Phase 1/2 Dose-Rising, Safety, Tolerability and Efficacy Study of Topical SOR007 for Cutaneous Metastases

Protocol Identifying Number: SOR007-2017-01

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Version Number: 7.0

Date: 28 December 2018

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
BID	'Bis in Die' or Twice per Day
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central Nervous System
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
FDA	The U.S. Food and Drug Administration
FTU	Finger Tip Unit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IP	Intraperitoneal
IRB	Institutional Review Board
IV	Intravenous
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NRS-11	Numeric Rating Scale
NSCLC	Non-Small Cell Lung Cancer
PCA	Precipitation with Compressed Antisolvents
PK	Pharmacokinetics
PI	Principal Investigator
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumours

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLC	Systems Development Life Cycle
SMC	Safety Monitoring Committee
SOC	Standard of Care
TEAE	Treatment-emergent Adverse Event
USC	University of Southern California
USP/NF	United States Pharmacopeia/National Formulary
WBC	White Blood Cell

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 1/2 Dose-Rising, Safety, Tolerability, and Efficacy Study of Topical SOR007 for Cutaneous Metastases
Protocol Number:	SOR007-2017-01
Version Number:	7.0
Date:	28 December2018
IND Number:	135896
Investigational Product:	SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment
Sponsor:	NanOlogy, LLC 231 Bonetti Dr., Suite 240 San Luis Obispo, CA 93401-7310 805-595-1300

The Sponsor, NanOlogy, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to IND 135896; in accordance with 21 CFR Part 312, US Biotest, Inc., shall be considered the sponsor with regard to all activities related to the IND.

SIGNATURE

Sponsor's Representative - Name and Title:
Gere diZerega, MD
US Biotest, Inc.

Gere diZerega
Gere diZerega (Jan 3, 2019)

Signature of Sponsor's Representative

Jan 3, 2019

Date

STATEMENT OF COMPLIANCE

I have read the attached protocol (SOR007-2017-01) Phase 1/2 Dose-Rising, Safety, Tolerability, and Efficacy Study of Topical SOR007 for Cutaneous Metastases, Version 7.0 dated 28 December 2018 and agree to comply with the contents of this document.

I agree to comply with applicable FDA regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

This document is a confidential communication of US Biotest, Inc. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of US Biotest, Inc. However, this document may be disclosed to appropriate institutional review boards, ethics review committees, or authorized representatives of the Investigator or of boards of health under the condition that they are requested to respect the confidentiality of the document.

The signature of the Principal Investigator below constitutes his/her agreement.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL SUMMARY

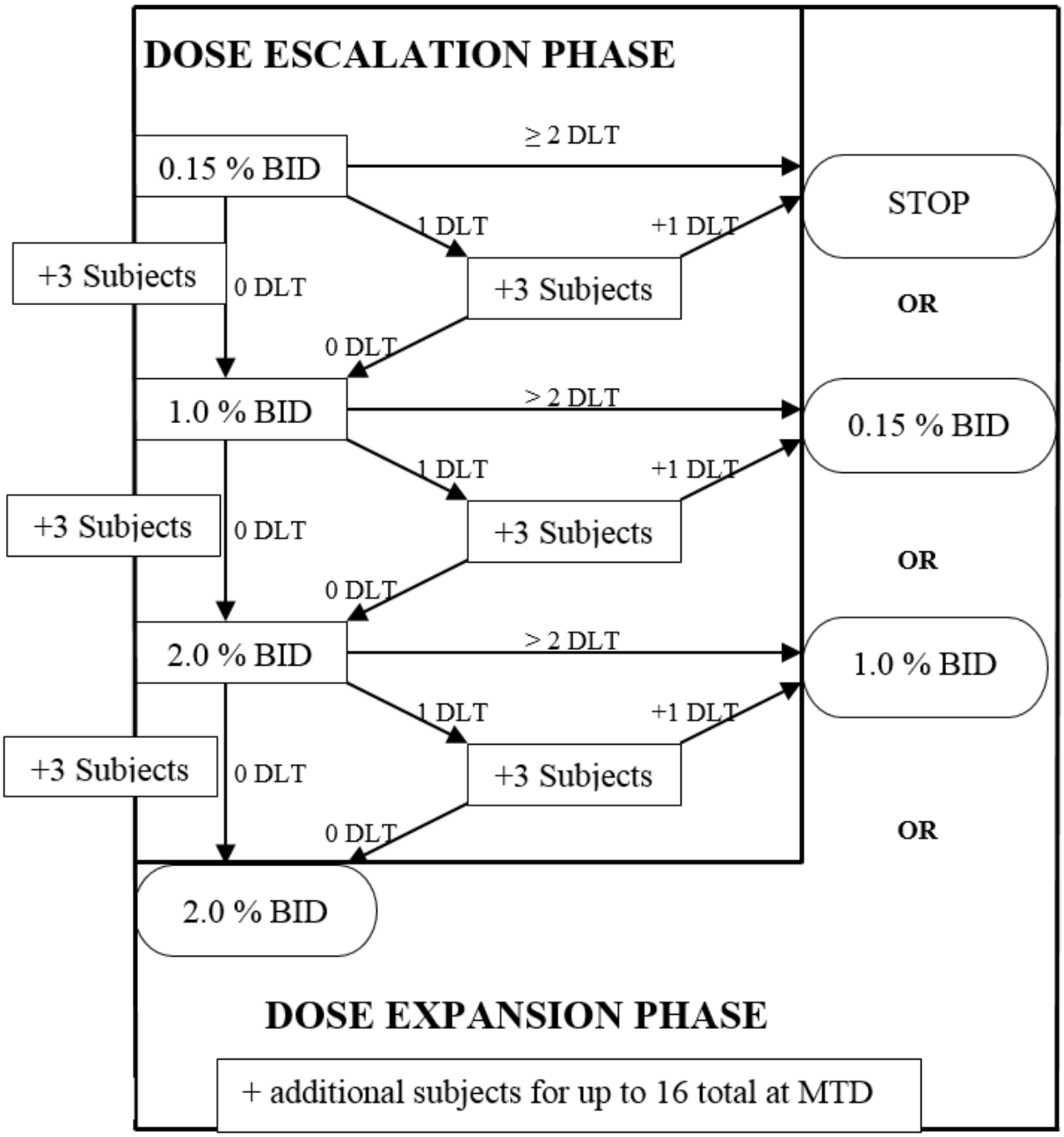
Protocol #:	SOR007-2017-01
Title:	Phase 1/2 Dose-Rising, Safety, Tolerability and Efficacy Study of Topical SOR007 for Cutaneous Metastases.
Summary:	This is a Phase 1/2, open-label, dose-rising study evaluating the safety, tolerability and preliminary efficacy of three concentrations of SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment (0.15%, 1.0%, and 2.0%) applied topically twice daily for 28 days to non-melanoma cutaneous metastases, with the option of extending treatment an additional 28 days to total 56 days. Subjects will be screened and eligibility confirmed up to 14 days prior to treatment with SOR007. A treatment area of 50 cm^2 containing at least one eligible lesion will be selected by the Investigator at baseline by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter). Using a gloved hand, subjects will apply one Finger Tip Unit (FTU) of SOR007 to the 50 cm^2 treatment area twice daily at approximately the same time each day for 28 to up to 56 days. Subjects will attend the clinic on Day 1 (Visit 2) for dose application training and observation of the first treatment application, returning 24 hours later for pharmacokinetic sample collection. Additional visits will be on Days 8, 15, 29, and 43 for 28 treatment days, or on Days 8, 15, 29, 57 and 70 for 56 treatment days. The final visit will be completed by phone or in the clinic (per Investigator determination), ≥ 30 days after the last study drug dose to review adverse events. At each visit, at least two global and two close-up color photographs of the treatment area will be taken (with a ruler for scale) by the Investigator. The photographs will be uploaded from each visit to a secure, password protected Citrix ShareFile or site restricted-access file, within 2 days of the visit. The Sponsor will then analyze lesion size using ImageJ. The study will include a dose escalation phase and a dose expansion phase. <u>Dose Escalation Phase:</u> During the dose escalation phase, the study will follow a standard 3+3 dose-ascending design, with the first cohort of three subjects commencing treatment with 0.15% SOR007. A Safety Monitoring Committee (SMC) will review all available data after the last subject in each cohort of three subjects completes 15 days of treatment to determine whether dose escalation may continue. If a single dose limiting toxicity (DLT) is

