STATISTICAL ANALYSIS PLAN

CONFIDENTIAL

Oraxol

KX-ORAX-002

PHASE: I

A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel

Date: 17 Sep 2019

Version: Final 1.0

Sponsor:
United States:
Kinex Pharmaceuticals, Inc.
20 Commerce Drive
Cranford, New Jersey 07016, US
Tel: +1 908-340-6996

New Zealand:
Zenith Technology Corporation, Ltd.
156 Frederick Street
Dunedin 9016, New Zealand
Tel: +64 3–477 9669

APPROVAL SIGNATURE(S)

PROTOCOL TITLE: A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel

PROTOCOL NUMBER: KX-ORAX-002

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

SIGNATURES: DATE:

David Cutler Digitally signed by David Cutler Date: 2019.09.19 10:01:52 -04'00'
....
David Cutler, MD, FRCP (C)
Medical Monitor

SIGNATURES: DATE:

....
Jay Zhi, PhD
Senior Director of Clinical Pharmacology

SIGNATURES: DATE:

....
Summer Hsieh
Sr. Biostatistician

APPROVAL SIGNATURE(S)

PROTOCOL TITLE: A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel

PROTOCOL NUMBER: KX-ORAX-002

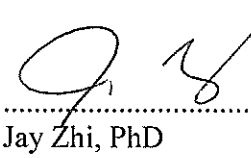
By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and safety analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based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

SIGNATURES: DATE:

.....

David Cutler, MD, FRCP (C)
Medical Monitor

SIGNATURES: DATE:



9/19/19

.....

Jay Zhi, PhD
Senior Director of Clinical Pharmacology

SIGNATURES: DATE:

.....

Summer Hsieh
Sr. Biostatistician

APPROVAL SIGNATURE(S)

PROTOCOL TITLE: A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel

PROTOCOL NUMBER: KX-ORAX-002

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

SIGNATURES: DATE:

....
David Cutler, MD, FRCP (C)
Medical Monitor

SIGNATURES: DATE:

....
Jay Zhi, PhD
Senior Director of Clinical Pharmacology

SIGNATURES: DATE:

 19-Sep-2019
Summer Hsieh
Sr. Biostatistician

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AUC	Area under the curve
BE	Bioequivalence
BLQ	Below limit of quantification
BSA	Body surface area
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
GMR	Geometric mean ratio
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNM	The Tumor, Node, Metastases status
WHO-DD	World Health Organization Drug dictionary

2 INTRODUCTION

This statistical analysis plan (SAP) has been developed after reviewing of the clinical study protocol (protocol v6.0, dated 09Nov2017).

This SAP describes the planned analysis of the safety and tolerability 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 and IV 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.

3 OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The Primary objective of the study is to compare the bioequivalence (BE) based on the area under the curve extrapolated to infinity ($AUC_{0-\infty}$) of orally administered paclitaxel (Oraxol) at the estimated clinical dose to that of intravenous (IV) paclitaxel.

3.1.2 Secondary objective(S)

The secondary objectives are to determine the safety and tolerability of Oraxol.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is area under the concentration-time curve zero time extrapolated to infinite time ($AUC_{0-\infty}$) derived for each participant by noncompartmental analysis using plasma concentration-time data for oral and IV paclitaxel.

3.2.2 Secondary Endpoints

Secondary endpoints include, but are not limited to the following PK parameters which will be derived for each participant by noncompartmental analysis using plasma concentration time data for oral and IV paclitaxel:

- Maximum observed concentration (C_{max})
- Area under the concentration–time curve zero time to time of last quantifiable concentration (AUC_{0-t})
- Time at which the highest drug concentration occurs (T_{max})
- Terminal elimination phase half-life ($t_{½}$)

In addition, the safety and tolerability of Oraxol compared with IV are secondary endpoints in the study. These will be assessed primarily by evaluation of AEs and laboratory findings. The results of other safety assessments (concomitant medications, vital signs, physical examinations, ECGs, and ECOG performance status) will also be evaluated.

