REVISION HISTORY

Revisions to KX-ORAX-002 Version 5.0 05 Jul 2017 (Amendment 04 protocol)
Current Version and Date: v6.0_09 Nov 2017 (Amendment 05)

Change	Rationale	Affected Protocol Sections
Revised eligibility criteria at Screening/Baseline for hemoglobin, from ≥100 g/L to ≥90 g/L	A lower threshold of 90 g/L hemoglobin is acceptable in terms of participant safety and will facilitate enrollment.	• Synopsis / Inclusion Criteria • Section 8.3.1
Made the provision that the study may be conducted internationally.	Additional sites may be added outside of New Zealand.	• Synopsis / Sites • Section 5 • Section 8.3 • Section 8.4.2.4
Provided a general reference to Health Authority(ies) and Ethics Committees.	Because the study may extend to countries outside of New Zealand; editorial.	• List of Abbreviations and Definition of Terms • Section 10.1 • Section 11.1 • Section 11.3 • Section 11.6 • Section 11.10 • Section 11.11
Deleted reference to a CRO (Pharmaceuticol Ltd).	Correction.	• Section 5

Revisions to KX-ORAX-002 Version 4.0 13 May 2017 (Amendment 03 protocol)
Current Version and Date: v5.0_05 July 2017 (Amendment 04)

Change	Rationale	Affected Protocol Sections
Added to inclusion criteria GGT values (<10 x ULN at Screening) to demonstrate adequate liver function.	Preliminary data suggest that subjects who receive Oraxol with screening GGT ≥10 x ULN may be at increased risk for early onset of severe neutropenia or serious adverse events.	• Synopsis/Inclusion Criteria #5 • Section 8.3.1/Inclusion Criteria #5

Revisions to KX-ORAX-002 Version 3.0 (Amendment 02 protocol)
Current Version and Date: v4.0_13 May 2017

Change	Rationale	Affected Protocol Sections
Per the Sponsor Protocol Clarification Letter, added new text that it is acceptable to place a pre-emptive PICC line in patients with difficult venous access if problems arise when taking blood from the peripheral IV catheter during PK sampling.	Clarification.	• Section 8.5.1.4.1
Added new text that subject is eligible when alkaline phosphatase (ALP) >5 x ULN if liver or bone metastasis are present and the major fraction of ALP is from bone metastasis, at the discretion of the Investigator.	Clarification.	• Synopsis/Inclusion Criteria • Section 8.3.1
Added a column to the schedules for Days 6-8 of the IV paclitaxel treatment period to differentiate from treatment and PK sampling on Days 1-5. For both sequences, the entire IV paclitaxel treatment period includes Days 1-8. Vital signs, concomitant medications, and adverse events that were to be collected on Days 6-8 of the IV paclitaxel treatment period will be assessed at the next visit.	Clarification. Because there is no PK sampling on Days 6-8, collection of these parameters required participants to remain at the site for an additional 3 days. Removal of these increases participants' comfort.	• Table 10/footnote b • Table 11/footnote b • Table 10 • Table 11
Removed designated study day for the Final Visit on the Schedules of Assessments.	Clarification; footnote c already describes when the Final Visit can occur.	• Table 10 • Table 11
Revised language related to data collection and data management. Removed reference to "CRF".	Clarification. Clarification; this is an EDC study.	• Section 8.6.1 • Section 8.6.2 • Section 11.4 • Throughout document
Made minor spelling, punctuation, and definition corrections.	Administrative.	• Throughout document

Revisions to KX-ORAX-002 Version 2.0 (Amendment 01 protocol)
Current Version and Date: v3.0_26 Jan 2017

Change	Rationale	Affected Protocol Sections
Revised description of delayed treatment/dose interruption by extending the allowed delay from 2 weeks to 3 weeks.	To provide scheduling flexibility.	• Synopsis - Study Design - Duration of Study Participation • Section 8.1 • Section 8.1.2.1 • Section 8.4.1.3 • Table 10/footnote b • Table 11/footnote b
Supplemented description of the PK analyses.	Clarification.	• Synopsis/PK Analyses • Section 8.7.1.7.1
Revised language related to sample size.	Clarification based on interim analysis of data from the first 6 participants in the study.	• Synopsis/Sample Size Rationale • Section 8.7.2
Stipulated that subjects whose Oraxol dosing is temporarily suspended may be re-enrolled at a later time.	Clarification.	• Section 8.1
Revised Section heading for Adverse Events Assessments to remove 'Other Events of Interest'; stipulated that laboratory AEs considered serious should be reporting using SAE reporting procedures. Revised description of other events of interest.	Clarification; other events of interest are noted in the following subsection. Clarification.	• Section 8.5.1.5.1 • Section 8.5.1.5.2
Revised where instructions for SAE reporting will be located (investigator file, not the safety management plan).	Clarification.	• Section 8.5.4.1
Removed reference to exposure to study drug through breastfeeding in section heading. Revised language relating to pregnancy reporting.	Text does not have language related to exposure through breastfeeding. Clarification.	• Section 8.5.4.2
Specified that the Oraxol IB should be used for SAE determination in the context of expedited reporting.	Clarification.	• Section 8.5.4.4
Revised language related to reporting other events of interest associated with overdose or medication error.	Clarification.	• Section 8.5.4.3.1
Revised language related to reporting treatment-emergent significant laboratory abnormality.	Clarification.	• Section 8.5.4.3.2

Revisions to KX-ORAX-002 Version 2.0 (Amendment 01 protocol)
Current Version and Date: v3.0_26 Jan 2017

Change	Rationale	Affected Protocol Sections
Provided criteria for excluding participants from analyses if they vomit.	Clarification for the PK Analysis Set.	• Section 8.7.1.2
Revised description of the safety analysis set.	Clarification to align with definition in Section 8.7.1.2.	• Section 8.7.1.8
Revised the Sponsor (medical) signatory.	Administrative.	• Protocol Signature Page

Revisions to KX-ORAX-002 Version 1.0 (original protocol)
Current Version and Date: v2.0_23 Jan 2016

Change	Rationale	Affected Protocol Sections
Additional wording to describe procedures for participants experiencing unacceptable toxicities during the Treatment Phase. Unacceptable toxicities for which study treatment may be delayed are provided in Appendix 2. Clarified that grades discussed in Appendix 2 are based on CTCAE v4.03. Instructions are provided allowing participants who experience unacceptable toxicity following Oraxol treatment during this study to be enrolled in Study KX-ORAX-003 with dose reduction as allowed in that protocol, if considered appropriate by the Investigator.	Investigator request for clarification concerning clinical management of toxicity.	• Synopsis / Study Design - Stages and Cohorts • Section 8.1 • Section 8.1.2.1 • Appendix 2
Additional wording to describe procedures for managing anaphylaxis and severe hypersensitivity reactions or minor infusion reactions if they occur after IV paclitaxel infusion and if PK sampling should continue. If the infusion is slowed or interrupted, the PK sampling will be modified. Appendix 3 describes the changes to the PK sampling times.	Investigator request for clarification on management of toxicity associated with IV paclitaxel infusion and PK sampling in participants with infusion reactions.	• Synopsis / PK sampling timepoints table (added footnote) • Section 8.1.2.1 • Section 8.5.1.4.1, Table 4 footnote b • Appendix 3
Additional instructions for management of nausea or vomiting after Oraxol treatment for doses subsequent to the first dose. Directions are provided in the event there is vomiting within 4 hours postdose Oraxol on PK sampling days.	Investigator request for clarification on the use of premedication and PK management of participants who vomit following Oraxol treatment.	• Section 8.1.2.1 • Section 8.5.1.4.1, Tables 6, 7, 8 footnote b
Inclusion Criteria #4: Adequate hematologic status at Screening/Baseline, value for absolute neutrophil count (ANC) revised from $\geq 1.0 \times 10^9$/L to $\geq 1.5 \times 10^9$/L.	Typographical correction.	• Synopsis / Inclusion Criteria • Section 8.3.1
Inclusion Criteria #4: Adequate hematologic status at Screening/Baseline, value for hemoglobin (Hgb) revised from 9.0 g/L to ≥100 g/L.	Typographical correction.	• Synopsis / Inclusion Criteria • Section 8.3.1

Revisions to KX-ORAX-002 Version 1.0 (original protocol)
Current Version and Date: v2.0_23 Jan 2016

Change	Rationale	Affected Protocol Sections
Participants who use warfarin are excluded from the study with the exception of those who are receiving warfarin and are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the investigator. They may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.	Investigator request for clarification on allowed use of anticoagulants.	• Synopsis / Exclusion Criteria • Section 8.3.2 • Section 8.4.7.2
Revised the chemical name of paclitaxel	Standardization of chemical nomenclature.	• Synopsis / Name of Active Ingredient • Section 8.4.2.1
Revised study drug code, chemical name and description of molecular weight of HM30181. Standardized use of product name of tablets (HM30181AK-US) vs study drug code (HM30181).	Standardization of chemical nomenclature.	• Section 8.4.2.2 • Throughout document
Changed address of Sponsor responsible for packaging/labeling of investigational materials	Administrative.	• Section 8.4.2.4
Revised prohibited medications noted in Section 8.4.7.2 to be consistent with exclusion criteria. Clarification that prohibited P450 (CYP) 3A4 and CYP2C8 inducers are strong inducers. To be consistent with KX-ORAX-003, examples of oral medications with a narrow therapeutic index known to be a P-gp substrate are provided. It is noted that a list of prohibited medications will be provided to the sites as part of the Pharmacy Manual. Reference 7 is deleted which adjusts numbering of other references.	Typographical correction and clarification.	• Synopsis / Exclusion Criteria • Section 8.3.2 • Section 8.4.7.2 • Section 9
Removed participant withdrawal as sole reason for noncompliance	Clarification.	• Section 8.4.8
Additional instructions for PK blood sampling are included, specifically, about not using a central line; information on the placement of an IV catheter for this purpose is provided.	Clarification.	• Section 8.5.1.4.1

Revisions to KX-ORAX-002 Version 1.0 (original protocol)
Current Version and Date: v2.0_23 Jan 2016

Change	Rationale	Affected Protocol Sections
Revised dose calculation to be made according to the screening BSA; added text to qualify dose adjustment; stipulated that BSA will be recalculated if there is a ≥10% weight change, and that BSA will be calculated to 1 decimal place.	Clarification.	• Synopsis / Investigational product, dosage and mode of administration • Section 8.1 • Section 8.4.1.1 • Section 8.5.1.5.5 • Section 8.5.2.1, Table 10, footnote e • Section 8.5.2.1, Table 11, footnote e
Indicated measurement of weight at Baseline for Treatment Period 1.	Typographical correction.	• Section 8.5.2.1, Table 10 • Section 8.5.2.1, Table 11
Removed axis as part of ECG recording.	This parameter will not be reported routinely.	• Section 8.5.1.5.7
Instructions added on management of participants who have clinically significant ECG abnormalities identified post dosing	Investigator request for clarification of safety management.	• Section 8.5.1.5.7
The status of treatment compliance is removed as part of information gathered if a participant who discontinued and does not return for visits.	All treatments are given at the study site.	• Section 8.5.5
Miscellaneous edits and correction of formatting	Administrative.	Throughout document

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	KX-ORAX-002
Study Protocol Title:	A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel
Investigational Product Name:	Oraxol
UTN Number:	U1111-1167-2526

SIGNATURES

Authors:

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09 NOV 2017
Date

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Kinex Pharmaceuticals, Inc.

9 Nov 2017
Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	KX-ORAX-002
Study Protocol Title:	A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel
Investigational Product Name:	Oraxol
UTN Number:	U1111-1167-2526

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name, degree(s)>		
Investigator	Signature	Date

<Name of study site>

Study Site

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	KX-ORAX-002
Study Protocol Title:	A Randomized Crossover Study to Determine the Bioequivalence of Three Consecutive Daily Doses of Oraxol in Cancer Patients Treated With Intravenous Paclitaxel
Sponsor:	United States: Kinex Pharmaceuticals, Inc. 20 Commerce Drive Cranford, New Jersey 07016, US Tel: +1 908-272-0628 New Zealand: Zenith Technology Corporation, Ltd. 156 Frederick Street Dunedin 9016, New Zealand Tel: +64 3–477 9669
Investigational Product Name:	Oraxol
Indication:	Cancers treated with Intravenous Paclitaxel
Phase:	1
Approval Date:	v1.0 28 May 2015 (original protocol) v2.0 23 Jan 2016 (Amendment 01) v3.0 26 Jan 2017 (Amendment 02) v4.0 13 May 2017 (Amendment 03) v5.0 05 Jul 2017 (Amendment 04) v6.0 09 Nov 2017 (Amendment 05)
UTN Number:	U1111-1167-2526
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Kinex Pharmaceuticals, Inc. (the Sponsor). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound: Oraxol (oral HM30181AK-US tablet and paclitaxel capsule)

Name of Active Ingredient

HM30181 methanesulfonate monohydrate:

N-(2-(2-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-2H-tetrazol-5-yl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide Methanesulfonate monohydrate

Paclitaxel:

5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13- ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine

Study Protocol Title

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

Lead Principal Investigator

Christopher Jackson, MBChB, FRACP

Sites

Approximately 4-5 centers internationally

Study Period and Phase of Development

First participant in to last participant out, approximately 12-18 months

Phase 1

Objectives

Primary Objective:

- 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

Secondary Objective:

- To determine the safety and tolerability of Oraxol

Background

Oraxol is an oral dosage form of the IV chemotherapeutic agent paclitaxel (Taxol® and generics). It is administered orally as a combination of 2 separate drugs, a novel P-glycoprotein (P-gp) inhibitor, HM30181 methanesulfonate monohydrate and oral paclitaxel. Oraxol has been administered to approximately 111 patients with cancer at paclitaxel doses ranging from 60 mg/m^2 to 420 mg/m^2 once weekly to up to 270 mg per day given 5 days per week (approximately 150 mg/m^2 per day or 750 mg/m^2 per week) for 3 out of 4 weeks. The overall safety profile of Oraxol was similar to that of IV Taxol, with the exception that premedication is not required since the paclitaxel is administered orally and the formulation does not contain Cremophor®.