	identified in one of three subjects in the cohort, a further three subjects will be enrolled at the same dose level. If one or more DLT occur in the three additional subjects enrolled in the cohort, dose escalation will stop and the prior dose level will be regarded as the Maximum Tolerated Dose (MTD) and taken forward into the dose expansion phase. If no further DLT are identified, dose escalation will continue, until either a DLT is identified at a higher dose or the top dose of 2.0% SOR007 is reached. Dose Expansion Phase: In the dose expansion phase, additional subjects will be enrolled to reach a maximum of 16 total subjects at the MTD from the dose escalation phase. Subjects in the dose expansion phase will attend the clinic on the same visit days and receive the same evaluations as the dose escalation phase above. The option of 28 (Group A) or 56 (Group B) days of treatment will be per investigatior decision, dependent on subject disease progression, additional systemic chemotherapy or other metastatic treatment requirements.
Objectives:	Primary Objective: • To determine preliminary safety and tolerability of topical SOR007. Secondary Objectives: • To determine preliminary efficacy of topical SOR007; • To study potential reduction in pain at the treatment area; • To describe the pharmacokinetics of topical SOR007 Ointment applied to metastatic lesions.
Endpoint	Primary Outcome Measures: Safety and tolerability, as demonstrated by adverse events, changes in laboratory assessments, physical examination findings, and vital signs. Secondary Outcome Measures: Efficacy will be determined by the difference in the total area of eligible lesion(s) in the treatment area between baseline and Day 43 or 70 using a calibrated grid measurement system (ImageJ freeware) provided by the National Institutes of Health (NIH). Eligible lesions will be determined at baseline by the RECIST (Vn 1.1) definition of measurable tumors (≥ 10mm in its longest diameter) (Eisenhauer 2009).

	Objective Clinical Response (Complete Clinical Response (CR) + Partial Response (PR)) is defined as the percentage of patients who achieve complete clinical response or partial response 14 days after last treatment. Best overall response is defined as the best response recorded from the start of study treatment until the end of treatment. Reduction in pain at the treatment area will be measured by the Numeric Rating Scale (NRS-11) from baseline to Day 43 or 70. Systemic Exposure as determined by: T_{max}, C_{max}, AUC
Pharmacokinetics (PK)	Blood samples will be collected to analyze pharmacokinetic activity. Samples will be collected at 24 hours (+/- 2 hours) after the first study drug application. 28 Days of Treatment: At Visits 3 and 4 (prior to the first daily application) and at Visits 5 and 6 (at any time during the visit). 56 Days of Treatment: At Visits 3, 4 and 5 (prior to the first daily application) and at Visits 6 and 7 (at any time during the visit).
Population:	A minimum of three up to a maximum of 28 male and female subjects, ≥ 18 years of age, with non-melanoma cutaneous metastases.
Phase:	1/2
Number of Sites:	Up to four
Description of Study Agent:	SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment (SOR007) at concentrations of 0.15%, 1.0%, and 2.0%.
Study Duration:	The study duration is estimated to take 15 months, from start of enrollment to the last subject's last visit.
Participant Duration:	Individual subject participation is estimated to be 75 or 102 days, including the screening period.

SCHEMATIC OF STUDY DESIGN

Figure 1. Dose Escalation Algorithm – Flow Chart



1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

The Sponsor, NanOlogy, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to IND 135896; in accordance with 21 CFR Part 312, US Biotest, Inc., shall be considered the sponsor with regard to all activities related to the IND.

Name and Description of Study Agent.

Investigational drug product SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment (SOR007) is being developed for the topical treatment of cutaneous metastases. SOR007 consists of Uncoated Nanoparticle Paclitaxel suspended in an ointment vehicle. All excipients are compendial grade (*USP/NF*) and approved for topical route of administration at concentrations equal to or less than the Maximum Potency detailed in the FDA Inactive Ingredients Database.

SOR007 is also being investigated under IND 126915 for the treatment of moderate to severe plaque psoriasis and actinic keratosis (Sponsor: DFB Soria, LLC). NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension ("NanoPac") contains the same nanoparticulate paclitaxel as SOR007, although the nanoparticulate paclitaxel in NanoPac is sterile (Sponsor: NanOlogy, LLC). NanoPac is being developed for the treatment of peritoneal malignancies under IND 073529, the treatment of pancreatic neoplasms under IND 132692, and the treatment of adenocarcinoma of the prostate under IND 132694.