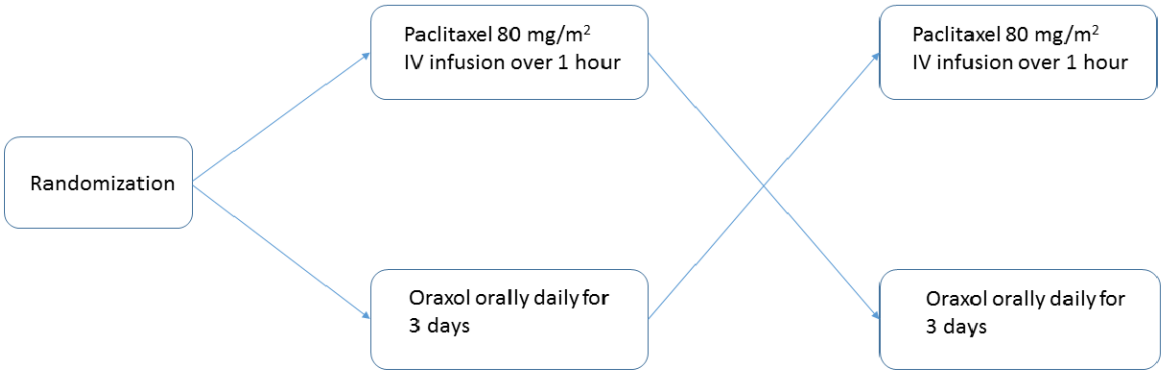
The relationship of AEs with PK exposure parameters (C_{max} and AUC_{0-t}) will be explored via descriptive statistics in Tables as well as Figures (e.g. side-by-side Boxplots).

4 STUDY DESIGN

This is a randomized, multicenter, open-label, 2-stage study with a 2-treatment period crossover study to determine the bioequivalence of three consecutive daily doses of Oraxol in cancer patients treated with intravenous paclitaxel. The 2-treatment period crossover design is shown in Figure 1.

The study will be carried out in 2 stages. Stage 1 will consist of an initial cohort (Cohort 1) of up to 6 evaluable participants who will receive a dosing regimen of Oraxol consisting of a 15-mg oral HM30181 plus and oral paclitaxel dose of 205mg/m^2 once daily for 3 consecutive days. An interim analysis of PK data from Cohort 1 will be conducted to determine if the administered regimen would appear likely to achieve BE of Oraxol to IV paclitaxel. If it appears unlikely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$ data from Cohort 1 data, the dose of paclitaxel in Oraxol may be further adjusted by a maximum of +/- 25% in an additional cohort (Cohort 2) of up to 6 participants in Stage 1. After the interim analysis, a decision will be made by consensus of the DSMB, Sponsors and the Principal Investigator as to what dose should be administered in Stage 2. An additional 18 to 42 participants will be enrolled into Stage 2 based on the Stage 1 results ($AUC_{0-\infty}$).

Figure 1 Crossover Study Design for Study KX-ORAX-002



Participants in both stages will be randomized to receive either treatment sequence A or B. Randomization will be conducted using a computer-generated central randomization scheme that will be reviewed and approved by an independent statistician. An overview of the 2-treatment period crossover study design and the dosing and PK sampling timing for each sequence are presented in Table 1.

Table 1. Study Design, Dosing and PK Sampling in Study KX-ORAX-002

	Pretreatment Phase		Treatment Phase		
	Screening	**Baseline**	**Treatment Period 1**	**Treatment Period 2**	**Final Visit**
Sequence A (Oraxol, IV paclitaxel)	Day -28 to Day -2	Day -1	Days 1-3 (dosing) Days 1-9 (treatment period) Days 1-9 (PK sampling)[a,b]	Day 1 (dosing) Days 1-8 (treatment period) Days 1-5 (PK sampling)[a]	Within 2 weeks after last PK sample
Sequence B (IV paclitaxel, Oraxol)	Day -28 to Day -2	Day -1	Day 1 (dosing) Days 1-8 (treatment period)[c] Days 1-5 (PK sampling)[a]	Days 1-3 (dosing) Days 1-9 (treatment period) Days 1-9 (PK sampling)[a,d]	Within 2 weeks after last PK sample

a: Pharmacokinetic sampling timepoints may be adjusted based on the Stage 1 results.
b: For Sequence A, Treatment Period 1 ends on the morning of Day 9 (144 hrs after the third dose of Oraxol). If Day 9 of Treatment Period 1 is also Day 1 of Treatment Period 2, the last PK sampling timepoint in Treatment Period 1 may serve as the predose timepoint for IV paclitaxel in Treatment Period 2.
c: For Sequence B, Treatment Period 1 ends on the morning of Day 8 (168 hrs after IV paclitaxel dosing).
d: For Sequence B, a predose PK sampling must be taken prior to Oraxol dosing on Day 1 in Treatment Period 2, as the PK sampling for IV paclitaxel ends on Day 5 of Treatment Period 1.