A variety of dosage regimens are approved for the therapeutic use of Taxol, including 135 mg/m^2, and 175 mg/m^2 administered as both 3-hour and 24-hour infusions once every 3 weeks. These various doses and infusion durations led to a wide range in C_{max} values (195 – 3650 ng/mL) while the paclitaxel exposure (AUC) for these doses vary to a lesser extent (6300 – 15,007 ng·hr/mL). An alternative dosing regimen of 80 mg/m^2 weekly which may be associated with better outcomes is

increasingly used, including in New Zealand.

Results of a study recently completed in New Zealand (ORAX-01-14-NZ) show that the absolute bioavailability (BA) of paclitaxel in Oraxol is approximately 14%. Therefore, an oral paclitaxel dose of 205 mg/m^2 administered for 3 consecutive days per week (ie, a total weekly dose of 615 mg/m^2) is likely to produce a paclitaxel exposure (AUC) similar to that of 80 mg/m^2 IV paclitaxel per week.

Study Design

This is a multicenter, open-label, 2-stage study with a 2-treatment period crossover design. Eligible participants are adults with cancer for whom weekly therapy with IV paclitaxel at a dose of 80 mg/m^2 over 1 hour is indicated.

Stage 1 will consist of an initial cohort (Cohort 1) up to 6 evaluable participants who will receive a dosing regimen of Oraxol consisting of a 15-mg oral HM30181AK-US tablet plus an oral paclitaxel dose of 205 mg/m^2, both administered once daily for 3 consecutive days. The stages and cohorts are further described in the "Study Design - Stages and Cohorts" table below. An interim analysis of pharmacokinetic (PK) data from Cohort 1 will be conducted to determine if the administered regimen would appear likely to achieve BE ($AUC_{0-\infty}$), if tested in a greater number of participants in Stage 2. If it appears unlikely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$ data, a second cohort (Cohort 2) of up to 6 evaluable participants may be enrolled in Stage 1, and the dose of paclitaxel in Oraxol may be adjusted by a maximum of +/- 25%. If Cohort 2 is enrolled, a second interim analysis will be conducted.

After the interim analysis/analyses (depending on the outcomes), a decision will be made by consensus of the DSMB, Kinex, Zenith Technology, and the Principal Investigator as to what dose should be administered in Stage 2. The DSMB will consist of a clinical oncologist, an ethicist, an independent statistician, and additional members, as deemed necessary. A DSMB charter will describe the planned evaluations and decision points used to determine the dose for Stage 2. An additional 18 to 42 evaluable participants will be enrolled into Stage 2 based on the Stage 1 results ($AUC_{0-\infty}$). Thus a total of up to 54 evaluable participants could potentially be enrolled in this study (6 each from Stage 1, Cohorts 1 and 2, and up to 42 participants in Stage 2).

Study Design – Stages and Cohorts

Stage 1:

Cohort 1

An initial cohort of up to 6 participants will be treated at an oral paclitaxel dose of 205 mg/m^2 once daily for 3 consecutive days to confirm that it is an acceptable regimen. The standard deviation (SD) and the 90% 2-sided confidence interval (CI) on $AUC_{0-\infty}$ will be determined. If it appears likely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$, additional participants will be enrolled in Stage 2 at this dose.

Cohort 2

If it appears unlikely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$ data from the first cohort, the dose of paclitaxel in Oraxol may be further adjusted by a maximum of +/- 25% in an additional cohort of up to 6 participants in Stage 1.

Stage 2:

An additional 18 to 42 participants will be enrolled in Stage 2 at the dosing regimen from Stage 1 that is considered most likely to demonstrate bioequivalence. Including the 6 participants from Stage 1, a total of 24 to 48 participants will receive the Stage 1 dose that is considered most likely to demonstrate bioequivalence.

The study includes a Pretreatment and Treatment Phase. The Pretreatment Phase consists of Screening and Baseline Periods. During the 2-treatment crossover sequence (Sequence A or B) in the Treatment Phase, participants will be treated with a single dose of IV paclitaxel 80 mg/m^2 infused over 1 hour and a dosing regimen of Oraxol expected to achieve BE to the IV paclitaxel dosing regimen. (The actual Oraxol dosing regimen will depend on the cohort, as explained above). Treatment may be delayed for unacceptable toxicities (Appendix 2). A Follow-up Period will occur after completion of both treatment periods.

The treatment sequences will be:

A. Oraxol (HM30181AK-US tablet + paclitaxel capsules) on Days 1, 2, and 3 of Treatment Period 1 followed by IV paclitaxel on Day 1 of Treatment Period 2
B. IV paclitaxel on Day 1 of Treatment Period 1 followed by Oraxol on Days 1, 2, and 3 of Treatment Period 2

Participants will be randomized to receive either treatment Sequence A or B (see below).

	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 the 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 the last PK sample

IV = intravenous; PK = pharmacokinetic.
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.

For Sequence A, the second treatment may be administered 6 days after completion of the 3-day Oraxol dosing (ie, on Day 9) in Treatment Period 1 and the 144-hour PK sample has been collected. For Sequence B, the second treatment may be administered 7 days after completion of the IV paclitaxel dosing in Treatment Period 1 (ie, on Day 8).

The second period of randomized treatment may be delayed for up to 3 weeks, if needed, to allow the participant to recover to ≤ Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment.

Pharmacokinetic blood samples will be collected according to designated timepoints. Pharmacokinetic sampling timepoints may be adjusted based on the Stage 1 results.

Participants who successfully complete this study may be eligible to receive additional treatment with Oraxol in a follow-on, safety, clinical response, and PK study. Participants who experience unacceptable toxicity following Oraxol treatment in this study, may enroll in Study KX-ORAX-003, with dose reduction as allowed in that protocol, if considered appropriate by the Investigator.

Inclusion Criteria

Eligible participants must have/be:

1. Signed written informed consent
2. Males and females ≥18 years of age on day of consent
3. Cancer patients for whom treatment with IV paclitaxel at 80 mg/m^2 has been recommended by their oncologist, either as monotherapy or in combination with other agents
4. Adequate hematologic status at Screening/Baseline:
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   - Platelet count ≥100 x 10^9/L
   - Hemoglobin (Hgb) ≥90 g/L
5. Adequate liver function at Screening/Baseline as demonstrated by:
   - Total bilirubin of ≤20 µmol/L or ≤30 µmol/L for participants with liver metastasis
   - Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if liver metastasis is present
   - Alkaline phosphatase (ALP) ≤3 x ULN or ≤5 x ULN if liver or bone metastasis are present
   - ALP >5 x ULN if liver or bone metastasis are present and the major fraction of ALP is from bone metastasis, at the discretion of the Investigator
   - Gamma glutamyl transferase (GGT) <10 x ULN
6. Adequate renal function at Screening/Baseline as demonstrated by serum creatinine ≤177 µmol/L or creatinine clearance >50 mL/min as calculated by the Cockcroft and Gault formula
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
8. Life expectancy of at least 3 months
9. Willing to fast for 8 hours before and 4 hours after Oraxol administration
10. Willing to abstain from alcohol consumption for 3 days before the first dose of study drug through the completion of protocol-specified PK sampling in Treatment Period 2
11. Willing to refrain from caffeine consumption for 12 hours before each treatment period through the completion of protocol-specified PK sampling for that dose
12. Women must be postmenopausal (>12 months without menses) or surgically sterile (ie, by hysterectomy and/or bilateral oophorectomy) or, if sexually active, must be using effective contraception (ie, oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for the duration of their participation in the study. Women of childbearing potential must agree to use contraception for 30 days after their last dose of study drug.
13. Sexually active male participants must use a barrier method of contraception during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.

Exclusion Criteria

Eligible participants must not have/be:

1. Currently taking a prohibited concomitant medication:
   - Strong inhibitors (eg, ketoconazole) or strong inducers (eg, rifampin or St. John's Wort) of cytochrome P450 (CYP) 3A4 (within 2 weeks prior to the start of dosing in the study)
   - Strong inhibitors (eg, gemfibrozil) or strong inducers (eg, rifampin) of CYP2C8 (within 2 weeks prior to the start of dosing in the study)
   - Known P-glycoprotein (P-gp) inhibitors or inducers. Participants who are taking such medications but who are otherwise eligible may be enrolled if they discontinue the medication ≥1 week before dosing and remain off that medication through the end of PK sampling after the administration of the second study treatment
   - An oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to start of dosing in the study
2. Use of warfarin. Participants receiving warfarin who are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the Investigator, may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.
3. Unresolved toxicity from prior chemotherapy (participants must have recovered all significant toxicity to ≤ Grade 1 CTCAE toxicity from previous anticancer treatments or previous investigational agents). This does not extend to symptoms or findings that are attributable to the underlying disease
4. Received investigational agents within 14 days or 5 half-lives prior to the first study dosing day, whichever is longer
5. Women of childbearing potential who are pregnant or breast feeding
6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, clinically significant myocardial infarction within the last 6 months, unstable angina pectoris, clinically significant cardiac arrhythmia, bleeding disorder, chronic pulmonary disease requiring oxygen, or psychiatric illness/social situations that would limit compliance with study requirements
7. Major surgery to the upper gastrointestinal (GI) tract, or have a history of GI disease or other medical condition that, in the opinion of the Investigator may interfere with oral drug absorption
8. A known history of allergy to paclitaxel. Participants whose allergy was due to the IV solvent (such as Cremophor) and not paclitaxel will be eligible for this study.
9. Any other condition which the Investigator believes would make a subject's participation in the study not acceptable

Investigational product, dosage and mode of administration

Test drug: Oraxol (oral HM30181 + paclitaxel)

- HM30181 methansulfonate monohydrate – supplied as 15-mg HM30181AK-US tablets
- Paclitaxel – supplied as 30-mg capsules

Reference Drug: IV paclitaxel – supplied as Taxol or generic from a single manufacturer

Dosing will be as follows:

Oraxol:

- 15 mg oral HM30181AK-US tablet daily for 3 consecutive days plus oral paclitaxel capsules administered once daily for 3 consecutive days. The HM30181AK-US tablet will be administered 1 hour before the oral paclitaxel capsules; no premedication is allowed before the first dose of Oraxol. Premedication may be given before subsequent doses for hypersensitivity reactions and/or nausea or vomiting.
    - Stage 1, Cohort 1: oral paclitaxel capsules dose - 205 mg/m^2 once daily for 3 consecutive days.
    - or if needed, Stage 1, Cohort 2: oral paclitaxel capsules adjusted dose of a maximum of +/- 25% of the 205 mg/m^2 dose once daily for 3 consecutive days
    - Stage 2: dose determined in Stage 1 as likely to achieve BE based on PK interim analysis/analyses

Paclitaxel:

- 80 mg/m^2 IV paclitaxel (from a single manufacturer) infused over 1 hour plus premedication per standard local practice.

The dose of oral paclitaxel for Stage 1, Cohort 1 will be calculated as the number of 30-mg capsules needed to dose participants with 615 mg/m^2 over 3 days based on screening body surface area (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. The dose of oral paclitaxel for Stage 1, Cohort 2 and Stage 2 will be calculated similarly based on results of the planned interim analyses.

Duration of Study Participation

The total duration of participation for each participant will be up to a maximum of 80 days as follows:

Phase	Periods	Days
Pretreatment Phase	Screening Period and Baseline Period	up to 28 days
Treatment Phase	Treatment Periods 1 and 2:	16 to 17 days (plus up to 21 days if treatment delay is needed)
	Follow-up Period:	up to 14 days

Assessments

Activity Assessments: Not applicable

Pharmacokinetic: PK sampling times for measurement of plasma concentrations of study drug are shown below.

Treatment	PK Sampling Timepoints
Oraxol (HM30181 + paclitaxel) Treatment Period 1 or 2:	Day 1 dosing: predose, and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, and 12 hours **after the first dose** (Day 1) Day 2 dosing: predose, and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, and 12 hours **after the second dose** (Day 2) Day 3 dosing: predose, and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours **after the third dose** (Days 3-9)
IV Paclitaxel[a] Treatment Period 1 or 2:	Predose, during infusion at 2, 5, 8, 12, 20, 40, and 60 minutes, after infusion at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32, 48, 56, 72, and 96 hours (Days 1-5)

a. In the event that the IV paclitaxel infusion is slowed or temporarily interrupted due to IV paclitaxel infusion reaction, PK blood sampling should continue according to the modified schedule in Appendix 3.

Pharmacodynamic: Not applicable

Pharmacokinetic-Pharmacodynamic: Not applicable

Safety: Safety will be assessed by recording all adverse events (AEs) including serious adverse events (SAEs) and concomitant medications, laboratory evaluation of hematology, biochemistry, and urinalysis values, measurement of vital signs, evaluation of electrocardiograms (ECGs) and ECOG performance status, and the performance of physical examinations.

Bioanalytical Methods

Plasma concentrations of study drug will be measured using a validated assay.

Statistical Methods

A total of 24 to 48 evaluable participants receiving the selected Stage 1 dose will be evaluated for BE between Oraxol and IV paclitaxel based on a 2-sided 90% CI of log-transformed $AUC_{0-\infty}$ between 80% and 125%.

Participants evaluable for BE will be those who receive both study treatments and complete scheduled post-treatment PK evaluations. Nonevaluable participants will be replaced until up to 48 participants have completed the study at the dose determined in Stage 1 as likely to achieve BE based on PK interim analysis/analyses.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables 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. Categorical variables will be summarized by counts and by percentage of participants in corresponding categories. All raw data obtained from the electronic case report form (eCRF) as well as any derived data will be included in data listings.

Pharmacokinetic Analyses

Plasma concentrations for paclitaxel only will be analyzed to determine the following PK parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (2-sided 90% CIs); paclitaxel plasma concentrations will be normalized to 615 mg/m^2 or the final agreed dose for Stage 2 for Oraxol and 80 mg/m^2 for IV paclitaxel. Pharmacokinetic analysis and statistical analysis will be based on normalized plasma concentrations. T_{max} and other summary PK parameters and individual timepoints will be tabulated and displayed graphically and listed for all participants.

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 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.

Safety Analyses

All participants who receive at least 1 dose of paclitaxel will be included in the safety analyses. For AEs, verbatim terms on the eCRF will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.1 or later). The CTCAE criteria v4.03 (or later) will be used to grade severity of the AEs. Participant incidence of AEs will be displayed by SOC. The incidence of AEs will be summarized by treatment, treatment period, and treatment sequence. Adverse events will also be summarized by severity and relationship to the study drug and treatment sequence. Participant incidence of SAEs will also be displayed. Laboratory parameters will be summarized using descriptive statistics at baseline and at each subsequent timepoints. Changes from baseline will also be summarized.