Non-clinical Summary

Key findings of nonclinical studies with nanoparticulate paclitaxel include:

- *In vitro* dermal penetration studies using human cadaver skin and the Franz diffusion cell system were conducted with prototype gel and ointment formulations of Uncoated Nanoparticle Paclitaxel to evaluate the rate and extent of in vitro dermal and transdermal delivery of paclitaxel. In the first study, three 1% Uncoated Nanoparticle Paclitaxel gels (designated as DowF1 through DowF3) and four 1% Uncoated Nanoparticle Paclitaxel ointments (designated as DowF4 through DowF7) were evaluated. In the second study, one 0.5% (designated as DowF8), four 1% (designated as DowF10 through DowF13), and one 2% (designated as DowF9) Uncoated Nanoparticle Paclitaxel ointments were tested, along with a second lot of 1% Uncoated Nanoparticle Paclitaxel ointment (designated DowF6 formulation). There was negligible transdermal flux of paclitaxel in the first or second study. In the first study, DowF6 (1% SOR007 Ointment) demonstrated the highest total epidermal/dermal delivery (2.2% of the applied dose). In the second study, DowF8 (0.5% SOR007 Ointment) delivered 4.5% of the applied dose to the epidermis and dermis.

- Paclitaxel toxicokinetics were determined on Days 1 and 28 following once-daily topical administration of 0% (0 mg/kg/day) 0.3% (4.9 mg/kg/day), 1% (16.5 mg/kg/day) or 3% (49.9 mg/kg/day) SOR007 to the dorsum of 6 Göttingen minipigs/sex/group. Sex differences in paclitaxel mean C_{max} and AUC_{0-24} values were generally less than 2-fold; therefore, results and discussions were based on combined-sex data. Exposure to paclitaxel increased with increasing SOR007 dose; however, the increases in mean C_{max} and AUC_{0-24} values were less than dose proportional. There were no observed adverse effects at the highest dose, 49.9 mg/kg/day, with an associated combined-sex C_{max} of 12.5 ng/mL and an AUC (0-24) of 149 ng•hr/mL. Significant paclitaxel accumulation was noted following repeated-once daily topical application for 28 days.
- A single-dose, GLP intraperitoneal (IP) toxicity study in the rat, conducted under IND 073529, compared nanoparticulate paclitaxel dosed to the maximum tolerated dose (MTD) versus Taxol® dosed to the MTD. Results of this study indicated that the toxicity associated with IP administration of nanoparticulate paclitaxel is less than that associated with IP Taxol administration.
- Subcutaneous administration of a single dose (20 mg/kg) of nanoparticulate paclitaxel in a non-GLP study in male rats resulted in no evidence of ulceration, irritation or other drug-related toxicity.

Clinical Summary

SOR007 has not been administered to humans for topical treatment of cutaneous metastases. A Phase 1 clinical trial of SOR007 for the indication of moderate to severe plaque psoriasis was completed under IND 126915 (Protocol SOR007-2016-01). Thirteen subjects with chronic plaque type psoriasis received occlusive application of six topical formulations: SOR007 at 0.15%, 0.3%, 1.0%, and 2.0%, vehicle, and an active comparator approximately daily for up to 10 treatments over a 12-day period. Approximately 200 µL of each formulation was be applied on each dosing day. The total body surface area exposed to SOR007 was 4.52 cm^2, or 0.03% total body surface area of a 1.6 m^2 human. The daily dose was approximately 5.7 mg per day, for a total of approximately 57 mg of Uncoated Nanoparticle Paclitaxel per subject. Calculated on a mg/kg or mg/m^2 basis, the paclitaxel applied topically over the 12-day study would be approximately 0.1 mg/kg (3.8 mg/m^2) per day, or 1.0 mg/kg (38 mg/m^2) total exposure for a 60-kg subject. The primary endpoint was the change from baseline in psoriatic skin thickness (assessed by measurement of the thickness of the echolucent band (ELB) of the psoriatic infiltrate using 22 MHz sonography). Clinical assessment, photo documentation, and PK analysis were also performed. No treatment related AEs were reported by the subjects who had up to 10 daily topical applications of SOR007. There were no reports of local skin reactions seen under the hydrocolloid dressing during the 12-day study period.

Twelve subjects completed the trial and were available for PK analysis. Blood was drawn on Day 11 prior to dosing and then again at 1, 4, 8 and 24 hours after dosing. Following topical application

of ~5.7 mg daily dose (57 mg cumulative dose) of SOR007, Day 11 plasma paclitaxel concentrations over the 24-hr sampling interval were below the limit of quantitation (LLOQ of 10 pg/mL) for 59 of the 60 samples tested. Paclitaxel was quantifiable only in the 1-hour PK sample from a single subject, and this level (17.7 pg/mL) was near the lower limit of quantitation. Thus, paclitaxel systemic exposure was negligible in psoriatic patients concomitantly receiving 200 µL each of the 0.15, 0.3, 1, and 2% SOR007 ointment formulations.

1.2 Rationale

Cutaneous metastases occur in up to 10% of cancer patients (excluding melanoma) (Spratt 2014; Alcaraz 2014). Cutaneous metastases can cause considerable morbidity, leading to infection, bleeding, disfigurement and pain. The negative impacts to quality of life (QOL) for this population with advanced disease can be devastating (Spratt 2014).

Despite the prevalence and impact of cutaneous metastases, a standard of care remains elusive. Treatment is complicated by underlying disease, poor patient performance, previous radiation therapy and short duration of overall survival. These factors make surgery and radiation unfeasible in most patients (Sideras 2008; Campana 2016; Cabula 2015). Systemic chemotherapy has negligible impact on most cutaneous metastases (Fernandez-Anton Martinez 2013; Spratt 2014). Additional therapies for cutaneous metastases include electrochemotherapy (ECT), photodynamic therapy (PDT), intralesional therapy (ILT), and topical therapy (TT). In a meta-analysis of 47 prospective studies of 4,313 cutaneous metastases, the objective response rate to the therapies (including radiotherapy) was 60.2% (Spratt 2014). ECT demonstrated the best response rate (complete response rate 47.5%); however, ECT is an inpatient procedure requiring general anesthesia and often results in notable pain and dermatologic toxicity (inflammation, hyperpigmentation, and ulceration) (Cabula 2015). The less invasive alternatives, such as intralesional therapy and topical therapy demonstrate reduced efficacy in comparison to ECT. When effective reduction of cutaneous metastases cannot be achieved, as is often the case, healthcare providers must fall back on palliative wound care remedies (Fernandez-Anton Martinez 2013). There is therefore a significant unmet need for an effective, less invasive alternative therapy for cutaneous metastases in patients already struggling with significant morbidity from the symptoms of and treatments for advanced primary cancer.