5 DETERMINATION OF SAMPLE SIZE

5.1 Original Sample Size Assumptions

Based on the within-subject variability of at most 30% through a comparison of pharmacokinetics of Oraxol to Taxol, a sample size of 24 to 48 patients is needed to achieve BE within the 80% - 125% confidence limits with 90% statistical power.

5.2 Final Sample Size Assumptions

The final sample size is re-considered after interim analysis of the PK data from the 6 participants in Stage 1. Analysis of variance (ANOVA) was performed (α=0.05) on the log_{10}-transformed $AUC_{0-\infty}$ for paclitaxel. The analysis of variance model included sequence, subjects nested within the sequence, period, and formulation as factors. The 90% confidence interval (CI) for $AUC_{0-\infty}$ was (74.61%, 101.66%), geometric mean ratio (GMR) for $AUC_{0-\infty}$ was 87.09% and intra-subject coefficient of variation (CV) for $AUC_{0-\infty}$ was 12.62.

Based on the first 6 evaluable participants from Stage 1, an additional 34 evaluable participants were enrolled into Stage 2. A total sample size of 40 evaluable participants was projected to provide 90% power for the 90% CI of the GMR for $AUC_{0-\infty}$ to fall in the range of 80% and 125%.

6 PATIENT DISPOSITION

The number of participants who are screened, screen failed, randomized, dosed and completed the study will be summarized. For those who discontinued the study early, the reason leading to study discontinuation will also be summarized by treatment group.

In addition, total number of participants will be summarized by treatment for each analysis set (Pharmacokinetic Analysis Set and Safety Analysis Set).

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, reason for discontinued from the study.

7 PROTOCOL DEVIATIONS

Information regarding subject identification, reason for protocol deviations/protocol violation will be presented in data listing.

8 ANALYSIS POPULATION

8.1 Safety Analysis Set

The safety analysis set is the group of participants who receive at least 1 dose of

paclitaxel (as Oraxol or IV) and have at least 1 post-dose safety assessment.

8.2 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set is the group of participants who receive both study treatments, complete scheduled post-treatment PK evaluations, and are protocol-compliant. Participants who vomit within twice the median T_{max} will be excluded from the primary analysis.

8.3 Randomized Set

The Randomized Set is the group of participants who have been assigned to randomization sequence.

9 STUDY POPULATION

9.1 Baseline and Demographic Characteristics

Demographic and baseline characteristics will be summarized by all participants in Safety Analysis Set.

Demographic data, including age (in years), age category (<65, ≥65), gender and race will be summarized by treatment sequence.

Baseline characteristics, including height, baseline weight, baseline BSA, ECOG at screening, tumor status at screening and metastatic sites will also be summarized in the same way as demographic data.

For continuous demographic variables, results will be summarized and presented as N, mean, SD, median, and minimum and maximum values. For categorical (nominal or ordinal) variables, the number and percentage of participants will be used. No statistical testing will be performed.

9.2 Medical History and Prior Medication

Medical and surgical history and current medical conditions will be recorded at Screening. All pertinent medical history must be noted in the eCRF. A complete oncologic medical history will also be recorded.

Medical history including oncology history (other cancer related diagnosis) and non-oncology medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for all patients in Safety Analysis Set. Oncology treatment history for surgery/radiation, non-oncology surgical history and non-oncology prior therapy will also be coded by MedDRA and summarized by SOC and PT.

All medications (prescription and nonprescription including vitamins and dietary supplements), treatments, and therapies including radiotherapy taken 28 days before the initiation of the study through the final study visit must be recorded in the electronic case

report form (eCRF). A complete oncologic treatment history will be recorded on the Oncologic Treatment History eCRF.

Prior medication is defined as medications that stopped before the first dose of study drug. Prior medication including oncology treatment history for chemotherapy and non-oncology prior medication will be summarized by drug and drug class (coded by the World Health Organization Drug (WHODrug) dictionary).

All medical history and prior medication will also be listed.

10 EXPOSURE AND COMPLIANCE

10.1 Extent of Exposure

Oraxol dosing will consist of 15 mg oral HM30181AK-US tablet daily for 3 consecutive days plus oral paclitaxel administered over the 3 dosing days. The dose of oral paclitaxel as the number of 30-mg capsules needed to dose participants with 615 mg/m^2 over 3 days based on screening BSA. The total number of capsules will be rounded up. If the number of capsules is not divisible by 3, a single extra capsule will be taken on Day 1; 2 extra capsules will be taken as 1 capsule each on Days 1 and 2.