Interim Analyses

There will be an interim analysis of PK data after each dose tested in Stage 1 to determine if the administered regimen would appear likely to achieve BE of Oraxol to IV paclitaxel. After the interim analysis/analyses (depending on the outcomes), a decision will be made by consensus of the DSMB, Kinex, Zenith Technology, 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 ($AUC_{0-\infty}$).

Sample Size Rationale

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.

Based on analysis of data from the first 6 evaluable participants in Stage 1, an additional 34 evaluable participants will be enrolled into Stage 2. A total sample size of 40 evaluable participants is 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%.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANZCTR	Australian New Zealand Clinical Trials Registry
BA	bioavailability
BE	bioequivalence
BSA	body surface area
CI	confidence interval
CRA	clinical research associate
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	(US) Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
GGT	gamma glutamyl transferase
HA	Health Authority
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IP	investigational product
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
MTD	maximum tolerated dose

Abbreviation	Term
NOS	not otherwise specified
P-gp	P-glycoprotein
PK	pharmacokinetic
PT	preferred term
RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCOTT	Standing Committee on Therapeutic Trials
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cells

5 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified Investigators under the United States sponsorship of Kinex Pharmaceuticals, Inc. with the New Zealand contract research organizations (CROs) (Zenith Technology Corporation, Ltd.) providing delegated services. This study will be conducted at approximately 4-5 centers internationally.

The name, telephone and fax numbers, and email addresses of the medical monitor and other contact personnel at the Sponsor and of the CROs will be listed in the Investigator Study File provided to each site.

6 INTRODUCTION

6.1 Indication

In this study, the pharmacokinetics (PK) of oral paclitaxel as Oraxol will be evaluated in adults with cancers for whom weekly therapy with intravenous (IV) paclitaxel at a dose of 80 mg/m^2 infused over 1 hour is indicated.

6.1.1 Oraxol

Oraxol is a combination product of 2 separate drugs; oral paclitaxel and a novel P-glycoprotein (P-gp) inhibitor, HM30181 methanesulfonate monohydrate. Experience to date indicates that co-administration of HM30181 methanesulfonate monohydrate allows for clinically relevant levels of paclitaxel to be achieved following oral dosing. Oraxol is intended to allow for oral treatment of cancers that would otherwise be treated with IV paclitaxel. Comprehensive data on the preclinical, toxicology, and clinical experience to date can be found in the Investigator's Brochure.

6.1.1.1 Clinical Experience with Oraxol

Previous human experience with HM30181 methanesulfonate monohydrate comes from 3 PK studies in healthy male subjects. In these studies, a total of 81 individuals received single oral doses of HM30181 methanesulfonate monohydrate ranging from 1 to 900 mg and 24 individuals received multiple doses ranging from 60 mg to 360 mg per day for 5 days. In addition to evaluating single- and multiple-dose safety and PK, 2 of these studies evaluated the effect of HM30181 methanesulfonate monohydrate on the PK of loperamide, a P-gp substrate, and 1 study also compared the effects of HM30181 methanesulfonate monohydrate to quinidine, a known P-gp inhibitor. These data indicate that exposure to HM30181 methanesulfonate monohydrate increases with dose, but not in a dose-proportional manner, and that the effect of HM30181 methanesulfonate monohydrate on P-gp may last for up to 15 days following a single dose of 10 mg or higher but is not as pronounced as that of 600 mg of quinidine.

Oraxol has been administered to approximately 111 patients with cancer at paclitaxel doses ranging from 60 mg/m^2 to 420 mg/m^2 once weekly to up to 270 mg per day given 5 days per

week (approximately 150 mg/m^2 per day or 750 mg/m^2 per week) for 3 out of 4 weeks. The overall safety profile of Oraxol was similar to that of IV Taxol®, with the exception that premedication is not required since the paclitaxel is administered orally and the formulation does not contain Cremophor®. To date, Oraxol has been evaluated in 4 studies. A summary of these studies is presented below. For further details, please refer to the Investigator Brochure.

The HM-OXL-101 study attempted to define the maximum tolerated dose (MTD) for Oraxol in 24 subjects with advanced solid cancer. This was a "3+3" design in which cycles were 28 days and dosing with HM30181A tablets and an oral liquid formulation of paclitaxel was given on Days 1, 8, and 15 of each cycle. Paclitaxel doses evaluated ranged from 60 to 420 mg/m^2. HM30181A doses were half of paclitaxel doses (30 to 210 mg/m^2). The MTD was not reached in this study and dose escalation was stopped because of PK nonlinearity at paclitaxel doses above 300 mg/m^2. The most common nonserious adverse events (AEs) were gastrointestinal (GI) AEs, hematologic AEs, and alopecia. Neutropenia was the event that led to either temporary (4 cases) or permanent (1 case) discontinuation of Oraxol. The only serious adverse event (SAE) occurred at the paclitaxel dose of 420 mg/m^2. This subject was hospitalized with cholangio-hepatitis and recovered after treatment with endoscopic retrograde biliary drainage. The event was considered unrelated to the study medication.

HM-OXL-201 was a 2-part study including an initial MTD assessment of Oraxol doses 90, 120, or 150 mg/m^2 paclitaxel per day for 2 days per week for 3 weeks out of a 4-week cycle (as liquid-filled capsules), with paclitaxel given concomitantly with a 15-mg HM30181A tablet on Day 1. In the second part of this study, the selected dose of Oraxol, 150 mg/m^2 per day, was given for 2 days per week, for 3 weeks out of a 4-week cycle. The Investigators were also given the flexibility of giving an additional 15-mg tablet of HM30181A on Day 2 of each dosing week. A total of 56 subjects enrolled in this study, 10 subjects with advanced malignant tumors in Part 1 and 46 subjects with advanced gastric cancer in Part 2. The most common AEs were neutropenia, anorexia, diarrhea, nausea, and abdominal pain. In the first part of this study, 1 subject had SAEs of pyrexia and bacteremia (probably not related to study treatment). In the second part of the study, 26 SAEs occurred in 15 subjects. Of these, 3 subjects experienced at least 1 SAE considered at least possibly related to study treatment. These included 1 subject with diarrhea and neutropenia, 1 subject with fatigue, and 1 subject with nausea and vomiting. Among 43 subjects in the Intent-to-Treat population in the gastric cancer part of this study, 4 subjects (9.3%) had a partial response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Pharmacokinetic results from these 2 studies showed that the paclitaxel maximum concentration (C_{max}) and area under the curve extrapolated to infinity ($AUC_{0-\infty}$) increased with dose up to 300 mg/m^2 following administration of Oraxol. At doses above 300 mg/m^2, both C_{max} and AUC_{inf} plateaued. Half-life ($t_{1/2}$) ranged from 19.9 to 32.1 hours, consistent with published values for paclitaxel. Metabolic ratios of 3'p-hydroxy paclitaxel and 6α-hydroxy paclitaxel metabolites were approximately 0.1 to 0.25 and 0.04 to 0.13, respectively. Following 2 consecutive daily doses of Oraxol at doses of 60, 90, or 150 mg/m^2, minimal to no accumulation occurred in paclitaxel C_{max} and AUC. The C_{max} ranged from 202 to 280 ng/mL (Day 1) and 159 to 315 ng/mL (Day 2), with minimal increase in C_{max} across the

dose levels. The AUC_{0-24} ranged from 611 to 894 ng·hr/mL (Day 1) and 735 to 1081 ng·hr/mL (Day 2). Overall exposure on Day 2 was about 20% to 30% higher. These data indicate that Oraxol may represent a clinically useful alternative to IV paclitaxel.

Study ORAX-01-13-US is an ongoing "3+3" MTD study of Oraxol at a fixed dose of 270 mg (approximately 150 mg/m^2 per day) orally given 2 to 5 consecutive days per week for 3 out of 4 weeks. Preliminary data indicate that the most common AEs are gastrointestinal. Ten SAEs have been reported to date in 7 subjects; 1 case each of neoplasm posterior fossa mass, syncope, right upper quadrant pain, urosepsis, liver dysfunction, nausea, vomiting, abdominal pain, febrile neutropenia, and pain (NOS). Of these, febrile neutropenia, occurring in the 5-day cohort in Cycle 1 was the only SAE considered related to study treatment and is the only dose-limiting toxicity (DLT) reported to date.

A Phase 1 crossover study (Study ORAX-01-14-NZ) to determine the absolute bioavailability (BA) of Oraxol was conducted in New Zealand and is clinically complete. Oraxol doses were 270 mg paclitaxel orally daily (approximately 150 mg/m^2) on 2 consecutive days (n=6), 274 mg/m^2 administered daily on 2 consecutive days (n=2), and 313 mg/m^2 daily on 2 consecutive days (n=2). The reference treatment was paclitaxel 80 mg/m^2 IV, administered over 1 hour as a one-time infusion. Results show that the absolute BA of paclitaxel in Oraxol is approximately 14% but the total drug exposure (AUC) of oral paclitaxel plateaus at a dose of approximately 300 mg/m^2. Therefore, an oral paclitaxel dose of 205 mg/m^2 administered daily for 3 consecutive days per week (ie, a total weekly dose of 615 mg/m^2) is likely to produce a paclitaxel exposure similar to that of 80 mg/m^2 IV paclitaxel per week. The only SAE reported was urosepsis, which occurred prior to receiving study treatment.

6.1.1.2 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

Serious AEs commonly occur in patients with cancer. Manifestations typically reflect progression of disease, with the clinical presentation varying depending on the affected organ system.

6.2 Study Rationale

The regimen selected for initial evaluation in this study (15 mg oral HM30181AK-US tablet plus 205 mg/m^2 oral paclitaxel capsules both administered once daily for 3 consecutive days per week [ie, a total weekly dose oral paclitaxel of 615 mg/m^2]) is expected to produce paclitaxel exposure similar to that of 80 mg/m^2 IV paclitaxel administered over 1 hour given weekly. A variety of dosage regimens are approved for the therapeutic use of Taxol, including 135 mg/m^2, and 175 mg/m^2 administered as both 3-hour and 24-hour infusions once every 3 weeks. These various doses and infusion durations led to a wide range in C_{max} values (195 – 3650 ng/mL) while the paclitaxel exposure (AUC) for these doses vary to a lesser extent (6300 – 15,007 ng·hr/mL). An alternative dosing regimen of 80 mg/m^2 weekly, which may be associated with better outcomes, is increasingly used. This regimen is currently used in New Zealand. A recent meta-analysis suggests that weekly paclitaxel may

be superior to the approved regimen (175 mg/m^2 IV over 3 hours every 3 weeks) for advanced breast cancer.[2] A similar result has been reported in adjuvant use for breast cancer,[3] and weekly paclitaxel 80 mg/m^2 IV administered over 1 hour is increasingly accepted as a dosing regimen in treatment guidelines.[4,5]

7 STUDY OBJECTIVES

7.1 Primary Objective

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

7.2 Secondary Objective

The secondary objective of the study is to determine the safety and tolerability of Oraxol.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a multicenter, open-label, 2-stage study with a 2-treatment period crossover design. Eligible participants are adults with cancer for whom weekly therapy with IV paclitaxel at a dose of 80 mg/m^2 infused over 1 hour is indicated.

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 an oral paclitaxel dose of 205 mg/m^2, both administered once daily for 3 consecutive days. The stages and cohorts are further described below. An interim analysis of PK data from Cohort 1 will be conducted to determine if the administered regimen would appear likely to achieve BE (using $AUC_{0-\infty}$), if tested in a greater number of participants in Stage 2. If it appears unlikely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$ data, a second cohort of up to 6 evaluable participants may be enrolled in Stage 1 and the dose of paclitaxel in Oraxol may be adjusted by a maximum of +/- 25%. If this cohort is enrolled, a second interim analysis will be conducted.

After the interim analysis/analyses (depending on the outcomes), a decision will be made by consensus of the DSMB, Kinex, Zenith Technology, and the Principal Investigator as to what dose should be administered in Stage 2. The DSMB will consist of a clinical oncologist, an ethicist, an independent statistician, and additional members, as deemed necessary. A DSMB charter will describe the planned evaluations and decision points used to determine the dose for Stage 2. An additional 18 to 42 participants will be enrolled into Stage 2 based on the Stage 1 results ($AUC_{0-\infty}$). Thus a total of up to 54 evaluable participants could potentially be enrolled in this study (6 each from Stage 1, Cohorts 1 and 2), and up to 42 participants in Stage 2.

Study Stages: The study will be carried out in 2 stages as follows:

Stage 1:

Cohort 1

An initial cohort of up to 6 participants will be treated at an oral paclitaxel dose of 205 mg/m^2 once daily for 3 consecutive days to confirm that it is an acceptable regimen. The standard deviation (SD) and the 90% 2-sided confidence interval (CI) on $AUC_{0-\infty}$ will be determined. If it appears likely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$, additional participants will be enrolled in Stage 2 at this dose.

Cohort 2

If it appears unlikely that the selected regimen will meet the criteria for BE based on $AUC_{0-\infty}$ data from the first cohort of participants, the dose of paclitaxel in Oraxol may be further adjusted by a maximum of +/- 25% in an additional cohort of up to 6 participants in Stage 1.

Stage 2:

An additional 18 to 42 participants will be enrolled in Stage 2 at the dosing regimen from Stage 1 that is considered most likely to achieve bioequivalence. Consequently, there will be a total of 24 to 48 participants receiving the Stage 1 dose that is considered most likely to demonstrate bioequivalence.

Study Design:

The 2-treatment period crossover design is shown in Figure 1.