Paclitaxel, formulated as Taxol or Abraxane, is approved by FDA for several cancers known to cause skin metastases, including ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer (Taxol Package Insert, Abraxane Package Insert). Paclitaxel has also been used off-label with some effect in numerous other cancers, including bladder cancer, cervical cancer, endometrial cancer, esophageal cancer, squamous cell carcinoma of the head and neck, prostate cancer, gastric cancer, and testicular cancer, among others (DeVita 2001). This, in conjunction with paclitaxel's cytotoxic mechanism of action, provides the basis for the investigation of nanoparticulate paclitaxel (formulated as SOR007) for the topical treatment of cutaneous metastases. Based on nonclinical studies of SOR007, it is believed that the nanoparticles will achieve a depot effect, providing a continuous dose of paclitaxel to the diseased skin over time

with limited systemic exposure. It is also anticipated that topical treatment of cutaneous metastases with SOR007 will be well tolerated, allowing for repeat administration if necessary.

1.3 Potential Risks and Benefits

1.3.1 Known Potential Risks

There are currently no known risks associated with SOR007 applied topically to cutaneous metastases.

Intravenous administration of paclitaxel can lead to AE. Systemic exposure to paclitaxel by injection, ingestion or inhalation was associated with following AE:

- Bone marrow suppression;
- Hypersensitivity reaction;
- Hypotension;
- Peripheral neuropathy;
- Myalgia/Arthralgia;
- Infection;
- Mucositis;
- Nausea/Vomiting;
- Diarrhea;
- Neurotoxicity;
- Alopecia;
- Renal impairment;
- Hepatic impairment;
- Hypospermatogenesis;
- Injection site reaction.

Most AE associated with paclitaxel are temporary and will resolve in time. However, time to resolution of specific AE is unknown and can vary widely depending on concomitant medications, therapies, and medical condition.

Nonclinical studies have shown that paclitaxel can cause fetal harm when administered during pregnancy. There are no adequate and well-controlled clinical studies in pregnant women. If paclitaxel is used during pregnancy, or if a patient becomes pregnant while receiving paclitaxel, the patient should be apprised of the potential hazard to the fetus.

1.3.2 Known Potential Benefits

There are currently no known benefits for SOR007 applied topically to cutaneous metastases.

2 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the safety and tolerability of topical SOR007 ointment applied to cutaneous metastatic lesions. The secondary objectives are to obtain preliminary information on the efficacy of topical SOR007 ointment applied to the cutaneous metastatic lesions, reduction in pain and to describe the pharmacokinetics of topical SOR007 Ointment.

3 STUDY DESIGN AND ENDPOINTS

3.1 Description of the Study Design

This is a Phase 1/2, open-label, dose-rising study evaluating the safety, tolerability, and preliminary efficacy of three concentrations of SOR007 (0.15%, 1.0%, and 2.0%) applied topically to non-melanoma cutaneous metastases.

Subjects will be screened and eligibility confirmed up to 14 days prior to treatment with SOR007.

Safety Reviews

Regular safety reviews will be conducted by the Medical Monitor on an ongoing monthly basis throughout the dose escalation and dose expansion portions of the study. Safety data to be reviewed will include, but will not be limited to, medical history, physical examinations, disease status, vital signs, concomitant medications, adverse events, and laboratory results. The CTCAE (version 4.0) criteria will be used to classify the severity of adverse events and determine dose limiting toxicity.

The study will include a dose escalation phase and a dose expansion phase.

Dose Escalation Phase:

During the dose escalation phase, the study will follow a standard 3+3 dose-ascending design, with the first cohort commencing treatment on Day 1 with 0.15% SOR007 (see Figure 1). Dose escalation of SOR007 will be determined by the Safety Monitoring Committee (SMC) per the charter, which will be in place prior to the first subject entering the study. The SMC will review all available data after the last subject in each cohort of three subjects completes 15 days of treatment to determine whether dose escalation may continue.

If a single dose limiting toxicity (DLT) is identified in one of three subjects in the cohort, a further three subjects will be enrolled at the same dose level. If one or more DLT occur in the three additional subjects enrolled in the cohort, dose escalation will stop and the prior dose level will be regarded as the Maximum Tolerated Dose (MTD) and taken forward into the dose expansion phase. If no further DLT are identified, dose escalation will continue, until either a DLT is identified at a higher dose or the top dose of 2% is reached.

Dose Expansion Phase:

In the dose expansion phase, additional subjects will be enrolled to reach a maximum of 16 subjects at the dose level determined to be the MTD (or the top dose, 2.0% SOR007) in the dose escalation phase. The option of 28 or 56 days of treatment will be per investigatior decision, dependent on subject disease progression, additional systemic chemotherapy or other metastatic treatment requirements.

3.2 Primary Endpoint

Safety and tolerability, as demonstrated by adverse events, changes in laboratory assessments, physical examination findings, and vital signs.