Intravenous paclitaxel 80 mg/m^2 will be administered on Day 1 of either treatment period.

The calculated oral paclitaxel dose for each patient will be rounded up the closest number of 30-mg paclitaxel capsules. The total actual doses of oral paclitaxel, HM30181AK-US and IV paclitaxel will be summarized by treatment sequence.

Dosing information will also be listed in the data listing with corresponding fasting record.

10.2 Treatment Compliance

Overall compliance of study treatment will be performed on the safety analysis set. Oraxol compliance will be calculated based on the following formula for HM30181AK-US tablet and Oral Paclitaxel capsule respectively:

$$\text{Compliance}(\%) = \frac{Actual\ number\ of\ tables/\ capsules\ taken\ druing\ the\ period}{Planned\ number\ of\ tables/capsules\ during\ the\ period} \times 100$$

The planned number of HM30181AK-US tablets is 3. The planned number of administered Oral Paclitaxel capsules for patient will be calculated based on the dose of oral paclitaxel as the number of 30-mg capsules needed to dose participants with 615 mg/m^2 over 3 days based on screening BSA. The total number of capsules will be rounded up.

The actual number of tables/capsules taken during treatment period is calculated as the number of tablets dispensed-number of tablets returned.

IV Paclitaxel compliance will be calculated based on the following formula:

$$\text{Compliance}(\%) = \frac{Actual\ Dose\ Administered}{Planned\ Dose} \times 100$$

A summary table of compliance will be presented in 2 ways: descriptive statistics for compliance expressed as a continuous variable will be presented by treatment sequence. In addition, the number and percentage for compliance expressed as a categorical variable (<85%, 85-125% and >125%) will be presented by treatment sequence.

11 STATISTICAL ANALYSIS

11.1 Working Platform

Statistical analysis programs will be generated with SAS software.

11.2 Time-Points for Analysis

A final analysis will be conducted when study completion and database look are reached.

11.3 Methods for Handling Missing, Dropout, Outlier Data

Drug concentrations below limit of quantification (BLQ) will be flagged and used for descriptive statistics but not for PK parameter estimation. BLQ value will be set to zero for this study.

Except for the concentration data, there will be no imputation for missing data. Missing values will be regarded as missing.

11.4 General Consideration

Statistical analyses will be reported using summary tables, figures and data listings. Continuous data will be summarized with number of participant (N), mean, standard deviation (SD), median, minimum and maximum value. Summaries of PK parameters will also include the geometric mean and the coefficient of variation. Categorical data will be summarized with the number and percentage of participant. All raw data obtained from electronic case report form (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.

12 PHARMACOKINETIC ANALYSIS

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

The PK analysis will be performed on the Pharmacokinetic Analysis Set using plasma concentrations of oral paclitaxel (in Oraxol) and IV paclitaxel. Paclitaxel plasma

concentrations will be normalized to 615 mg/m^2 or the final agreed dose for Stage 2 for Oraxol and 80 mg/m2 for IV paclitaxel. Pharmacokinetic analysis and statistical analysis will be based on normalized plasma concentrations.

Plasma concentrations for paclitaxel only will be analyzed to determine the following PK parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The equivalence of the extent of absorption will be determined by comparing the $AUC_{0-\infty}$ of the selected dose of oral paclitaxel (as Oraxol) (administered over 3 consecutive days) to the $AUC_{0-\infty}$ of IV paclitaxel.

The individual plasma concentration time profiles for paclitaxel will be presented. Descriptive statistics (arithmetic mean, standard deviation and CV) will be performed on the plasma concentrations for paclitaxel at each sampling time under each treatment group. The mean plasma concentration-time data for paclitaxel for each sampling time will be listed and shown graphically.

Descriptive statistics such as arithmetic mean, standard deviation, geometric mean, min, median, max and CV for each pharmacokinetic parameter (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max} and $t_{1/2}$) on the original scale will be calculated by treatment group. Geometric mean will also be calculated.