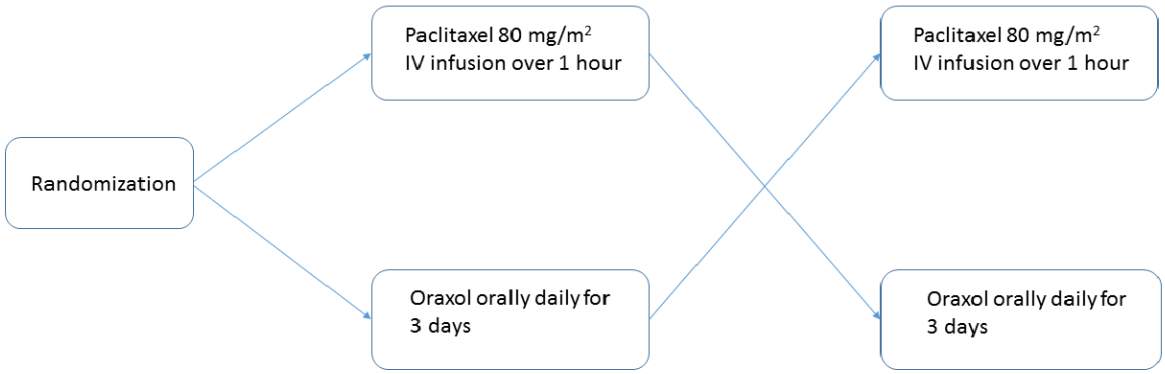


Figure 1 Crossover Study Design for Study KX-ORAX-002

The study includes a Pretreatment and Treatment Phase (see Table 1). The Pretreatment Phase consists of Screening and Baseline Periods. During the 2-treatment crossover sequence (Sequence A or B) in the Treatment Phase, participants will be treated with a single dose of IV paclitaxel 80 mg/m^2 infused over 1 hour and a dosing regimen of oral Oraxol expected to achieve BE to the IV paclitaxel dosing regimen (Table 1). (The actual Oraxol dosing regimen will depend on the cohort, as explained above). Treatment may be delayed

for unacceptable toxicities (see Section 8.1.2.1 and Appendix 2). A Follow-up Period will occur after completion of both treatment periods.

The treatment sequences will be:

A Oraxol (paclitaxel + HM30181) on Days 1, 2, and 3 of Treatment Period 1 followed by IV paclitaxel on Day 1 of Treatment Period 2

B IV paclitaxel on Day 1 of Treatment Period 1 followed by Oraxol on Days 1, 2, and 3 of Treatment Period 2

Participants will be randomized to receive either treatment Sequence A or B. Table 1 summarizes the study design and the dosing and PK sampling timing for each sequence.

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

IV = intravenous; PK = pharmacokinetic.

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.

For Sequence A, the second treatment may be administered 6 days after completion of the 3-day Oraxol dosing (ie, on Day 9) in Treatment Period 1 and the 144-hour PK sample has been collected. For Sequence B, the second treatment may be administered 7 days after completion of the IV paclitaxel dosing in Treatment Period 1 (ie, on Day 8).

The second period of randomized treatment may be delayed for up to 3 weeks if needed, to allow the participant to recover to ≤ Grade 1 Common Terminology Criteria for Adverse Events (CTCAE)[1] or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment.

Subjects whose Oraxol dosing is temporarily suspended may be re-enrolled at a later date.

Dosing:

Oraxol:

- 15 mg oral HM30181AK-US tablet daily for 3 consecutive days plus oral paclitaxel capsules administered once daily for 3 consecutive days. The HM30181AK-US tablet will be administered 1 hour before the oral paclitaxel capsules; no premedication is allowed before the first dose of Oraxol. Premedication may be given before subsequent doses for hypersensitivity reactions and/or nausea or vomiting.
    - Stage 1, Cohort 1: oral paclitaxel capsules dose - 205 mg/m^2 once daily for 3 consecutive days.
    - or if needed, based on PK interim analysis/analyses for BE, Stage 1, Cohort 2: oral paclitaxel capsules adjusted dose of a maximum of +/- 25% of the 205 mg/m^2 dose once daily for 3 consecutive days
    - Stage 2: dose determined in Stage 1 as likely to achieve BE based on PK interim analysis/analyses

IV paclitaxel:

- 80 mg/m^2 IV paclitaxel (from a single manufacturer) infused over 1 hour plus premedication per standard local practice.

The dose of oral paclitaxel for Stage 1, Cohort 1 will be calculated as the number of 30-mg capsules needed to dose participants with 615 mg/m^2 over 3 days based on screening body surface area (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. The dose of oral paclitaxel for Stage 1, Cohort 2 and Stage 2 will be calculated similarly based on results of the planned interim analyses.

Blood samples for PK assessments will be collected according to designated timepoints (see Section 8.5.1.4.1). Sampling timepoints may be adjusted based on the Stage 1 results.

Participants who successfully complete this study may be eligible to receive additional treatment with Oraxol at their assigned weekly dose in a follow-on safety, clinical response, and PK study (KX-ORAX-003). Participants who experience unacceptable toxicity following Oraxol treatment in this study, may enroll in Study KX-ORAX-003, with dose reduction as allowed in that protocol, if considered appropriate by the Investigator.

8.1.1 Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period and a Baseline Period for Treatment Period 1.

Participants will be screened within 28 days prior to the first dose of study drug. After the participant provides informed consent, all screening evaluations, as detailed in Table 10 and Table 11, will be performed to determine whether eligibility criteria are met.

Before Treatment Period 1, participants must have abstained from alcohol for 3 days and refrained from caffeine consumption for 12 hours. On Day -1, before each treatment period, participants will undergo baseline assessments as detailed in Table 10 and Table 11. Participants in treatment Sequence A are required to fast for 8 hours prior to receiving treatment in Treatment Period 1. Fasting prior to Treatment Period 1 is not required for participants in treatment Sequence B.

8.1.2 Treatment Phase

The Treatment Phase will include Treatment Period 1, a Baseline Period for Treatment Period 2, Treatment Period 2, and a Follow-Up Period.

8.1.2.1 Treatment Periods

Participants may be admitted to the clinical site the night before dosing of both Oraxol and IV paclitaxel. Participants will be instructed to fast for at least 8 hours before and 4 hours after Oraxol administration; no fasting is required before the IV paclitaxel dosing. For participants who are admitted to the clinical site on the day of Oraxol dosing, fasting will be verified and participants who have not fasted for the required 8 hours may have their Oraxol dosing delayed or rescheduled, at the discretion of the Investigator.

Participants should remain at the study site for at least the first 24 hours after dosing of IV paclitaxel for PK blood sample collection (see Section 8.5.1.4.1). Participants should remain at the study site, or at a nearby designated facility, for the first 72 hours after Day 1 dosing of Oraxol for PK blood sample collection (see Section 8.5.1.4.1). Participants will return to the study site for the remaining PK blood collections. If more convenient, at the discretion of the Investigator, the participants may be discharged to a local accommodation or remain housed at the study site for the entirety of the PK blood collection periods for both IV paclitaxel and Oraxol.

Participants must abstain from alcohol consumption for 3 days prior to Treatment Period 1 until the completion of protocol-specified PK sampling at the end of Treatment Period 2. In addition, they must refrain from caffeine consumption for 12 hours before each treatment period through the completion of protocol specified PK sampling for that treatment. Participants must not have water or other liquids for 1 hour after taking their last paclitaxel capsule. After the required 1 hour withholding of all liquids, water and decaffeinated coffee and tea will be provided.

The Treatment Phase will begin with the first dose of study drug administration in Treatment Period 1. Study treatments will be administered consecutively on Day 1 (IV paclitaxel) or Days 1, 2, and 3 (Oraxol) of Treatment Period 1 and Treatment Period 2. Oraxol may be administered in a general inpatient clinical research unit, while IV paclitaxel will be

administered in a qualified oncology unit. Transportation of participants between the general inpatient clinical research unit and the oncology unit will be provided.

For Sequence A, the second treatment may be administered 6 days after completion of the 3-day Oraxol dosing (ie, on Day 9) in Treatment Period 1 and the 144-hour PK sample has been collected. For Sequence B, the second treatment may be administered 7 days after completion of the IV paclitaxel dosing in Treatment Period 1 (ie, on Day 8).

Treatment may be delayed for unacceptable toxicities (see Unacceptable Toxicity section below). The second randomized treatment may be delayed for up to 3 weeks, if needed, to allow the participant to recover to ≤ Grade 1 CTCAE or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment. A Follow-up Period will occur after completion of both treatment periods.

The dose of IV paclitaxel used in this study (80 mg/m^2 infused over 1 hour weekly) is the dose commonly in clinical use in New Zealand and elsewhere. The oral paclitaxel dose in Oraxol (205 mg/m^2 daily for 3 consecutive days per week) is expected to result in similar paclitaxel exposure as the IV dose as observed in prior studies.

Unacceptable Toxicity

Unacceptable toxicities for which treatment may be delayed are listed in Appendix 2. A participant who has a treatment delay may resume treatment once the toxicity has resolved to CTCAE Grade 1 or less.

Participants who experience unacceptable toxicity following Oraxol treatment in this study (KX-ORAX-002), may enroll in Study KX-ORAX-003, with dose reduction as allowed in that protocol, if considered appropriate by the Investigator.

Safety Management

The Investigators at each clinical site are oncologists who are experienced in managing toxicities associated with paclitaxel chemotherapy. Treatments will be administered following successful completion of pre-dosing evaluations. Intravenous paclitaxel will be administered in an oncology unit using standard premedication. Oraxol will be administered in a clinical research unit, since premedication is not required for this treatment. Emergencies will be managed by unit staff in accordance with established procedures.

An Investigator and/or delegated oncology nurse will be on site on each Oraxol dosing day through 4 hours postdose. Serious AEs will be reviewed by the DSMB as well as the PK data.

Management of Infusion Reactions

If anaphylaxis and severe hypersensitivity reaction occur after IV paclitaxel infusion, IV paclitaxel infusion should be stopped and antihistamines, corticosteroids, etc, should be administered according to the instructions from the prescription information of the paclitaxel

manufacturer. Minor infusion reactions to IV paclitaxel will be managed according to each site's standard practice. This may include slowing, temporarily interrupting, or discontinuing the infusion, as clinically indicated, and administration of other medications as clinically indicated. In the event that the infusion is slowed or temporarily interrupted due to IV paclitaxel infusion reaction, PK blood sampling should continue according to the modified schedule in Appendix 3. Participants who do not receive the full dose of IV paclitaxel are considered inevaluable for PK.

Participants experiencing hypersensitivity-type reactions related to infusion of IV paclitaxel may continue to receive Oraxol treatment at their assigned dose either in this study or in KX-ORAX-003, if considered appropriate to the Investigator.

Participants who experience unacceptable toxicity following Oraxol treatment in this study (KX-ORAX-002), may enroll in Study KX-ORAX-003, with dose reduction as allowed in that protocol, if considered appropriate by the Investigator.

Management of Nausea or Vomiting

Premedication is not required for Oraxol and is not allowed before the first dose. Nausea or vomiting following the first dose of Oraxol may be managed with anti-emetic medications (eg, metoclopramide, IV or sublingual ondansetron, or other 5-HT 3 or NK-1 antagonists), including premedication for subsequent doses, as appropriate. On PK sampling days, in the event vomiting occurs within 4 hours postdose of oral paclitaxel, the Investigator should contact Zenith Technology immediately.

8.1.2.2 Follow-up Period

During the Follow-up Period, for participants who do not elect to enter the follow-on study for Oraxol, a Final Visit will occur within 2 weeks after the last PK sampling, preferably before the participant receives additional chemotherapy. For participants who elect to continue weekly Oraxol treatment in the follow-on study KX-ORAX-003, the Final Visit may serve as screening/baseline for the follow-on study.

8.2 Discussion of Study Design, Including Choice of Control Groups

This is an open-label, randomized, crossover, safety, and tolerability study to determine the absolute BA and extent of absorption of Oraxol. The crossover design is well established for BE studies, and allows each participant to act as his/her own control.

Randomization will be used in this study to avoid bias in the assignment of participants to treatment sequence, to increase the likelihood that known and unknown participant attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups.

8.3 Selection of Study Population

Eligible participants are adults with cancer for whom weekly therapy with IV paclitaxel at a dose of 80 mg/m^2 infused over 1 hour is indicated.

Up to approximately 54 evaluable participants will be randomized at approximately 4-5 centers internationally. Participants who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

8.3.1 Inclusion Criteria

Eligible participants must have/be:

1. Signed written informed consent
2. Males and females ≥18 years of age on day of consent
3. Cancer patients for whom treatment with IV paclitaxel at 80 mg/m^2 has been recommended by their oncologist, either as monotherapy or in combination with other agents
4. Adequate hematologic status at Screening/Baseline:
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   - Platelet count ≥100 x 10^9/L
   - Hemoglobin (Hgb) ≥90 g/L
5. Adequate liver function at Screening/Baseline as demonstrated by:
   - Total bilirubin of ≤20 µmol/L or ≤30 µmol/L for participants with liver metastasis
   - Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if liver metastasis is present
   - Alkaline phosphatase (ALP) ≤3 x ULN or ≤5 x ULN if liver or bone metastasis are present
   - ALP >5 x ULN if liver or bone metastasis are present and the major fraction of ALP is from bone metastasis, at the discretion of the Investigator
   - Gamma glutamyl transferase (GGT) <10 x ULN
6. Adequate renal function at Screening/Baseline as demonstrated by serum creatinine ≤177 µmol/L or creatinine clearance >50 mL/min as calculated by the Cockcroft and Gault formula
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1[6]
8. Life expectancy of at least 3 months
9. Willing to fast for 8 hours before and 4 hours after Oraxol administration

10. Willing to abstain from alcohol consumption for 3 days before the first dose of study drug through the completion of protocol-specified PK sampling in Treatment Period 2
11. Willing to refrain from caffeine consumption for 12 hours before each treatment period through the completion of protocol-specified PK sampling for that dose
12. Women must be postmenopausal (>12 months without menses) or surgically sterile (ie, by hysterectomy and/or bilateral oophorectomy) or, if sexually active, must be using effective contraception (ie, oral contraceptives, intrauterine device, double barrier method of condom and spermicide) and agree to continue use of contraception for the duration of their participation in the study. Women of childbearing potential must agree to use contraception for 30 days after their last dose of study drug.
13. Sexually active male participants must use a barrier method of contraception during the study and agree to continue the use of male contraception for at least 30 days after the last dose of study drug.