3.3 Secondary Endpoints

- For the purposes of the following secondary endpoints for efficacy, eligible lesion measurements and analysis of photographs will be conducted by the sponsor using ImageJ. Eligible lesion identification will be performed by the Investigator at the clinical site at screening and confirmed at baseline for eligibility determination only, by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter) (Eisenhauer 2009).
    - Objective tumor response, defined as the difference in the sum of eligible tumor diameter(s) within the treatment area between baseline and Day 43 or 70 (i.e. 14 days after the last dose in the dose escalation and expansion phases depending on dose regimen). Tumor surface area and response will be assessed at all visits. Change in surface area will be assessed using a calibrated grid measurement system (ImageJ freeware) provided by the NIH. Photographs will be uploaded to a secure Citrix ShareFile or site restricted-access file, by a designated site staff member within 2 days of each visit. The Sponsor will measure and analyze the lesions using ImageJ as they are received.
    - Objective Clinical Response is defined as subjects with Complete Clinical Response (CR) + Partial Response (PR), further defined as the percentage of patients who achieve complete clinical response or partial response 14 days after the last treatment with SOR007, measured as change in the sum of the longest diameter(s) of eligible target lesion(s) within the treatment area 14 days after last treatment. The response to treatment is then evaluated as a function of post-treatment total diameter divided by pre-treatment total diameter.
    - Best overall response is defined as the best response recorded from the start of study treatment until the end of the study (i.e. 28 Treatment days at Visit 6/Day 43 or 56 Treatment days at Visit 7, Day 70).
    - Complete clinical response (CR) is defined as absence of any detectable residual disease in eligible lesion(s) within the treatment area; partial response (PR) as at least a 30% decrease in the sum of the diameters of the eligible lesion(s) within the

treatment area compared to baseline (Visit 2); and progressive disease (PD) as at least a 20% increase in the sum of diameters of eligible lesion(s) within the treatment area, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of at least 5 mm. Stable disease (SD) is defined as the sum of eligible lesion diameter(s) between that defined as PR or PD.
    - The appearance of new non-target lesions during participation in this study does NOT constitute progressive disease.
- Pain at the treatment area will be measured by the Numeric Rating Scale (NRS-11). Change in pain will be analyzed from baseline to Day 43 or 70.
- To describe the pharmacokinetics of topical SOR007 Ointment applied to metastatic lesions.

3.4 Exploratory Endpoints

Appearance of new lesions within the treatment area.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Participant Inclusion Criteria

1. Signed informed consent;
2. Male and female patients ≥ 18 years of age;
3. Malignancies resulting in cutaneous metastasis originating from: breast, lung, head and neck, pancreatic, urinary bladder, prostate, testicular, ovarian, uterine, cervical, gastric, adrenal, thyroid, parathyroid cancers, or other solid tumors;
4. Cutaneous metastases diagnosis confirmed prior to consent by preferred institutional methodology which may include, but is not limited to: biopsy; conventional radiography; imaging techniques to include bone scan (scintigraphy), computed tomography (CT), fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT), magnetic resonance imaging (MRI), F-fluoromisonidazole-(F-FMISO) PET/CT, fluorothymidine-(FLT) PET/CT, fluoroestradiol-(FES) PET/CT, and PET/MRI;
5. ECOG Grade 0 – 2, with minimum life expectancy of at least 3 months;
6. At least one baseline eligible lesion. Per RECIST criteria (version 1.1), an eligible lesion at baseline is considered measurable when ≥ 10mm diameter in the longest diameter;
7. Willing to refrain from using lotions, creams, etc. during the treatment period to the treatment area;
8. Subjects with adequate organ and bone marrow function as defined below:
    - ANC ≥ 1,500/µl
    - Hemoglobin ≥ 9.5 grams/dL
    - Platelets ≥ 75,000/µl
    - AST (aspartate transaminase or SGOT)/ALT (alanine aminotransferase or SGPT) ≤ 3.0 x ULN and total bilirubin ≤ 2.0 x ULN with no evidence of cholestasis

- Creatinine ≤ 1.5x ULN;

9. Last dose of any systemic non-taxane cytotoxic chemotherapy completed at least one day prior to Day 1. Last dose of any systemic taxane cytotoxic chemotherapy completed at least 4 weeks prior to Day 1;
10. Willing to use appropriate birth control for patients of child-bearing potential;
11. Abstinence from all manner of physical contact near the treatment area during and up to 2 weeks after the treatment phase.

4.2 Participant Exclusion Criteria

1. Open or ulcerated wound(s) extending through the dermis within the treatment area;
2. Colorectal, hepatocellular, gallbladder, cholangiocarcinoma, neuroendocrine, melanomas, hematological and central nervous system (CNS) malignancies;
3. Active viral hepatitis A, B, or C or preexisting or acute liver disease;
4. Systemic treatment or localized treatment to target area with the following within the 4 weeks prior to the first treatment visit: radiotherapy, intralesional therapy; laser therapy surgery (other than biopsy) local hyperthermia, levulinic acid, 5-fluorouracil, high potency corticosteroids (including systemic steroids), retinoids, diclofenac, hyaluronic acid, imiquimod;
5. Elective surgery for treatment of the cutaneous metastases during the study and up to 4 weeks after the treatment period. Cutaneous metastases are required to remain in-situ and measurable for up to 2 weeks after last treatment to achieve study objectives;
6. Known allergic reactions, irritations or sensitivity to the active ingredients or other components of SOR007;
7. Symptoms of a clinically significant illness that may place the subject at risk by trial participation or influence the outcome of the trial in the four weeks before first treatment and during the trial;
8. Participation in the treatment phase of another clinical trial within the four weeks prior to treatment in this clinical trial;
9. Investigator's opinion of subject's probable noncompliance or inability to understand the trial and/or give adequate informed consent;
10. Evidence of current chronic alcohol or drug abuse;
11. Pregnancy and/or lactating.

4.3 Strategies for Recruitment and Retention

Sufficient subjects will be screened to allow for a minimum of three subjects up to a maximum of 28 subjects to be enrolled in the trial. It is not anticipated that any advertising will be required for recruiting to the study. Subjects will be recruited and screened for eligibility and will proceed to treatment in cohorts of three. A low ECOG grade is required to maximize the probability that subjects will participate for the full duration of the study.

Total study duration is estimated at about 15 months.

4.4 Participant Withdrawal or termination

4.4.1 Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request. Any reason for withdrawal and/or early termination will be documented in the source notes and in the Electronic Data Capture system (EDC).

Other than the potential for local toxicity reactions, there is no reason currently anticipated that would cause the Investigator to terminate a subject's participation in the study once treatment has been initiated. It is very important that any events occurring be captured and followed for the safety of the subject.

Subjects may be non-compliant with the study protocol in a way that much of the data is not captured which would usually require withdrawal for non-compliance. For the purposes of this study, subjects should not be withdrawn in this situation.

Clinical AE, laboratory abnormalities, or other medical conditions/situations may occur which would usually require cessation of study treatment. In these instances, it is very important that all of these events be captured, followed, and documented, and therefore a subject should not be withdrawn but rather followed up to study completion.

Should the Investigator feel it to be in the best interest of the subject to be withdrawn from the study, the Investigator will immediately contact the Medical Monitor to discuss the reasons for withdrawal.

