablets/capsules taken during the treatment phase is the “Number of Capsules Administered” recorded on Administer Oraxol eCRF.

The following summaries and listings will be provided:

- A summary table of compliance will be presented for all patients in Safety Analysis Population. Compliance will be summarized in 2 ways. Descriptive statistics for compliance expressed as a continuous variable will be presented. In addition, the number and percentage for compliance expressed as a categorical variable (<85%, 85-125%, >125% and missing data) will be presented.
- A by-patient listing of study drug dispensed and returned as well as overall compliance will be provided.

13. ANALYSIS OF PRIMARY ENDPOINT

13.1 Pharmacokinetic Analysis and Presentation

The intent of this section is to provide guidance for the statistical analyses of the PK data of orally administered paclitaxel. All patients in the PK Evaluation Population will be included in the PK analysis.

PK analysis will be performed by Zenith Technology Corporation, Ltd.

13.1.1 Noncompartmental Pharmacokinetic Parameters

Primary endpoints include the following PK parameters derived by noncompartmental analysis using the plasma concentration-time data of Oraxol.

Plasma concentrations for paclitaxel only will be analyzed to determine the following PK parameters:

Parameter	Definition
------------------	-------------------

AUC₀₋₅₂	Area under the curve from time 0 to time 52 hours
C_{max}(0-24)	Maximum observed plasma concentration between Day 1 and Day 2 dosing
C_{max}(24-48)	Maximum observed plasma concentration between Day 2 and Day 3 dosing
C_{max}(48-52)	Maximum observed plasma concentration after Day 3 dosing
T_{max}(0-24)	Time to reach maximum plasma concentration between Day 1 and Day 2 dosing
T_{max}(24-48)	Time to reach maximum plasma concentration between Day 2 and Day 3 dosing
T_{max}(48-52)	Time to reach maximum plasma concentration after Day 3 dosing
C_{trough}	observed pre-dose plasma concentration on day-2 and d-3, respectively

Pharmacokinetic analysis will be carried out using actual sampling time.

Concentrations that are below the lower limit of quantitation (LLOQ) will be set to zero.

If multiple peaks are of equal magnitude the earliest T_{max} will be reported.

Pharmacokinetic parameters will be summarized using the mean, SD, median, minimum, and maximum. Summaries of PK parameters will also include the geometric mean and the coefficient of variation.

Individual concentration and corresponding AUC timepoint data will be tabulated in both nominal and actual sampling times and listed for all subjects. The concentration timepoint (in actual times) data will also be presented graphically for each subject.

13.1.2 Population Pharmacokinetic Analysis

Using the PK samples collected at designated timepoints, a population PK analysis will be explored with pooling the PK data from other studies (to increase sample size). The effect of patient factors on paclitaxel PK will be explored that may explain interpatient variability in PK parameters. Paclitaxel AUC, as well as C_{max}, will then be tested for association of changes with toxicity endpoints, such as neutropenia or incidence of neuropathy. If an observable trend exists among changes in any of these AEs, a

pharmacokinetic/pharmacodynamic (PK/PD) model will be developed to evaluate the exposure-response relationship between the time course of paclitaxel plasma exposure (eg, AUC, C_{max}) in relation to changes in neutropenia and/or neuropathy. Demographic and clinical data (ie, ethnicity, age, BSA, ECOG performance status, etc) will be utilized to assess interpatient variability in the model.

The results of this analysis will be reported separately.

14. ANALYSIS OF SECONDARY ENDPOINTS

14.1 Safety

All patients in the Safety Analysis Population will be included in the safety analyses.

Safety data will be summarized using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters, vital signs, physical examinations and 12-lead ECG results. For all safety analyses, Study Day1 will be defined as the date of the first dose of study medication.

14.1.1 Extent of Exposure

Study medication of Oraxol will be administered with for 3 consecutive days per week in combination with 15 mg oral HM30181 methanesulfonate monohydrate for 16 weeks as follows:

- Oraxol – 15 mg oral HM30181 methanesulfonate monohydrate plus 205 mg/m² oral paclitaxel administered once daily for 3 consecutive days, weekly for 16 weeks (HM30181 will be administered 1 hour before oral paclitaxel on all dosing days.)

The calculated oral paclitaxel dose (based on BSA) for each patient will be rounded up to the closest number of 30-mg paclitaxel capsules.

- The total actual dose (mg) of Oraxol and HM30181AK-US administered in the Safety Analysis Population will be summarized.
- The overall duration (weeks) of Oraxol and HM30181AK-US will be summarized for all patients in the Safety Analysis Population.

The treatment duration is calculated as below:

$[(\text{Date of last administration of Oraxol} - \text{date of first administration of Oraxol}) + 1] / 7$.

If the date of last administration is unknown, the last available administration date will be used. The result will then be divided by 7 and rounded to 2 decimals.

- A by-patient listing of detailed information of dose administration of Oraxol and HM30181AK-US during treatment period will be provided.

- A by-patient listing of Oraxol dispensed will be presented.

14.1.2 Adverse Events

For all AEs, verbatim terms on the CRF/eCRF will be mapped to SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0). The CTCAE criteria v4.03 will be used to grade severity of the AEs. Patient incidence of AEs will be displayed by SOC and PT. The incidence of AEs will be summarized by all patients in the Safety Analysis Population. Adverse events will also be summarized by severity and relationship to study medication. Patient incidence of SAEs will also be displayed.