The primary PK parameters will be compared between IV paclitaxel (reference) and oral paclitaxel (test) formulations. Analysis of variance (ANOVA) will be performed (α=0.05) on the un-transformed and log_{10}-transformed PK parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for paclitaxel. The ANOVA model will include sequence, subjects nested within the sequence, period, and formulation as factors. The significance of the sequence effect will be tested using the subjects nested within the sequence as the error term.

Two-sided 90% CIs for the log-transformed ratio of test/reference of the least squares means obtained from the ANOVA for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ will be estimated.

The equivalence of the extent of absorption will be determined by comparing the log-transformed $AUC_{0-\infty}$ of the oral paclitaxel to the log-transformed $AUC_{0-\infty}$ of IV paclitaxel. If the 90% CIs for $AUC_{0-\infty}$ fall within 80% to 125%, it will be concluded that the oral paclitaxel (in Oraxol) is bioequivalent to IV paclitaxel.

T_{max} and other summary PK parameters and individual timepoints will be tabulated and displayed graphically and listed for all participants.

13 SAFETY

13.1 Adverse Events

All adverse events (AEs) will be coded with MedDRA (version 16.1 or later) and summarized by system organ class (SOC) and preferred term (PT). The CTCAE criteria v4.03 (or later) will be used to grade the severity of the AEs. Only treatment-emergent AEs (TEAEs) will be summarized. TEAEs will be defined as:

- those AEs with an onset after the start of dosing in each treatment period and
- those pre-existing AEs that worsen after the start of dosing in each treatment period

If an AE could not be determined by the definition shown above for partial dates or missing dates, it would be considered as TEAE unless it stopped before the first dose date/time of study treatment.

An AE will be assigned to the study formulation received in the first dose period if the AE occurred after drug administration in the first dose period and prior to taking the study formulation in the second period. An AE will be assigned to the study formulation received in the second dose period if the AE occurred after drug administration in the second period.

The overall AE information including incidence of AE, TEAEs, TEAEs related to study treatment, grade 3 or grade 4 TEAEs, serious TEAE, serious TEAE related to study treatment, TEAE leading to study drug discontinuation and AE leading to Deaths will be summarized by treatment group, treatment period, and treatment sequence.

In addition, the incidence of TEAEs and treatment related TEAEs will be summarized by PT nested within SOC. TEAEs and treatment related TEAEs will also be summarized by PT nested within SOC for worst severity. Similarly, the incidence of serious TEAEs, treatment related serious TEAEs, TEAEs leading to study drug discontinuation and TEAEs leading to Death will be summarized by PT nested within SOC for each treatment group, treatment period, and treatment sequence.

All AEs, AEs leading to death and AEs leading to study drug discontinuation will be provided in data listing separately.

Participant incidence of SAEs will also be displayed.

The relationship of selected AEs with PK exposure parameters (C_{max}, AUC_{0-t}) will be explored descriptively (summary statistics in Tables) as well as graphically (side-by-side boxplots). For summary tables, PK parameters will be summarized for patients by groups either with or without selected AEs (Nausea, vomiting, neutropenia, diarrhea, etc.). Oraxol treatment will be summarized separately, in comparison with IV treatment. For side-by-side boxplots, y-axis will be the values of PK parameters (C_{max}, AUC_{0-t}), and x-axis will be 4 categories: with or without AEs for Oraxol and IV treatments, respectively.

Selected AEs will be presented in a separate plot.

13.2 Laboratory Evaluations

Safety analysis set will be used for the summary of laboratory assessments includes hematology, blood chemistry and urinalysis (mainly dipstick while microscopic test is possible). Laboratory values base on various units collected from eCRF will be normalized with SI units.

Actual values and change from baseline of following continuous laboratory variables will be summarized using descriptive statistics at each scheduled visit by treatment.

- Hematology: all parameters
- Blood Chemistry: all parameters
- Urinalysis: hydrogen ion concentration (PH) and specific gravity.

Categorical laboratory variables will also be summarized by number and percentage of subjects at each scheduled visit by treatment.

Examination value at Day -1 will be the baseline value for each period. The examination at Day -1 of period 2 will be the posttreatment of period 1. The examination at final visit will be the posttreatment of period 2.

Parameters will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the corresponding normal range. Results will be summarized using shift tables for selected items to evaluate categorical changes from baseline to end of study with respect to reference normal range values (lower than, within, higher than).

Laboratory values after baseline will be evaluated for markedly abnormal value based on the CTCAE v4.03 (or later) criteria. The number and percentage of patients reporting markedly abnormal value with high and low categories will be summarized for each parameter by treatment group. For the incidence of markedly abnormal laboratory values, each participant may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

All laboratory values, with corresponding fasting records, will be provided in the data listings.