4.4.2 Handling of Participant Withdrawals or Termination

The sponsor should be notified immediately when a subject is removed or withdrawn from the study after treatment with investigational agent. Every attempt should be made to capture as much information following treatment as possible.

In the event a subject is withdrawn they would undergo final study visit evaluations (Visit 6 End-of-Study evaluations) which include but are not limited to vital signs, AE collection and concomitant medication updates.

Subjects that refuse or fail to appear for clinic visits following SOR007 treatment and fail to respond to or cooperate with reasonable and diligent attempts at contact should not be discontinued from the study but be considered lost-to-follow-up. Reasonable and diligent contact attempts should be documented appropriately to include dates and phone call details. Emails and registered mail correspondence should be filed in the subject's medical record to document due diligence.

If a subject repeatedly misses study visits or remains non-compliant following SOR007 treatment, and where the majority of data is not available, the option to replace that subject in the cohort exists, however the data that is collected from the non-compliant subject may still be used in the evaluations in this study.

4.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated by the site or sponsor for sufficient reasonable cause. Written notification, documenting the reason for the study suspension or termination, will be provided by the suspending or terminating party to sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reasons for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Insufficient compliance with protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility
    - During the dose escalation phase, the majority of the lesions in the 50 cm^2 treatment area of study subjects who receive the maximum tolerated dose of SOR007 are found to increase in size at the end of the 28 or 56 days of treatment period. If the study is considered futile, it will be terminated and the dose expansion phase will not proceed.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, and/or FDA.

5 STUDY DRUG

5.1 Study Drug(s) Description

5.1.1 Acquisition

The drug substance, paclitaxel, USP, is supplied by Phyton Biotech, LLC, Delta, BC, Canada. Bulk paclitaxel is converted to nanoparticles using a PCA technique, which employs supercritical carbon dioxide and acetone to generate paclitaxel nanoparticles within a well- characterized particle size distribution. The study drug, SOR007, will be manufactured by Dow Development Laboratories (DDL) and provided for use in this study as an ointment.

The study drug will not be shipped to the study site until all Regulatory Documentation has been provided by the site and the site is ready for study Initiation, at which time the study drug will be released for shipment. Shipment will be via courier, temperature controlled 68˚ to 77˚F (20˚ to 25˚C) and will occur prior to and in conjunction with the Site Initiation visit. Study drug will be shipped to the site Pharmacy where it will be stored according to the conditions required (see 5.1.3).

5.1.2 Formulation, Appearance, Packaging, and Labeling

The study drug, SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment, is formulated with nanoparticulate paclitaxel at levels ranging from 0.15% to 2% suspended in an a sealed 15g laminate tube and will be labeled to include the following:

Subject #: _____ Date Opened _____ / _____ / _____
Study Number: SOR007 - _____
Product Name: SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment X%, 15 g
Store at 20-25°C (68-77°F)
Keep out of the reach of children.
Caution: New Drug – Limited by Federal (or United States) Law to investigational use.
DFB Soria, LLC, US Biotest, 231 Bonetti Drive, Suite 240, San Luis Obispo, CA 93401

5.1.3 Product Storage and Stability

Stability studies show that SOR007 ointment is stable when stored at controlled room temperature (25 °C/60% relative humidity) for up to 6 months and accelerated conditions (40 °C/75% relative humidity) for up to 6 months.

Prior to administration at the hospital/clinic, the SOR007 ointment tubes will be stored at the Pharmacy, temperature controlled at 20˚ to 25˚C (68˚ to 77˚F); excursions permitted between 15-30°C (59-86°F).

5.1.4 Preparation

SOR007 will be supplied as finished drug product in small tubes.

5.1.5 Dosing and Administration

Application of SOR007 will occur twice daily, at approximately the same times each day (morning and evening), for 28 or 56 days. Using a gloved hand, subjects will self-apply one Finger Tip Unit (FTU) of SOR007 to the entire 50 cm^2 treatment area previously outlined by the delegated study staff in permanent marker. Note: There may be multiple lesions in the 50 cm^2 marker-outlined area.

A FTU is defined as the amount of ointment expressed from a tube with a 5 mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger of an adult. The "distal skin-crease" is the skin crease over the joint nearest the end of the finger. One FTU will cover approximately 50cm^2, the entire treatment area. One FTU = 0.5 g, which will amount to approximately 1 g/day or 7 g/week of ointment.

Prior to administration of SOR007, the treatment area should be gently cleansed. Apart from drug application and area cleansing, all physical touching of the treatment area, including application of oils, creams and harsh soaps, is to be strictly avoided. Subjects will be provided with an instruction card as a guide for application and will receive application training by study staff at Visits 2, 3, 4 and 5, as needed.

5.1.6 Route of Administration

Topical.

5.1.7 Dosing and Dose Escalation

This study will be conducted in two phases: a dose escalation phase structured with a standard 3+3 dose-ascending design (Figure 1) and a dose expansion phase enrolling sufficient subjects to reach a maximum of 16 total subjects total at the maximum tolerated dose (MTD) or highest dose of SOR007 (0.15%, 1.0% or 2.0%) as determined in the dose escalation phase (see Section 7.6).

Safety reviews for decisions on dose escalation will be conducted after the last subject in each cohort of three subjects completes 15 days of treatment. Guidance on the criteria to be used in the determination of the benefit/risk balance for dose escalation can be found in Section 7.5 Study Halting Rules.

5.1.8 Dose Adjustments/Modifications/Delays

None.

5.1.9 Duration of Treatment

Twice-daily dosing will begin on Day 1 and continue up to Day 28 or 56 if no DLT are observed. If all lesions within the treatment area resolve at any point during treatment, the Investigator may determine that it is in the best interest of the subject to cease treatment with SOR007.

28 Treatment Days

If treatment with SOR007 ceases at any point prior to Day 28 treatment subjects should complete Visit 6 - End of Study procedures and the Visit 7 safety assessment study evaluations (See 6.5.4).

56 Treatment Days

If treatment with SOR007 ceases at any point prior to Day 56 treatment subjects should complete Visit 7 - End of Study procedures and the Visit 8 safety assessment study evaluations (See 6.5.4).