8.3.2 Exclusion Criteria

Eligible participants must not have/be:

1. Currently taking a prohibited concomitant medication:
    - Strong inhibitors (eg, ketoconazole) or strong inducers (eg, rifampin or St. John's Wort) of cytochrome P450 (CYP) 3A4 (within 2 weeks prior to the start of dosing in the study)
    - Strong inhibitors (eg, gemfibrozil) or strong inducers (eg, rifampin) of CYP2C8 (within 2 weeks prior to the start of dosing in the study)
    - Known P-glycoprotein (P-gp) inhibitors or inducers. Participants who are taking such medications but who are otherwise eligible may be enrolled if they discontinue the medication ≥1 week before dosing and remain off that medication through the end of PK sampling after the administration of the second study treatment.
    - An oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to start of dosing in the study
2. Use of warfarin. Participants receiving warfarin who are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the Investigator, may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.
3. Unresolved toxicity from prior chemotherapy (participants must have recovered all significant toxicity to ≤ Grade 1 CTCAE toxicity[1] from previous anticancer treatments or previous investigational agents). This does not extend to symptoms or findings that are attributable to the underlying disease
4. Received investigational agents within 14 days or 5 half-lives prior to the first study dosing day, whichever is longer
5. Women of childbearing potential who are pregnant or breastfeeding

6. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, clinically significant myocardial infarction within the last 6 months, unstable angina pectoris, clinically significant cardiac arrhythmia, bleeding disorder, chronic pulmonary disease requiring oxygen, or psychiatric illness/social situations that would limit compliance with study requirements
7. Major surgery to the upper GI tract, or have a history of GI disease or other medical condition that, in the opinion of the Investigator may interfere with oral drug absorption
8. A known history of allergy to paclitaxel. Participants whose allergy was due to the IV solvent (such as Cremophor®) and not paclitaxel will be eligible for this study.
9. Any other condition which the Investigator believes would make a subject's participation in the study not acceptable

8.3.3 Removal of Participants from Therapy or Assessment

The Investigator may discontinue treating a participant with study treatment or withdraw the participant from the study at any time for safety or administrative reasons. The participant may decide to discontinue study treatment or withdraw from the study at any time for any reason.

Participants may be discontinued early from the study treatment due to:

- Death
- Progression of disease
  - radiologic progression of disease not associated with AE(s)
  - radiologic progression of disease associated with AE(s)
  - other clinical findings indicating disease progression, eg, pain with bone metastases or seizure with brain metastases
- AEs not associated with progression of disease
- Withdrawal of consent (participant will be asked but not required, to provide a reason)
- Termination of the study by the Sponsor
- Other (specify)

If the study is terminated by the Sponsor, the Investigator will promptly explain to the participant involved that the study will be discontinued and provide appropriate medical treatment and other necessary measures for the participant.

8.4 Treatments

Detailed information regarding study drugs will be in the Pharmacy Manual provided to the sites.

8.4.1 Treatments Administered

The investigational product (IP) in the study is Oraxol.

Oraxol is a combination product of 2 separate drugs: oral paclitaxel capsules and HM30181AK-US tablets.

The comparator drug in the study is IV paclitaxel, supplied as Taxol or generic from a single manufacturer.

Information regarding study treatments is provided in Table 2.

Table 2 Treatments Administered in KX-ORAX-002

	Strength	Oral Dose Form	Number Dispensed and Frequency	Study Days Administered
Investigational Product				
HM30181AK-US	15 mg	Tablet	1 × 15-mg tablet, on designated treatment mornings, 1 hour before oral paclitaxel	Days 1, 2, and 3 of each treatment period
Oral paclitaxel	30 mg	Capsule	Number dispensed based on calculated doses (see Section 8.4.1.1) once on designated treatment mornings	Days 1, 2, and 3 of each treatment period
Reference Treatment				
IV paclitaxel	N/A	N/A	80 mg/m^2 infused over 1 hour on designated treatment morning	Day 1 of each treatment period

IV = intravenous, N/A = not applicable.

8.4.1.1 Oraxol

Participants will be instructed to have fasted for at least 8 hours before and 4 hours after Oraxol dosing. The amount of water consumed with HM30181 and oral paclitaxel dosing must be documented.

Oraxol dosing will consist of 15 mg oral HM30181AK-US tablet daily for 3 consecutive days (Days 1, 2, and 3 of either treatment period) plus oral paclitaxel administered over the 3 dosing days. The HM30181AK-US tablet will be administered 1 hour before the oral paclitaxel capsules; no premedication is allowed before the first dose of Oraxol. Premedication may be given before subsequent doses for hypersensitivity reactions and/or nausea or vomiting (see Section 8.4.7.2).

The dose of oral paclitaxel in the study will be determined as described in Section 8.1; the doses are expected to produce exposure similar to IV paclitaxel 80 mg/m^2 infused over 1 hour.

The dose of oral paclitaxel for Stage 1, Cohort 1 will be calculated 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. The dose of oral paclitaxel for Stage 1, Cohort 2 and Stage 2 will be calculated similarly based on results of the planned interim analyses.

8.4.1.2 Intravenous Paclitaxel

No fasting is required before IV paclitaxel dosing.

Intravenous paclitaxel 80 mg/m^2 will be administered in a qualified oncology unit as a one-time infusion over 1 hour on Day 1 of either treatment period. Premedication will be administered according to standard local practice.

8.4.1.3 Criteria for Temporary Discontinuation of Treatment and Resumption of Treatment

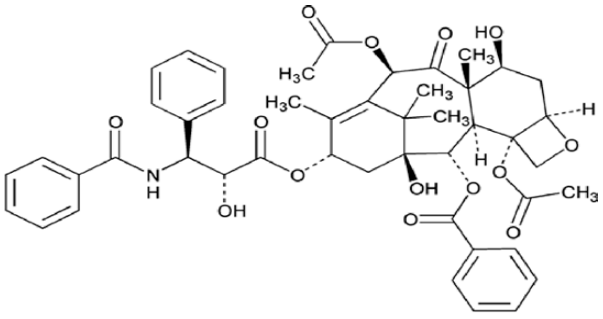
The second period of randomized treatment may be delayed for up to 3 weeks, if needed, to allow the participant to recover to ≤ Grade 1 CTCAE or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment.

8.4.2 Identity of Investigational Product

Oraxol is a combination product of 2 separate drugs: oral paclitaxel capsules and HM30181AK-US tablets.

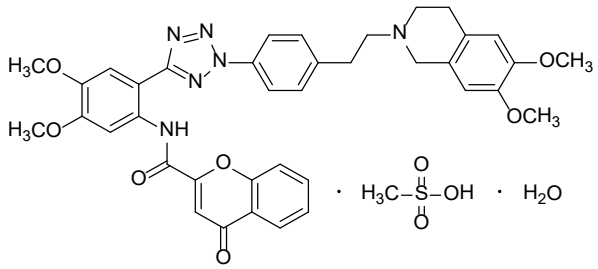
8.4.2.1 Chemical Name, Structural Formula of Paclitaxel

- Study drug code: Paclitaxel
- Chemical name: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13- ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine
- Molecular formula: $C_{47}H_{51}NO_{14}$
- Molecular weight: 853.91
- Structural formula:



8.4.2.2 Chemical Name, Structural Formula of HM30181 Methanesulfonate Monohydrate

- Study drug code: HM30181
- Chemical name: N-(2-(2-(4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-2H-tetrazol-5-yl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide Methanesulfonate monohydrate
- Molecular formula: $C_{38}H_{36}N_6O_7 \cdot CH_3SO_3H \cdot H_2O$
- Molecular weight: 802.85 (methanesulfonate monohydrate salt) / 688.72 (free base)
- Structural formula:



8.4.2.3 Comparator Drug

Commercially available IV paclitaxel in Cremophor EL (Taxol or generic from a single manufacturer)

8.4.2.4 Labeling for Study Drug

Study drugs will be obtained and/or packaged and labeled in a manner consistent with the study design, by:

Oral Paclitaxel Capsules	**HM30181AK-US Tablets**	**IV Paclitaxel**
Kinex Pharmaceuticals, Inc. 1001 Main Street Suite 600 Buffalo, NY 14203 United States	Kinex Pharmaceuticals, Inc. 1001 Main Street Suite 600 Buffalo, NY 14203 United States	Commercially available IV paclitaxel in Cremophor EL (Taxol or generic from a single manufacturer) that is approved for medical use

Labels for investigational product (Oraxol [oral paclitaxel and HM30181AK-US]) will be in accordance with national/local regulations of the participating country and will contain the following information:

- Protocol number
- Name of study drug
- Strength of study drug
- Formulation
- Lot number
- Date of manufacture
- Expiry date
- Storage conditions, including temperature
- Warning statement
- Statement saying "Limited to Investigational Use Only"
- Name of Sponsor
- Participant number (to be added by site)
- Participant initials (to be added by site)

8.4.2.5 Storage Conditions

Study drug will be stored in a secure location with access limited to the Investigators and designees. Study drug will be stored in accordance with labelled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the total duration of the trial and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system or a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

Paclitaxel capsules and HM30181AK-US tablets that are dispensed to participants should be kept at room temperature (15°C to 30°C) until used. Paclitaxel for infusion should be stored under the conditions noted on the commercial packaging.

8.4.3 Method of Assigning Participants to Treatment Groups

Participants will be randomized to receive either treatment Sequence A or B (see Table 1).

Assignment to treatment sequence will be based on a computer-generated central randomization scheme that will be reviewed and approved by an independent statistician. The randomization code will be stored in a secure location with access limited to the Investigators and designees. The randomization scheme and identification for each participant will be included in the final clinical study report for this study.

In Stage 1, no center can enter more than 4 of the first 6 participants at any dose level without authorization from Kinex.

In Stage 2, no center can enter more than half of the number of participants estimated to achieve bioequivalence. For example, if BE is estimated to involve 36 participants, 6 of whom come from Stage 1, a center cannot enter more than 15 participants in Stage 2 without authorization from Kinex.

Replacement participants will be assigned to the same treatment sequence as the participant they replace.

8.4.4 Selection of Doses in the Study

The dose of oral paclitaxel in the study will be determined as described for each stage of the study (see Section 8.4.1.1); the doses are expected to produce exposure similar to IV paclitaxel 80 mg/m^2 infused over 1 hour.

The dose of IV paclitaxel used in this study (80 mg/m^2 over 1 hour weekly) is the dose commonly in clinical use in New Zealand and elsewhere.

8.4.5 Selection and Timing of Dose for Each Participant

See Section 8.1 for a discussion of Oraxol and IV paclitaxel dosing.

The dose of HM30181 of 15 mg daily is being used in current studies of Oraxol based on PK data from healthy volunteer studies that examined the inhibitory effect of HM30181 on gut P-gp (see the Investigator's Brochure). The HM30181AK-US tablet will be administered 1 hour before the oral paclitaxel capsules.

8.4.6 Blinding

The study will not be blinded.

8.4.7 Prior and Concomitant Therapy

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.

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. The Investigator will record any AE on the Adverse Events eCRF for which the concomitant medication/therapy was administered.

8.4.7.1 Drug-Drug Interactions

Possible drug interactions with Oraxol include those known to occur with paclitaxel treatment. Treatment with HM30181 may also lead to possible drug interactions attributable to inhibition of P-gp in the gut. Thus increased exposure from co-administration of Oraxol with oral medications that are P-gp substrates is possible. This may be clinically significant when the medications involved have a narrow therapeutic index (eg, digoxin or dabigatran). Also, a possible increased or decreased exposure to paclitaxel may occur when Oraxol is taken together with P-gp inhibitors or inducers, respectively.

8.4.7.2 Prohibited Concomitant Therapies and Drugs

Participants are excluded from participation in this study are those who are currently taking:

- a medication known to be a strong inhibitor (eg, ketoconazole) or strong inducer (eg, rifampin or St. John's Wort) of cytochrome P450 (CYP) 3A4 within 2 weeks prior to the start of dosing in the study
- a medication known to be a strong inhibitor (eg, gemfibrozil) or strong inducer (eg, rifampin) of CYP2C8 within 2 weeks prior to the start of dosing in the study
- a medication known to be a P-gp inhibitor or inducer within 1 week before dosing in the study. Participants must remain off that medication through the end of PK sampling after the administration of the second study treatment.
- an oral medication with a narrow therapeutic index known to be a P-gp substrate (eg, digoxin, dabigatran) within 24 hours prior to the start of dosing in the study

A list of drugs prohibited due to potential drug-drug interactions will be provided to the sites as part of the Pharmacy Manual.

Participants should not start such medications while enrolled in this protocol.

Use of warfarin is not permitted. Participants receiving warfarin who are otherwise eligible and who may be appropriately managed with low molecular weight heparin, in the opinion of the Investigator, may be enrolled in the study provided they are switched to low molecular weight heparin at least 7 days prior to receiving study treatment.

For participants treated with Oraxol, no premedication is allowed before the first dose. Premedication in these participants may be given before subsequent doses if clinically indicated in the judgment of the Investigator. Steroids or H-1 receptor antagonists should be given only for prophylaxis or treatment of hypersensitivity reactions; 5-HT 3 or NK-1 antagonists should be used for prophylaxis or initial treatment of nausea or vomiting.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration.

8.4.8 Treatment Compliance

Records of treatment compliance for each participant will be kept during the study. Designated study personnel will review treatment compliance during investigational site visits and at the completion of the study. Because all study drugs are administered at the study site/s, participants should be 100% compliant, unless doses are not administered.

8.4.9 Drug Supplies and Accountability

The Investigator and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following the Sponsor's instructions. In this matter, the Investigator and study staff must adhere to GCP guidelines, as well as national requirements.

Under no circumstances will the Investigator allow the study drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the study. An accurate and timely record of the receipt of all clinical supplies and dispensing of study drug to the participant must be maintained. This includes, but is not limited to:

- documentation of receipt of clinical supplies
- study drugs dispensing
- study drugs accountability log
- all shipping service receipts

All forms will be provided by the Sponsor (or its designee). Any comparable forms that the investigational site wishes to use must be approved by the Sponsor. A copy of the drug accountability record must be provided to the Sponsor at the end of the study.

Retention samples from each site will need to be maintained per Food and Drug Administration (FDA) guidance.[7] Details regarding handling of retention samples of study drug will be provided in the Pharmacy Manual.

The clinical research associate (CRA) will review drug accountability during monitoring site visits and at the completion of the study.

8.5 Study Assessments

All assessments and timing of the assessments should be performed according to the Schedule of Procedures and Assessments (Table 10 and Table 11).