Only those AEs that were **treatment-emergent** will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The Listing of patients with AEs leading to death will be presented by MedDRA SOC and PT.

The number and percentage of patients with treatment-emergent AEs (TEAEs) leading to study discontinuation will be summarized by MedDRA SOC and PT. A patient data listing of all AEs leading to study discontinuation and leading to study drug discontinuation will be provided.

Treatment-emergent and treatment-related AEs for the subjects will be summarized. Treatment-related is defined as patients experienced any TEAEs with the relationship of “Definitely Related”, “Probably Related” or “Possibly Related” to study drug (Oraxol).

Summaries of TEAEs with CTCAE Grade ≥ 3 will be provided by SOC and PT in descending order of incidence.

Treatment-emergent AEs are defined as:

- those AEs with an onset after the start of dosing and
- those pre-existing AEs that worsen after the start of dosing.

14.1.3 Laboratory Evaluations

Laboratory parameters provided in protocol Table 5 will be summarized using descriptive statistics at baseline and at each subsequent timepoint. Changes from baseline will also be summarized.

Clinical laboratory results after baseline will be evaluated for markedly abnormal values based on the normal range by PI judgement. In addition, shift tables will be provided to assess changes in laboratory values from baseline to each post-baseline visit. The number and percentage of subjects with different categories of CTCAE v4.03 grading for laboratory results will be counted in this shift table.

14.1.4 Vital Signs

Vital signs including pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature with their changes from baseline values will be summarized by all patients in Safety Analysis Population at each scheduled visit.

- A by-patient listing of vital signs will be also provided at each visit.

14.1.5 12-Lead Electrocardiograms

For quantitative ECG measurements (heart rate, PR interval, QRS duration and QT interval, and QTcF), summary statistics of the actual measurement collected at baseline and each post-baseline visit (as well as change from baseline) will be presented by all patients in Safety Analysis Population.

The following summaries and listings will be provided:

- The number and percentage of patients with a clinically significant abnormal ECG or non-clinically significant abnormal ECG after the start of study medication will be summarized by visits for all patients in Safety Analysis Population.
- A by-patient listing of ECG results will be listed. Patients with a clinically abnormal ECG as determined by the investigator will be marked.

14.1.6 Physical Examinations

- A by-patient listing of all physical examination assessments include abnormal physical examination will be provided at each visit.

14.1.7 Other Safety Variables

- A by-patient listing of ECOG performance status responses will be provided.
- A by-patient listing of pregnancy tests will be provided.

14.2 Activity Analysis

Tumor response rate and its 95% confidence interval (CI) will be evaluated based on the number of subjects with any post-baseline CR or PR per RECIST criteria both as evaluated by the Investigator and by the central radiology review committee.

The following activity analysis before End of Study (Week 16) will be analyzed by both investigator and central radiology data based on Response Evaluable Population:

- Best Overall Response: The best overall response is the best response recorded from the start of the study treatment until the end of treatment. The best overall response will be summarized by CR, PR, SD and inevaluable (NE) according to revised RECIST version 1.1 for all patients in Response Evaluable Population.. If

subjects discontinued study after the first SD assessment would be considered NE.

- Tumor Response Rate: The tumor response rate (CR and PR) and its 95% CI will be summarized by visits for all patients in Response Evaluable Population. The 95% CI will be computed by the Clopper-Pearson interval.
- Target sum of RECIST lesion diameters (mm) with percent change from baseline/Nadir and previous will be summarized by visits for all patients in Response Evaluable Population.
- A by-patient listing of tumor assessment including target sum of RECIST lesion diameters, percent change from baseline, target response, non-target response, new lesions present, and timepoint response will be also provided. All the tumor data collected during long-term follow-up visits before pre-defined data cut-off date will be listed, if applicable.

For the time-to-event data, PFS and OS will be analyzed based on Response Evaluable Population. The Kaplan-Meier method is used to estimate the medians of these variables with 95% CIs.

- PFS is defined as time from the start of treatment to first PD or death, which comes earlier, due to any cause in weeks. For patients not reporting PD or death, date of last tumor assessment, the new anticancer treatment date and Week 16 with 2 days of window (Day 114) which comes earlier will be the censored date.
- OS is defined as time from the start of treatment to death due to any cause in weeks. For patients not reporting death, date of last known to be alive and Week 16 with 2 days of window (Day 114) which comes earlier will be the censored date.
- By-patient listing of long-term progression and survival status data collected before pre-defined data cut-off date will be also provided, if applicable.

15. INTERIM ANALYSES

No interim analysis is planned for this study.

16. DEVIATIONS FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSIS

The Response Evaluable Population is defined in SAP [Section 8.3](#), which include all subjects who receive at least 1 dose of study treatment and have at least 1 post-treatment tumor response evaluation. All activity analysis and time-to-event analysis will be analyzed based on Response Evaluable Population.

The population pharmacokinetic analysis is defined in SAP [Section 13.1.2](#), will be explored with pooling the PK data from other studies (to increase sample size) and reported separately.

C_{\min} , a potentially imprecise term, has been replaced by C_{trough} .

C_{avg} that can be estimated in more than one approach has been deleted.

AUC_{τ} is less precise (e.g., could be referred to 24-h interval) than AUC_{52h} that will be provided for this study.

The definition of PK Evaluable Population is revised in SAP [Section 8.2](#), which include subject who receive at least 1 dose of study treatment and have a least 1 post-treatment PK evaluation on Week 4 regardless of protocol eligibility will be included for PK analysis.

17. REFERENCE LIST

None