Due to the nature of both the disease and of paclitaxel, it is possible that the epithelial/dermal covering over the treated target cutaneous metastatic lesion will break down after initiation of treatment with SOR007. SOR007 may, in this scenario, continue to be applied to the treatment area. If new ulceration occurs, this is considered a DLT. Following review of the study data, the Medical Monitor will provide written documentation confirming all treatment cessations for each applicable subject.

5.1.10 Dosing Compliance

Subject compliance will be tracked by visual inspection of the returned SOR007 ointment tubes and weighing of the returned SOR007 ointment tubes. At the baseline visit, the sealed, unused SOR007 ointment tube will be weighed in the site pharmacy when given to the subject to obtain

the full tube baseline weight. Each dispensed SOR007 ointment tube will be weighed again by the pharmacy when returned by the subject. This step (weighing of tubes) may also be conducted by the clinic personnel per institution policy. Scales and calibration weights may be provided to sites where there is no access to a 'weighing scale'. The subjects will be trained to self-dose (application) by delegated study staff. The subjects will apply the first dose to the 'marker-outlined area' under study staff supervision. Subjects will be instructed on how to care for the treatment area (cleansing), what to avoid (creams, lotions, harsh soaps), SOR007 storage and requirements to bring SOR007 ointment tubes to each subsequent visit (Visits 3, 4, 5 or 6, if applicable), at which point all returned tubes will be visually inspected and weighed in the pharmacy. The subjects will be provided new SOR007 ointment tube(s) at Visits 2, 3, 4 or 5, if applicable. Subjects may use any SOR007 ointment tube(s) until it is empty, before starting a new SOR007 ointment tube. Subjects will also be provided an instruction card at the study start and a diary at each clinic visit as a dosing reminder and to document all SOR007 self-dosing details, adverse events and concomitant medications taken. For subjects that have difficulty applying the study drug or requiring assistance, a care-giver or spouse may be trained in study drug application, if allowed by the institution and/or IRB.

5.2 Study Drug Accountability Procedures

The Investigator or designee will maintain adequate records showing the receipt, dispensing, return, or other disposition of the study drug, including the date, quantity, batch or code number (if applicable), and identification of subjects (number, initials (as allowed by local confidentiality requirements)) who received study medication.

Accountability will be conducted on the individual tubes.

Used tubes will be retained in the Pharmacy for accountability purposes and will not be disposed of until sponsor accountability monitoring is completed. Used tubes will be retained in the clinic until the site receives sponsor directives for used/unused study drug tube return to the sponsor or delegate.

Under no circumstances will the Investigator supply clinical material to other Investigators or clinicians or allow the supplies to be used other than as directed by this protocol without prior written permission from the sponsor.

6 STUDY PROCEDURES AND SCHEDULE

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

The following procedures and evaluations will be performed as part of this study:

- Review and documentation of demographics, significant past and current medical history, including allergies;

- Review and documentation of concomitant prescription and non-prescription medications;
- Review and documentation of diagnosis of cutaneous metastases of non-melanoma origin and previous treatments including surgical and chemotherapeutic records;
- A pregnancy test at screening for female subjects;
- A comprehensive physical examination at screening only; at all subsequent visits, the investigator will perform a physical examination only if deemed necessary, otherwise no physical examination needed per protocol;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Body weight and height (at screening only);
- Pain at the treatment area will be assessed with the Numeric Rating Scale (NRS-11) at screening Visit 1 and at each study visit.
- Measurement of lesions with calipers;
- Photography of the treatment area (Section 6.3)
- SOR007 to be applied topically to the treatment area by gloved hand twice daily for 28 or 56 days;
- Blood samples for routine hematology and serum chemistry at every visit;
- PK blood collection at 24 hours after the first application (Day 1/Visit 2 plus 24 hours), and Visits 3, 4, 5 and 6 and 7, if applicable.
- Urine dipstick at screening and last subject visit; and
- Subject diary to be completed daily.
- Every effort should be made to schedule the subject clinic visits early in the morning to ensure the 'morning' and 'evening' application routines are adhered to and conducted at approximately the same time every day.

6.1.2 Standard of Care Study Procedures

Standard of care treatment at the Investigator's institution is not part of this study. Medical care during this study is at the discretion of the Investigator. At the time of the first study drug dose, the subject should not be scheduled for systemic chemotherapy. If, after the first study drug dose application, due to progression of disease or at the Investigator's discretion, the need arises for chemotherapeutic intervention, such treatment will be initiated at any time during the conduct of the study (See 6.6). All treatments and medications must be recorded in the subject's record. Surgical excision may only be scheduled at least 4 weeks after last treatment with SOR007 in order to achieve the objectives of this study. If the Investigator determines that it is in the subject's best interest to receive surgical excision or other prohibited treatment sooner than four weeks after last

treatment with SOR007, the subject will be permitted to receive such treatment in accordance with Section 6.6.2.

6.2 Treatment Area Selection

At baseline (Visit 2), the Investigator will identify a treatment area of 50 cm^2 containing at least one eligible lesion. Per RECIST criteria (version 1.1), an eligible lesion is considered measurable when ≥ 10mm diameter in the longest diameter.

The Investigator will outline the treatment area in permanent marker. All lesions within the treatment area will be measured by caliper at baseline to confirm eligibility and will be documented in the source. There may be multiple lesions present, in addition to the target lesion, in the 50 cm^2 outlined area. All lesions in the treatment area will be measured and tracked as described in this protocol (Section 3.3).

6.3 Photographic Documentation

The sponsor will provide detailed procedures for Photographs in the Procedure Manual.

Photographic documentation using a standard focal length digital camera of the treatment areas will be performed at baseline (Day 1/Visit 2) and at each subsequent study visit (Days 8, 15, 29, and 57, and 70, if applicable) or early withdrawal from the study, as applicable. The photographs will be taken under standardized conditions. Cameras and associated equipment will be provided to all Investigators, if needed. At least two global photos will be taken to reference the treatment area's location on the subject's body and at least two close-up photos of the treatment area will be taken. In every close-up photo, the required photographic documentation of the treatment area will include a centimeter ruler to reference scale and a label with the subject number, calendar date and study visit number. No non-study specific information will be included in the label. Study staff will be instructed to upload the subject photographs to a secure, password protected Citrix ShareFile or site restricted-access file, that will be accessible only by the site, the Medical Monitor, and the Sponsor. The Sponsor will analyze the images and measure the lesions using the Image J JAVA image processing program as photographs are uploaded by the Investigator.