8.5.1 Assessments

8.5.1.1 Demography

Participant demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

8.5.1.2 Baseline Assessments

8.5.1.2.1 MEDICAL HISTORY

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 will include:

- A complete medical and surgical history; childhood diseases are not required and common colds are not required unless it is ongoing at Screening
- A complete oncology history (all malignancies including the malignancy currently being treated, regardless of diagnosis date or status, eg, skin cancer >5 years). The Tumor, Node, Metastases (TNM) status at time of diagnosis and Screening will be recorded for the malignancy currently being treated.
- A complete oncology treatment history including all commercial and investigational products, radiation therapy, and other prescribed and nonprescription therapies dating back to the initial diagnosis of the malignancy currently being treated

8.5.1.2.2 PRIOR MEDICATIONS

Prior medications taken within 28 days before Day 1, including nonprescription remedies, vitamins, etc, will be recorded at Screening.

8.5.1.2.3 HEIGHT

Height will be recorded only at Screening and will be used to calculate BSA.

8.5.1.3 Efficacy Assessments

Not applicable

8.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

8.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

As designated on the Schedule of Procedures/Assessments (Table 10 and Table 11), blood samples (approximately 6 mL per testing timepoint) will be collected for analysis of plasma concentrations of both formulations (oral and IV) of paclitaxel.

The actual time of PK sampling will be recorded.

Central lines should not be used for blood sample collection. Blood samples for PK sampling should be obtained through an IV catheter placed contralateral to a central line or the IV catheter used for the administration of IV paclitaxel. However, it is acceptable to place a pre-emptive peripherally inserted central catheter (PICC) line for patients with difficult venous access at the discretion of the clinical Investigator, for taking a limited number of blood PK samples if problems arise when taking blood from the peripheral IV catheter during PK sampling. Special procedures for taking blood from a central line will be provided by the Sponsor as a Protocol Clarification Letter.

Table 3 presents the amounts of blood (mL) that will be collected over the course of the study for PK analysis.

Table 3 Blood Collection Volumes for Pharmacokinetic Analyses

	IV Paclitaxel	Oraxol (HM30181 and paclitaxel)
Volume per timepoint (mL)	6	6
Number of timepoints	25	42
Total (mL)	150	252
Overall Total (mL)	402	

IV = intravenous.

A breakdown of PK sampling for IV dosing is presented in Table 4 (Days 1 and 2) and Table 5 (Days 3-5); PK sampling for oral paclitaxel dosing is presented in Table 6 (Day 1), Table 7 (Day 2), and Table 8 (Days 3-9).

Samples will be analyzed for paclitaxel levels using a validated assay.

A description of collection, handling, and shipping procedures for PK samples will be provided to the sites.

Table 4 Pharmacokinetic Sampling for IV Paclitaxel Days 1 and 2 (Treatment Periods 1 or 2)

Day of Treatment Period	Day 1																			Day 2	
Time	0 (Predose)	2 m	5 m	8 m	12 m	20 m	40 m	60 m	0.25 h	0.5 h	0.75 h	1 h	2 h	3 h	4 h	6 h	8 h	12 h	18 h	24 h	32 h
		During IV infusion[a,b]							**After end of IV infusion**												
PK sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

h = hours; IV = intravenous; m = minutes; PK = pharmacokinetic.

a: IV paclitaxel dosing will begin at approximately 0830 at the oncology unit.

b: In the event that the IV paclitaxel infusion is slowed or temporarily interrupted due to IV paclitaxel infusion reaction, PK blood sampling should continue according to the modified schedule in Appendix 3.

Table 5 Pharmacokinetic Sampling for IV Paclitaxel Days 3 to 5 (Treatment Periods 1 or 2)

Day of Treatment Period	Day 3		Day 4	Day 5
Time (hours)	48	56	72	96
	After end of IV infusion			
PK sample	X	X	X	X

PK = pharmacokinetic.

Table 6 Dosing and Pharmacokinetic Sampling for Oraxol Day 1 (Treatment Periods 1 or 2)

Day of Treatment Period	Day 1													
Time (hours)	-1	0 (Predose)	0	0.5	0.75	1	1.25	1.5	2	3	4	6	8	12
Dosing[a]				**After completion of Day 1 dosing**										
HM30181	X													
Oral paclitaxel[b]			X											
PK sample[c]		X	-	X	X	X	X	X	X	X	X	X	X	X

PK = pharmacokinetic.

a: Oraxol (HM30181 + oral paclitaxel) dosing at the clinical site. HM30181AK-US tablets will be administered at approximately 0700 on Days 1, 2, and 3. Oral paclitaxel capsules will be administered 1 hour later at approximately 0800 on Days 1, 2, and 3.

b: In the event vomiting occurs within 4 hours postdose of oral paclitaxel, the Investigator should contact Zenith Technology immediately.

c: Approximately 6 mL per PK sample.

Table 7 Dosing and Pharmacokinetic Sampling for Oraxol Day 2 (Treatment Periods 1 or 2)

Day of Treatment Period	Day 2													
Time (hours)	-1	0 (Predose)	0	0.5	0.75	1	1.25	1.5	2	3	4	6	8	12
Dosing[a]				**After completion of Day 2 dosing**										
HM30181	X													
Oral paclitaxel[b]			X											
PK sample[c]		X	-	X	X	X	X	X	X	X	X	X	X	X

PK = pharmacokinetic.

a: Oraxol (HM30181 + oral paclitaxel) dosing at the clinical site. HM30181AK-US tablets will be administered at approximately 0700 on Days 1, 2, and 3. Oral paclitaxel capsules will be administered 1 hour later at approximately 0800 on Days 1, 2, and 3.

b: In the event vomiting occurs within 4 hours postdose of oral paclitaxel, the Investigator should contact Zenith Technology immediately.

c: Approximately 6 mL per PK sample.

Table 8 Dosing and Pharmacokinetic Sampling for Oraxol Days 3 to 9 (Treatment Periods 1 or 2)

Day of Treatment Period	Day 3													Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Time (hours)	-1	0 (Predose)	0	0.5	0.75	1	1.25	1.5	2	3	4	6	8	12	24	48	72	96	120	144
Dosing[a]				**After completion of Day 3 dosing**																
HM30181	X																			
Oral paclitaxel[b]			X																	
PK sample[c]		X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PK = pharmacokinetic.

a: Oraxol (HM30181 + oral paclitaxel) dosing at the clinical site. HM30181AK-US tablets will be administered at approximately 0700 on Days 1, 2, and 3. Oral paclitaxel capsules will be administered 1 hour later at approximately 0800 on Days 1, 2, and 3.

b: On PK sampling days, in the event vomiting occurs within 4 hours postdose of oral paclitaxel, the Investigator should contact Zenith Technology immediately.

c: Approximately 6 mL per PK sample.

8.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable

8.5.1.5 Safety Assessments

Safety assessments will consist of determining and recording all AEs including CTCAE grades v4.03[1] (or later) (for both increasing and decreasing severity) and SAEs.

Safety assessments also include recording of concomitant medications; performance of physical examinations, measurements of weight and vital signs, and evaluation of electrocardiograms (ECGs) and ECOG performance status; and laboratory evaluation of hematology, biochemistry, and urinalyses, as detailed in the sections below and in the Schedule of Procedures and Assessments (Table 10 and Table 11).

8.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) are Oraxol (HM30181 and oral paclitaxel) and IV paclitaxel.

The criteria for identifying AEs are:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- any new disease or exacerbation of an existing disease (Note, however, that in instances of progression of disease, the clinical manifestations would be reported as an AE and the progression of disease itself, as a reason for discontinuation of treatment)
- any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- recurrence of an intermittent medical condition (eg, headache) not present at Baseline

All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the participant signs the study ICF through the last participant contact. Participants who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF.

Participants with onset of an AE or deterioration of a pre-existing condition will be followed until resolution, resolved with sequelae, or under medical care. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Adverse events associated with progression of disease should be recorded on the AE eCRF.

Laboratory Adverse Events

An abnormal laboratory result should be considered by the Investigator to be an AE if it:

- results in the withdrawal of study drug
- results in withholding of study drug pending some investigational outcome
- results in the initiation of an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE with regard to the participant's medical profile

All AEs observed during the study will be reported on the eCRF.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all laboratory findings in all participants and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF. Any laboratory abnormality considered to constitute an SAE should be reported using the SAE procedures described in Section 8.5.4.1.

ECG changes and associated clinical symptoms determined to be clinically significant by the Investigator will be reported as AEs. An ECG abnormality in a participant with symptoms may meet the criteria for an AE as described in this protocol. In these instances, the AE corresponding to the symptomatic ECG abnormality will be recorded on the Adverse Events eCRF.

For symptomatic ECG abnormalities meeting criteria as SAEs, the study site must submit an SAE report, including the ECG report to the Sponsor, or designee, using the SAE reporting procedures (Section 8.5.4.1).

The Investigator must categorize each AE according to its severity and its relationship to study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03[1] (or later) as follows:

Grade 1 = Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 = Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3 = Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4 = Life-threatening consequences: urgent intervention indicated

Grade 5 = Death related to AE

Investigators will collect all CTCAE grades for AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. The criteria for assessing severity are different from those used for seriousness (see Section 8.5.1.5.2, Serious Adverse Events and Other Events of Interest for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- temporal relationship of the onset of the event to the initiation of the study treatment
- the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- whether the event is known to be associated with the study treatment or with other similar treatments
- the presence of risk factors in the study participant known to increase the occurrence of the event
- the presence of nonstudy treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF using the following criteria:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent or underlying disease or other drugs or conditions

Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions

Unlikely Related: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, conditions or concurrent or underlying disease provide plausible explanations

8.5.1.5.2 Serious Adverse Events and Other Events of Interest

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (ie, the participant was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the participant or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest, which include pregnancy and overdose (see Section 8.5.1.5.1), are to be captured and reported on a pregnancy or overdose form as appropriate as soon as possible, but no later than 1 business day from the date the Investigator becomes aware of the event. These events of interest are to be considered as SAEs only if they meet one of the above criteria. Treatment-emergent significant laboratory abnormalities should be reported as AEs and must be evaluated to see if they represent SAEs. If the treatment-emergent significant laboratory abnormality is considered to be an SAE, it

should be reported using SAE reporting procedures (Section 8.5.4.1) and is considered an event of interest.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- hospitalization for administration of study drug or insertion of access for administration of study drug, provided that the hospitalization is not prolonged due to complication

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

8.5.1.5.3 Concomitant Medications

Concomitant medications will be assessed at Screening, at Baseline of each treatment period, on every day of each treatment period, and at the Final Visit (Table 10 and Table 11). 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. The Investigator will record any AE on the Adverse Events eCRF for which the concomitant medication/therapy was administered.

8.5.1.5.4 Physical Examinations

A complete physical examination will be performed at Screening and at Baseline of each treatment period, and at the Final Visit (Table 10 and Table 11).

A complete physical examination will include an assessment of general appearance, head, eyes, ears, nose, and throat (HEENT), thorax (including cardiovascular and respiratory), abdomen, skin, musculoskeletal, extremities, and neurological examination.

Additional examinations will be performed as clinically indicated to assess AEs. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

8.5.1.5.5 Weight and Body Surface Area

Weight will be recorded at Screening, at Baseline of each treatment period, and at the Final Visit (Table 10 and Table 11). Height (recorded at Screening) and weight (with indoor clothing) will be measured to calculate BSA. BSA will be calculated to 1 decimal place. Sites may use any of the established formulae for BSA, but must use the same formula for all participants at their site, and the method of BSA calculation must be recorded on the eCRF for each participant. Dosing of Oraxol and IV paclitaxel will be calculated according to the screening BSA. If weight changes by ≥10%, BSA will be recalculated and dose may be

adjusted by the Investigator if clinically indicated, providing there are no concerns regarding increased toxicity from dose adjustment.

8.5.1.5.6 VITAL SIGNS

Vital sign (pulse rate, systolic and diastolic blood pressure, respiratory rate, and body temperature) measurements will be taken after the participant has been seated for at least 5 minutes at the visits designated on the Schedule of Procedures and Assessments (Table 10 and Table 11). All blood pressure measurements should be performed on the same arm, preferably by the same person at the designated visits. Serial vital signs may be obtained to confirm accurate readings.

8.5.1.5.7 ELECTROCARDIOGRAMS

A 12-lead ECG is to be completed 5 times: at Screening, Baseline for Treatment Period 2, on-treatment 1 hour postdosing on Day 1 of each treatment period, and at the Final Visit (Table 10 and Table 11). The Screening and Final Visit ECGs may be performed at a convenient time during the visit. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The ECG data recorded on the eCRF must include rate, rhythm, intervals, and QTcF.

Participants with a clinically significant ECG abnormality following IV paclitaxel or Oraxol treatment may continue to receive treatment with Oraxol as clinically indicated. Alternatives to medications known to be associated with ECG abnormalities (eg, ondansetron and QTc prolongation) should be considered in participants with QTc prolongation. Participants with QTc prolongation following Oraxol treatment may continue to receive Oraxol treatment in study KX-ORAX-003, with dose reductions as allowed in that protocol as clinically indicated.

8.5.1.5.8 LABORATORY MEASUREMENTS

Blood and urine will be collected for clinical laboratory tests. Collection of both blood and urine may be conducted at a local laboratory or at the clinic site. Approximately 20 mL of blood will be collected for clinical laboratory testing, including the pregnancy test when required, at Screening, at Screening/Baseline for Treatment Period 1, Baseline for Treatment Period 2, and the Final Visit (Table 10 and Table 11). Participants must be fasted for the Screening and Final Visit laboratory assessments. Fasting is recommended, but not required at other laboratory assessment times. Fasting status must be documented for all laboratory samples.

Microscopic urinalysis will be conducted only when clinically indicated based on dipstick results (laboratory protocol), or as determined by the Investigator. When conducted, microscopic urinalysis results will be recorded on the eCRF.

Clinical laboratory sampling and testing may be conducted anytime within 72 hours prior to the scheduled assessment time. Laboratory test results, including pregnancy test, must be reviewed and acceptable to the Investigator before dosing.

A Laboratory Manual will be provided to detail handling, processing, and shipping procedures. Local laboratories will be used to measure laboratory parameters.

The clinical laboratory tests to be measured during the study are provided in Table 9.