13.3 Concomitant Medications

Any medication (including nonprescription medications) or therapy administered to the participant during the course of the study (starting at the date of informed consent) will be recorded on the Concomitant Medication eCRF.

Concomitant medications/therapies will be defined as medications/therapies that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study medication.

Summary table of concomitant medications will be summarized by Anatomical-Therapeutic-Chemical (ATC) Level 1 and standardized drug name coded by the World Health Organization Drug (WHODrug) dictionary and treatment for Safety Analysis Set.

Summary table of concomitant therapies will be summarized by SOC and PT coded by the MedDRA dictionary and treatment for Safety Analysis Set.A concomitant medication/therapy is considered to be associated with Oraxol if (1) its start date is within the time interval from the first dosing date of Oraxol (inclusively) to the first dosing date of IV Paclitaxel (exclusively) in treatment sequence A or (2) its start date is within the time interval from the first dosing date of Oraxol (inclusively) to the final visit (inclusively) in treatment sequence B.

Similarly, a concomitant medication/therapy is considered to be associated with IV Paclitaxel if (1) its start date is within the time interval from the first dosing date of IV Paclitaxel (inclusively) to the first dosing date of Oraxol (exclusively) in treatment sequence B or (2) its start date is within the time interval from the first dosing date of IV Paclitaxel (inclusively) to the final visit (inclusively) in treatment sequence A.

Concomitant medications by Anatomical-Therapeutic-Chemical (ATC) Level 1 and standardized drug name using WHODrug dictionary will be listed.

A by-patient listing of concomitant medications will be also provided ATC1 and standardized drug name.

13.4 Vital Signs

Assessments of vital signs include body temperature, respiratory rate, pulse rate, systolic and diastolic blood pressure.

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

13.5 12-Lead Electrocardiograms (ECG)

Safety Analysis Set will be used for the analysis of 12-lead ECG. Quantitative ECG measurements include heart rate, PR interval, QRS duration, QT interval and QTcF interval with their actual values and change from baseline values will be summarized by treatment.

Results of rhythm status and ECG result will be summarized by visit and treatment.

All 12-lead ECG data, including details of abnormal findings from investigators, will be provided in a data listing.

13.6 Physical Examination and Other Safety Parameters

13.6.1 Physical Examination

Evaluation of physical examinations will be listed for all participants in Safety Analysis Set. Abnormality detected during the study will be also recorded and listed.

13.6.2 ECOG

Eastern Cooperative Oncology Group (ECOG) performance status responses (grade from 0 to 5) will be summarized by treatment, treatment period, and treatment sequence, and visit. A by-patient listing of ECOG performance status responses will be also provided.

13.6.3 Pregnancy Tests

Results of pregnancy tests will be listed for all participants as applicable.

14 INTERIM ANALYSES

Interim safety and PK data for DSMB Meeting was summarized in 22 Aug 2016 with data cutoff date 12 Aug 2016[2]. The DSMB meeting was held on 19 Sep 2016. An interim report for bioavailability analysis and sample size for this study was finalized with v1.0, dated 21 Oct 2016[1].

Bioavailability testing was used to compare PK data acquired in a crossover study from an initial cohort (6 participants) treated with 205 mg/m2 Oraxol and 80 mg/m2 IV Taxol. Individual $AUC_{0-\infty}$ parameter estimates derived from noncompartmental analysis that were used for bioavailability testing and variability estimation are presented[1]. It[1] shows the estimated $AUC_{0-\infty}$ GMR (90% CI) derived from bioequivalence testing for the initial 6 subject cohort, which was 87.09% (74.61 – 101.66%)[2]. $AUC_{0-\infty}$ intra- subject variability (CV%) were estimated to be 12.62% for the initial 6 subject cohort [1].

15 DEVIATIONS FROM PROTOCOL ANALYSIS

Additional analysis on the relationship of AEs with PK exposure parameters (C_{max}, AUC_{0-t}) will be explored descriptively (summary statistics in Tables) as well as graphically (side-by-side boxplots).

16 REFERENCE LIST

1. Interim Bioavailability Analysis and Clinical Trial Simulations to Predict Sample Size for Study KX-ORAX-002
2. Study KX-ORAX-002 Interim Safety and PK Data for DSMB Meeting 22 August 2016