Table 9 Clinical Laboratory Tests

Category	Parameters
Hematology	Red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW)
Chemistry	
Electrolytes	Chloride, potassium, sodium, bicarbonate (HCO_3)
Liver function tests	Alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, uric acid
Urinalysis	hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 8.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

For laboratory abnormalities meeting the criteria of SAEs (see Section 8.5.1.5.2), the site must electronically transmit the SAE report including the laboratory report to the Sponsor using the SAE form (see Section 8.5.4.1).

8.5.1.5.9 Other Safety Assessments

Pregnancy Testing

Serum or urine pregnancy tests will be obtained in females of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at Screening and within 72 hours before Day 1 dosing of each treatment period, and at the Final Visit (Table 10 and Table 11). Test results must be reviewed before dosing.

8.5.1.5.10 Eastern Cooperative Oncology Group Status

The participant's performance status should be assessed according to ECOG criteria (Appendix 1). ECOG performance status will be assessed at Screening, Baseline for Treatment Period 2, and at the Final Visit.

8.5.1.6 Other Assessments

Participants will be asked a treatment preference question at the Final Visit.

8.5.2 Schedule of Procedures/Assessments

8.5.2.1 Schedule of Procedures/Assessments

Table 10 and Table 11 present the schedule of procedures/assessments for Treatment Sequence A and B, respectively.

Table 10 Schedule of Procedures/Assessments for Sequence A (Oraxol in Treatment Period 1)

Phase	**Pretreatment**		**Treatment**									
Period	**Screening**	**Treatment Period 1 Baseline[a]**	**Treatment Period 1[b]**				**Treatment Period 2 Baseline[a]**	**Treatment Period 2[b]**				**Follow-up**
Day/Visit	Day -28 to Day -2	Day –1	Day 1	Day 2	Day 3	Days 4-9	Day -1	Day 1	Day 2	Days 3-5	Days 6-8	Final Visit[c]
Informed consent	X											
Inclusion/Exclusion Assessment	X											
Demographics	X											
Medical/Oncology History	X											
Prior and/or Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[d]	X	X					X					X
Weight and BSA[e]	X	X					X					X
Height	X											
Vital signs[f]	X	X	X	X	X	X	X	X	X	X		X
ECOG Performance Status	X						X					X
12-lead ECG	X		X[g]				X	X[g]				X
Pregnancy test[h]	X	X					X					X
Hematology/Biochemistry[i]	X	X					X					X
Urinalysis	X	X					X					X
Administer study medication[j]			X	X	X			X				
PK blood samples[k]			X	X	X	X		X	X	X		
Adverse events[l]	X	X	X	X	X	X	X	X	X	X		X
Treatment preference question												X

BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PK = pharmacokinetic.

a. All baseline data should be collected and assessed within 72 hours prior to dosing on Day 1 of each treatment period.
b. Treatment Periods: Oraxol = Days 1 to 9; IV paclitaxel = Days 1 to 8. The second period of randomized treatment may be delayed for up to 3 weeks, if needed, to allow the participant to recover to ≤ Grade 1 CTCAE or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment.
c. The Final Visit may occur as early as the last day of PK sampling in Treatment Period 2, up to 2 weeks after the end of PK sampling, and preferably before the participant

Table 10 Schedule of Procedures/Assessments for Sequence A (Oraxol in Treatment Period 1)

receives any additional chemotherapy. For participants who elect to continue weekly Oraxol treatment, the Final Visit may serve as screening/baseline for the follow-on study; for these participants, the Final Visit should occur within 72 hours prior to receiving the Week 1 dose of Oraxol in the follow-on study. If the participant withdraws informed consent, Final Visit assessments should be completed as much as possible during the final visit on study. If the participant is taken off for other reasons (eg, toxicities), the Final Visit should be completed within 2 weeks after the withdrawal from study and preferably before the participant receives any additional chemotherapy.

d. Complete physical examinations will be performed at Screening and the Final Visit. All other physical examinations do not require complete examinations but will be targeted to the signs and symptoms related to Adverse Event Reporting. Physical examinations performed on Day -2 do not need to be repeated on Day -1.

e. BSA will be calculated to 1 decimal place based on screening body weight and height. Weight will be recorded pretreatment for each treatment period. If weight changes by ≥10%, BSA will be recalculated. Study drug doses may be adjusted using the new BSA by the clinical Investigator, if clinically indicated, providing there are no concerns regarding increase toxicity from dose adjustment.

f. Vital signs to include pulse rate, systolic/diastolic blood pressure, respiration, and temperature. Vital sign measurement should be taken before dosing and once daily on nondosing days. Vital signs should be taken in the morning on inpatient days, or when participants are first seen at the clinical site on outpatient days.

g. ECGs will be performed 1 hour postdosing on Day 1 of each treatment period.

h. Serum or urine pregnancy test to be obtained in females of childbearing potential at Screening and within 72 hours prior to Day 1 dosing in either treatment period. Baseline pregnancy testing in Treatment Period 1 does not need to be obtained if the screening test was obtained within 72 hours of Day 1 dosing.

i. Participants must be fasted for the Screening and Final Visit laboratory assessments. Fasting is recommended but not required at other laboratory assessment times. It must be noted if participants were in a fasted or fed state at the time of blood collection. Clinical laboratory sampling and testing should be conducted anytime within 72 hours prior to the scheduled assessment time.

j. Oraxol will be administered at the inpatient clinical site. IV paclitaxel will be administered at the oncology unit. For Sequence A, participants will receive Oraxol on Days 1, 2, and 3 of Treatment Period 1 and IV paclitaxel on Day 1 of Treatment Period 2.

k. PK blood samples (approximately 6 mL at each testing timepoint) will be collected at the sites. Please refer to Section 8.5.1.4.1 for all PK sampling timepoints.

l. Collection of all adverse event information will begin immediately after the signing of the informed consent and will continue through the Final Visit.

Table 11 Schedule of Procedures/Assessments for Sequence B (IV Paclitaxel in Treatment Period 1)

Phase	Pretreatment		Treatment									
Period	Screening	Treatment Period 1 Baseline[a]	Treatment Period 1[b]				Treatment Period 2 Baseline[a]	Treatment Period 2[b]				Follow-up
Day	Day -28 to Day -2	Day –1	Day 1	Day 2	Days 3-5	Days 6-8	Day –1	Day 1	Day 2	Day 3	Days 4-9	Final Visit[c]
Informed consent	X											
Inclusion/Exclusion Assessment	X											
Demographics	X											
Medical/Oncology History	X											
Prior and/or Concomitant Medications	X	X	X	X	X		X	X	X	X	X	X
Physical Examination[d]	X	X					X					X
Weight and BSA[e]	X	X					X					X
Height	X											
Vital signs[f]	X	X	X	X	X		X	X	X	X	X	X
ECOG Performance Status	X						X					X
12-lead ECG[g]	X		X[g]				X	X[g]				X
Pregnancy test[h]	X	X					X					X
Hematology/Biochemistry[i]	X	X					X					X
Urinalysis	X	X					X					X
Administer study medication[j]			X					X	X	X		
PK blood samples[k]			X	X	X			X	X	X	X	
Adverse events[l]	X	X	X	X	X		X	X	X	X	X	X
Treatment preference question												X

BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; PK = pharmacokinetic.

a. All baseline data should be collected and assessed within 72 hours prior to dosing on Day 1 of each treatment period.
b. Treatment Periods: Oraxol = Days 1 to 9; IV paclitaxel = Days 1 to 8. The second period of randomized treatment may be delayed for up to 3 weeks, if needed, to allow the participant to recover to ≤ Grade 1 CTCAE or baseline toxicity from the prior study treatment or to allow the participants flexibility in scheduling inpatient treatment.

Table 11 Schedule of Procedures/Assessments for Sequence B (IV Paclitaxel in Treatment Period 1)

c. The Final Visit may occur as early as the last day of PK sampling in Treatment Period 2, up to 2 weeks after the end of PK sampling, and preferably before the participant receives any additional chemotherapy. For participants who elect to continue weekly Oraxol treatment, the Final Visit may serve as screening/baseline for the follow-on study; for these participants, the Final Visit should occur within 72 hours prior to receiving the Week 1 dose of Oraxol in the follow-on study. If the participant withdraws informed consent, Final Visit assessments should be completed as much as possible during the final visit on study. If the participant is taken off for other reasons (eg, toxicities), the Final Visit should be completed within 2 weeks after the withdrawal from study and preferably before the participant receives any additional chemotherapy.
d. Complete physical examinations will be performed at Screening and the Final Visit. All other physical examinations do not require complete examinations but will be targeted to the signs and symptoms related to Adverse Event Reporting. Physical examinations performed on Day -2 do not need to be repeated on Day -1.
e. BSA will be calculated to 1 decimal place based on screening body weight and height. Weight will be recorded pretreatment for each treatment period. If weight changes by ≥10%, BSA will be recalculated. Study drug doses may be adjusted using the new BSA by the clinical Investigator, if clinically indicated, providing there are no concerns regarding increase toxicity from dose adjustment.
f. Vital signs to include pulse rate, systolic/diastolic blood pressure, respiration, and temperature. Vital sign measurement should be taken before dosing and once daily on nondosing days. Vital signs should be taken in the morning on inpatient days, or when participants are first seen at the clinical site on outpatient days.
g. ECGs will be performed 1 hour postdosing on Day 1 of each treatment period.
h. Serum or urine pregnancy test to be obtained in females of childbearing potential at Screening and within 72 hours prior to Day 1 dosing in either treatment period. Baseline pregnancy testing in Treatment Period 1 does not need to be obtained if the screening test was obtained within 72 hours of Day 1 dosing.
i. Participants must be fasted for the Screening and Final Visit laboratory assessments. Fasting is recommended but not required at other laboratory assessment times. It must be noted if participants were in a fasted or fed state at the time of blood collection. Clinical laboratory sampling and testing should be conducted anytime within 72 hours prior to the scheduled assessment time.
j. Oraxol will be administered at the inpatient clinical site. IV paclitaxel will be administered at the oncology unit. For Sequence B, participants will receive IV paclitaxel on Day 1 of Treatment Period 1 and Oraxol on Days 1, 2, and 3 of Treatment Period 2.
k. PK blood samples (approximately 6 mL at each testing timepoint) will be collected at the sites. Please refer to Section 8.5.1.4.1 for all PK sampling timepoints.
l. Collection of all adverse event information will begin immediately after the signing of the informed consent and will continue through the Final Visit.

8.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in oncology studies as well as in the routine clinical care of patients with cancer.

8.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

8.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the event. Instructions for SAE reporting will be provided in the Investigator File.

All SAEs, regardless of causality assessment, must be collected through the last participant contact and followed to resolution or, if resolution is unlikely, to stabilization. SAEs reported to the site from the time of the last participant contact up to 30 days after the last contact, will be collected. These SAEs will be discussed in the clinical study report. Any SAE event judged by the Investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion. For participants who continue Oraxol treatment in the follow-on study (KX-ORAX-003), any new SAEs reported after the Final Visit will be captured in the database for study KX-ORAX-003.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by electronically transmitting the completed SAE form.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the Investigator's assessment of causality. All supporting documents should be sent de-identified and should contain the assigned participant number. Send only supporting documents directly related to the event.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

8.5.4.2 Reporting of Pregnancy

Any pregnancy whether occurring in a subject or in the female partner of a male subject for which the estimated date of conception was either before the last visit or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 8.5.4.1).

Pregnancies must be reported by electronic transmission as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies is provided in the Investigator File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A participant who becomes pregnant must be withdrawn from study treatment. If the female partner of a male participant becomes pregnant, that male participant may continue in the study, but should be requested to provide outcome information on the pregnancy.

8.5.4.3 Reporting of Other Events of Interest

8.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose or Medication Error

Study drug overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied.

Any study drug overdose during the study should be noted on the Study Medication eCRF.

All AEs associated with overdose or medication error should be captured on the Adverse Event eCRF. The overdose must be reported by electronic transmission as soon as possible, but no later than 1 business day from the date the Investigator becomes aware of the event. Contact information for reporting of overdose will be provided in the Investigator File. The overdose form should be used for reporting. If the overdose is associated with an SAE, an SAE report form should be completed and sent along with an overdose form.

8.5.4.3.2 Reporting of Treatment-Emergent Significant Laboratory Abnormality

Any treatment-emergent significant laboratory abnormality observed during the clinical study should be evaluated by the Investigator to determine if the abnormality meets the criteria as an SAE. If the treatment-emergent significant laboratory abnormality meets the criteria for an SAE as specified in Section 8.5.1.5.2, it should be reported as directed in Section 8.5.4.1. If the treatment-emergent significant laboratory abnormality does not meet the seriousness criteria, it must still be reported on an Adverse Event eCRF.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- is within normal limits at Baseline and has increased in severity to meet CTCAE v4.03[1] (or later) grading criteria for laboratory values of Grade 3 or above
- is outside normal limits at Baseline and increases in severity to CTCAE v4.03 (or later) grading criteria for laboratory values of Grade 4 or above
- is otherwise considered by the Investigator to meet serious criteria as defined in Section 8.5.1.5.2

8.5.4.4 Expedited Reporting

The Sponsor (or its designee) must inform Investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific timeframes). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

In determining what SAEs meet criteria for expedited reporting, the following reference safety information will be used:

For Oraxol: The current version of the Oraxol Investigator's Brochure
For IV paclitaxel: The approved national labeling in each country

8.5.4.5 Breaking the Blind

Not applicable

8.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local and regional requirements.

8.5.5 Completion/Discontinuation of Participants

A participant may elect to discontinue from the study at any time for safety, medical, or personal reasons. See Section 8.3.3 for reasons why participants may be discontinued early from study treatment. In addition to the primary reason, the participant may have indicated one or more secondary reasons for discontinuation. Investigators must document the actual reason(s) why they decided to discontinue participants, or why participants withdrew consent, as applicable. Study disposition information will be collected on the Disposition eCRF.

Participants who withdraw from study treatment (with the exception of death or withdrawal of consent) will be encouraged to complete the Final Visit assessments at the time of withdrawal as indicated in the Schedule of Procedures/Assessments (Table 10 and Table 11).

A participant who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the eCRF.

A participant removed from the study for any reason may be replaced. Participants may be replaced until up to 48 have completed the study at the dose determined in Stage 1 as likely to achieve BE based on PK interim analysis/analyses.

8.5.6 Abuse or Diversion of Study Drug

Not applicable

8.5.7 Confirmation of Medical Care by another Physician

The Investigator will instruct participants to inform site personnel when they are planning to receive medical care by another physician. At each visit, the Investigator will ask the participant whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the participant is going to receive medical care by another physician, the Investigator, with the consent of the participant, will inform the other physician that the participant is participating in the clinical study.

8.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

8.6.1 Data Collection

Data required by the protocol will be documented in the participant source documentation and entered into a validated electronic data capture (EDC) system.

Responsible site personnel will enter the information required by the protocol onto the eCRFs in accordance with the eCRF Completion Guidelines that are provided. A CRA will visit each site as documented in the monitoring plan to verify the data on eCRFs for completeness and accuracy against the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF.

Data that are provided by an external vendor will be transferred and validated according to the procedures specified in the Data Management Plan.

All data derived from the study will be the property of the Sponsor and should not be made available in any form to third parties without written permission from the Sponsor, except for authorized representatives of the Sponsor or appropriate regulatory authorities.

8.6.2 Clinical Data Management

There will be a Data Management Plan to detail all relevant data management activities, from eCRF design to database lock.

Quality control for all relevant data management activities and data validation procedures will be applied to ensure the validity and accuracy of the clinical data.

8.7 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee 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.

A total of 24 to 48 evaluable participants receiving the selected Stage 1 dose will be evaluated for bioequivalence between Oraxol and IV paclitaxel based on a 2-sided 90% CI of log-transformed $AUC_{0-\infty}$ between 80% and 125%.

Participants evaluable for BE will be those who receive both study treatments and complete scheduled post treatment PK evaluations. Nonevaluable participants will be replaced until up to 48 participants have completed the study at the dose determined in Stage 1 as likely to achieve BE based on PK interim analysis/analyses.

Statistical analyses will be reported using summary tables, graphs, and data listings. Continuous variables 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. Categorical variables will be summarized by counts and by percentage of participants in corresponding categories. All raw data obtained from the eCRF, as well as any derived data will be included in data listings.

8.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section.

8.7.1.1 Study Endpoints

8.7.1.1.1 PRIMARY ENDPOINTS

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.

8.7.1.1.2 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.

8.7.1.2 Definitions of Analysis Sets

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.

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 postdose safety assessment.

8.7.1.3 Disposition

All participants who are randomized will be tabulated by treatment group as to study discontinuation and the reasons for discontinuation as described in Section 8.3.3 and Section 8.5.5.

8.7.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized. 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.

8.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary drug codes.

Prior medications will be defined as medications that stopped before the first dose of study drug.

Concomitant medications will be defined as medications 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 drug. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. A listing of concomitant medications by drug and drug class will be included in the clinical study report for this protocol.

All medications will be presented in participant data listings.

8.7.1.6 Efficacy Analyses

Not applicable

8.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

8.7.1.7.1 PHARMACOKINETIC ANALYSES

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/m^2 for IV paclitaxel. Pharmacokinetic analysis and statistical analysis will be based on normalized plasma concentrations.

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[8] 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 selected dose of oral paclitaxel (as Oraxol administered over 3 consecutive days) 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.

8.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable

8.7.1.8 Safety Analyses

All participants in the Safety Analysis Set, ie, who receive at least 1 dose of paclitaxel (as Oraxol or IV) and have at least 1 postdose safety assessment will be included in the safety analyses.

Safety data, presented by treatment group (Oraxol or IV paclitaxel), 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, 12-lead ECG results, physical examination findings, and ECOG performance status. For all safety analyses, study Day 1 will be defined as the date of the first dose of study drug.

8.7.1.8.1 EXTENT OF EXPOSURE

The actual number of doses will be summarized by treatment period.

8.7.1.8.2 ADVERSE EVENTS

Treatment-emergent AEs (TEAEs) are 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

For AEs, verbatim terms on the eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA; version 16.1 or later). The CTCAE criteria v4.03[1] (or later) will be used to grade the severity of the AEs. Participant incidence of AEs will be displayed by SOC and PT. Adverse events will also be summarized by severity and relationship to the study drug and treatment sequence.

Participant incidence of SAEs will also be displayed.

The incidence of AEs will be summarized by treatment, treatment period, and treatment sequence, and will be presented in participant data listings as well.

The number (percentage) of participants with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment, treatment period, and treatment sequence. A participant data listing of all AEs leading to death will be provided.

The number (percentage) of participants with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment, treatment period, and treatment sequence. A participant data listing of all AEs leading to discontinuation from study drug will be provided.

8.7.1.8.3 LABORATORY VALUES

Laboratory parameters will be summarized using descriptive statistics at baseline and at subsequent timepoints. Changes from baseline will also be summarized.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from Baseline to follow-up.

Clinical laboratory results after baseline will be evaluated for markedly abnormal values based on the CTCAE v4.03[1] (or later) criteria for the Investigations SOC. 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.

8.7.1.8.4 VITAL SIGNS

Vital sign values will be evaluated on an individual basis by participant. Abnormal vital sign values will be identified as those outside (above or below) the reference range.

8.7.1.8.5 ELECTROCARDIOGRAMS

ECG data will be summarized for each individual participant.

8.7.1.8.6 OTHER ANALYSES

Pregnancy Tests

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

Physical Examinations

Physical examination findings will be listed for each participant.

Eastern Cooperative Oncology Group

ECOG performance status responses will be tabulated by treatment, treatment period, and treatment sequence.

8.7.2 Determination of Sample Size

Based on the within-subject variability of at most 30% through a comparison of the PK 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.

Based on analysis of data from the first 6 evaluable participants in Stage 1, an additional 34 evaluable participants will be enrolled into Stage 2. A total sample size of 40 evaluable participants is 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%.

8.7.3 Interim Analysis

There will be an interim analysis of PK data after each dose tested in Stage 1 to determine if the administered regimen would appear likely to achieve BE of Oraxol to IV paclitaxel. After the interim analysis/analyses (depending on the outcomes), a decision will be made by consensus of the DSMB, Kinex, Zenith Technology, 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 ($AUC_{0-\infty}$).

8.7.4 Other Statistical/Analytical Issues

Not applicable

9 REFERENCE LIST

1. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-1 4_QuickReference_8.5x11.pdf.

2. Mauri D, Kamposioras K, Tsali L, Bristianou M, Valachis A, Karathanasi I, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. Cancer Treat Rev. 2010 Feb;36(1):69-74. doi: 10.1016/j.ctrv.2009.10.006. Epub 2009 Nov 27. Review.

3. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008 Apr 17;358(16):1663-71. doi:10.1056/NEJMoa0707056.

4. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 3. 2014.

5. Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, and Senkus E, on behalf of the ESMO Guidelines Working Group. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012.

6. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. Courtesy of Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. http://www.ecog.org/general/perf_stat.html. Accessed April 2015.

7. Guidance for Industry: Handling and Retention of BA and BE Testing Samples. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). May 2001.

8. Guidance for Industry: Statistical Approaches to Establishing Bioequivalence. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). January 2001.

9. ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1): June1996.

10 PROCEDURES AND INSTRUCTIONS

10.1 Institutional Review Boards/Independent Ethics Committees

The protocol, any protocol amendments, and the informed consent form (ICF) will be reviewed and approved by a Health Authority (HA) and Ethics Committee (EC) and in New Zealand, by New Zealand Medicines and Medical Devices Safety Authority (Medsafe)/Standing Committee on Therapeutic Trials (SCOTT) before participants are screened for entry. Any protocol amendment and/or revision to the ICF will receive appropriate approval prior to implementation. Verification of unconditional approval of the protocol will be transmitted to the Sponsor prior to the shipment of drug supplies to the investigational site. The Investigators or the Sponsor will submit, depending on local regulations, periodic reports and inform the HA/EC and Medsafe (New Zealand) of any reportable AEs per International Council for Harmonisation (ICH) guidelines and local HA/EC standards of practice.

10.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

This study will be conducted in accordance with the requirements and principles of ICH GCP guidelines [ICH - E6 (R1) Guideline for GCP Harmonised Tripartite Guideline[9]], the World Medical Association Declaration of Helsinki 2013, Guideline on the Regulation of Therapeutic Products in New Zealand. Part 11: Clinical Trials – Regulatory Approval and Good Clinical Practice Requirements, and other applicable national or local regulations.

This study will meet requirements for FDA acceptance of foreign studies not conducted under an IND (21 CFR 312.120).

This protocol will be listed on the Australian New Zealand Clinical Trials Registry (ANZCTR) website.

10.3 Participant Information and Informed Consent

As part of administering the informed consent document, the Investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the participant, and the extent of maintaining confidentiality of the participant's records. Each participant must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The informed consent should be given by means of a standard written statement, written in nontechnical language. The participant should understand the statement before signing and dating it and will be given a copy of the signed document. At the Screening Visit, after the ICF and any other written information to be provided is read and explained, the participant will be asked to sign the ICF before any study-specific procedures are performed. No participant can enter the study before his/her informed consent has been obtained.

An unsigned copy of an approved ICF must be prepared in accordance with ICH E6[9], Section 4, and all applicable regulations. Each participant must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each participant will be verified by the Sponsor and kept on file at the study site and a copy will be provided to the study participant according to local procedures at the site.

The participant should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information should be documented.

11 ADMINISTRATIVE PROCEDURES

11.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. The protocol will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of participants, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable Ethics Committees. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all participants included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor's medical monitor and the EC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided the health or regulatory authority and ECs are immediately notified and appropriate documentation of the urgent protocol change are submitted per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the EC, but the health or regulatory authority and EC should be kept informed of such changes as required by local regulations.

11.2 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol (refer to ICH E6[9], Section 4.5).

11.3 Monitoring Procedures

The Sponsor's/CRO's CRA will maintain contact with the Investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The Investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and participant's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and EC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays, and other imaging reports, (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Medical history or other questionnaires completed by participants
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study participant's treatment between physicians or memoranda sent to the Ethics Committees
- eCRF components (eg, questionnaires) that are completed directly by participants and serve as their own source

11.4 Recording of Data

An eCRF must be completed for each participant by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document. Any correction to entries made on the eCRF must have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

11.5 Identification of Source Data

Data to be recorded on the eCRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the Investigator is responsible for retaining all study documents, including but not limited to the protocol, randomization list, copies of eCRFs, the Investigator's Brochure, and any regulatory agency registration documents, ICFs, and EC correspondence. The site should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records must also be retained for the minimum period specified by New Zealand requirements (ie, retain for at least 10 years).

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, qualified personnel designated by the Sponsor may conduct audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the Investigator must inform the Sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the Investigator (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The Investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to

each participant must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The Investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply prior to approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the study, the Investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the Sponsor/designee or, when approval is given by the Sponsor, will destroy supplies and containers at the site. See Section 8.4.9 for specific drug handling information.

11.9 Publication of Results

The Investigators shall have the right to publish the results from this study in accordance with the New Zealand Association of Clinical Research (NZACR) Clinical Trial Research Agreement.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the Investigator, the Investigator's staff, Medsafe (New Zealand), and the HA/EC, and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and nonuse shall in no way diminish such obligations as set forth in any Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the institution/Investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and nonuse set forth in any Confidentiality Agreement or Clinical Trial Agreement executed between the Investigator and the Sponsor/CRO.

11.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The EC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

The Investigator reserves the right to discontinue the study should his/her judgment so dictate. If the Investigator terminates or suspends a study without prior agreement of the

Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Sponsor and the EC and provide them with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Participant Insurance and Indemnity

The Sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 ECOG Performance Status

Grade	Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Adapted from Oken MM et al. Am J Clin Oncol. 1982;5:649-5.

Appendix 2 Unacceptable Toxicity (Common Terminology Criteria for Adverse Events [CTCAE] v4.03)

Unacceptable toxicity occurs when any of the events listed below are considered at least possibly related to the investigational product (IP):

- Grade 4 absolute neutrophil count (ANC) (<0.5 x 10^9/L)
- Grade 3 or 4 ANC plus fever (defined as temperature 38.5°C or greater; febrile neutropenia) or Grade 3 or 4 ANC with bacteremia or sepsis
- Grade 3 thrombocytopenia (<50 x 10^9/L platelets) for more than 7 days, or accompanied by clinically significant bleeding
- Grade 4 thrombocytopenia (<25 x 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 serious adverse events (SAEs) and which resolve back to Grade 1 or baseline within 7 days
    - alopecia
    - anorexia or asthenia which resolve within 7 days
- Nonhematologic toxicities and hematologic toxicities not mentioned above which cause a dose delay of >14 days

Appendix 3 Instructions for Collection of Pharmacokinetic Blood Samples if IV Paclitaxel Infusion is Interrupted

If the infusion is stopped and re-started, then the following changes should be made to the scheduled time of collection of the remaining PK samples:

- Collect the next sample at the time the infusion is stopped.
- Treat the patient as required.
- Restart the infusion at a slower rate (or as per hospital protocol).
- Take the next sample at the time the IV is restarted.
- All remaining samples scheduled during the infusion should be collected at even intervals.
- The 60-minute sample should be collected at the time the infusion ends.
- All post infusion samples will be calculated as usual from the infusion end time.

Examples of adjusting the infusion PK samples times are as follows:

A. If the IV infusion is stopped 10 minutes after sampling, sample numbers 1-4 would already have been collected (Sample #4 is scheduled at 8-minutes). The PK sample collections should be:

- Collect sample #5 at the time the IV is stopped.
- Collect sample #6 at the time the IV is restarted.
- Collect sample #7 at a time mid-way between when the IV is restarted and when the IV is scheduled to finish.
- Collect sample #8 at the time the IV finishes.
- Remaining sampling times shall be calculated from the IV finish time.

B. If the IV infusion is stopped 15 minutes after sampling, sample number 1-5 would already have been collected (Sample #5 is scheduled at 12-minutes). The PK sample collections should be:

- Collect sample #6 at the time the IV is stopped.
- Collect sample #7 at the time the IV is restarted.
- Collect sample #8 at the time the IV finishes.
- Remaining sampling times shall be calculated from the IV finish time.

Note: If the infusion is stopped and not re-started, then the PK samples do not need to be collected after the timepoint collected when the infusion was stopped.

If an IV is stopped after collection of sample # 6 (scheduled at 20-minutes) then that participant is considered inevaluable for PK.