6.4 Laboratory Procedures/Evaluations

6.4.1 Clinical Laboratory Evaluations

Clinical laboratory assessments will be conducted at the local CLIA certified laboratory routinely used by the Investigator.

The following laboratory tests will be performed at the Screening visit and Visits 2-6, and 7, if applicable:

- Routine complete total blood count including red blood cells (RBC), white blood cells (WBC), hemoglobin, hematocrit, platelets, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and

complete differential to include absolute and relative counts for all hematological parameters measured;

- Serum Chemistry, including albumin, total bilirubin, liver function tests (AST, ALT, GGT, ALP), blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, chloride, magnesium, and total protein;
- Urinalysis (dipstick), including specific gravity, pH, RBC, WBC, protein, and glucose will be performed at screening and Visit 7 for each subject.

6.4.2 Other Assays or Procedures

Blood samples will be collected to analyze pharmacokinetic (PK) activity for all subjects. Samples will be collected at 24 hours after the first application (Day 1/Visit 2 plus 24 hours), Visits 3, 4 and 5 (prior to the first daily application); Visits 6 and 7 (at any time during the visit).

6.5 Study Schedule

6.5.1 Screening

Visit 1 (Days -13 to Day 0)

The following screening procedures and assessments must be completed, documented and reviewed by the Investigator, within 14 days prior to the first topical SOR007 ointment administration. Institution standard of care laboratory and clinical assessments will be allowed if obtained prior to consent only if performed within the screening timeperiod or 14 days prior to Day 1:

- Written informed consent including comprehensive discussion of the study schedule, procedures and subject protocol requirements;
- Review of previous medical records, demographics, allergies, significant past medical history;
- Review and documentation of concomitant prescription and non-prescription medications;
- Review and documentation of diagnosis of cutaneous metastases of non-melanoma origin and previous treatments including surgical and chemotherapeutic records;
- A comprehensive physical examination;
- Vital signs (blood pressure, heart rate, respiration rate), temperature, body weight and height;
- ECOG performance status;
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11);

- Lesions will be measured with calipers. The target lesion will be determined at baseline by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter);
- Blood samples for routine hematology and serum chemistry, as per Section 6.4.1;
- Urinalysis by dipstick;
- Pregnancy test for female subjects;
- Review of inclusion and exclusion criteria and determination of eligibility.

6.5.2 Enrollment/Baseline

Visit 2 (Day 1)

The following procedures and assessments must be completed, documented and reviewed by the Investigator prior to the intended topical SOR007 ointment application:

- Medical history updates to include any events occurring since Visit 1, up to the first study treatment application;
- Review and documentation of current concomitant prescription and non-prescription medications;
- A problem-oriented physical examination, only if determined necessary by Investigator;
- Vital signs measurement (blood pressure, heart rate, respiration rate, temperature);
- Lesions will be measured with calipers. The target lesion will be confirmed at baseline by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter). All other lesion(s) in the treatment area will also be measured.
- Routine hematology, serum chemistry and urinalysis.
- Review of inclusion and exclusion criteria and determination of eligibility up to just prior to the first study treatment application, to confirm proceeding to treatment. After these assessments have been completed, the subject will receive topical application of SOR007.
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11) to be assessed prior to treatment area cleansing or drug application;
- The 50 cm^2 treatment area containing at least one eligible lesion will be selected by the Investigator, washed with warm soapy water and outlined with a permanent marker;
- Each lesion within the treatment area will be documented in the source and tracked for the duration of the study for changes in size and appearance;
- Photography of the treatment area and eligible lesion(s), incorporating a ruler for size evaluation;

- For this first application, the Investigator will demonstrate proper application technique as described in Section 5.1.5.

The subject will be supplied with the appropriate number of tubes of SOR007 for treatment application (until Visit 3) and a subject diary for daily completion. The subject will be instructed to self-apply SOR007 twice daily and to bring with them the SOR007 ointment tube to Visit 3 (Day 8).

PK Collection 24 Hours (+/- 2 hrs)

The subject will return to the clinic for PK sample collection at 24 hours (+/- 2 hours) after the Visit 2/Day 1 first SOR007 ointment application.

6.5.3 Treatment

Visit 3 (Day 8 ± 1 Day)

- Subject will return used SOR007 ointment tube for dosing compliance (Section 5.1.10) and study drug accountability (Section 5.2) purposes;
- Review and documentation of concomitant prescription and non-prescription medications;
- A problem-oriented physical examination only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate and temperature);
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11) prior to treatment area cleansing or drug application;
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;
- Blood sample collection for routine hematology and serum chemistry, as per Section 6.4.1;
- Day 8 PK sample collection prior to study drug application;
- Application of SOR007;
- Adverse events review;
- Subject will be supplied with the appropriate number of tubes of SOR007 for treatment application until the next visit;
- Subject diary from Visit 2 will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff; and
- A new diary to be provided to the subject for daily completion.

Visit 4 (Day 15 ± 1 Day)

- Subject will return SOR007 ointment tube for dosing compliance (Section 5.1.10) and study drug accountability (Section 5.2) purposes;
- Review and documentation of concomitant prescription and non-prescription medications;
- A problem-oriented physical examination only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11) prior to treatment area cleansing or drug application;
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;
- Blood sample collection for routine hematology and serum chemistry, as per Section 6.4.1*;*
- Day 15 PK sample collection prior to study drug application;
- Application of SOR007;
- Adverse events review;
- Subject will be supplied with the appropriate number of tubes of SOR007 for treatment until the next visit;
- Subject diary from Visit 3 will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff; and
- A new Visit 4 diary to be provided to the subject for daily completion.

Visit 5 (Day 29 + 2 Days)

- Subject will self-apply the last dose of SOR007 the evening prior to the visit;
- Day 29 PK sample collection at any time during the visit;
- Blood samples will be collected for routine hematology and serum chemistry, as per Section 6.4.1;
- Review and documentation of concomitant prescription and non-prescription medications;
- A problem-oriented physical examination; only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11);
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;

- Subject will return SOR007 ointment tube for dosing compliance (Section 5.1.10) and study drug accountability (Section 5.2) purposes;
- Adverse events review;
- Subject diary from Visit 4 will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff.
- A new Visit 5 diary to be provided to the subject for daily completion.

This visit will constitute the End-of-Treatment visit for Group A subjects. All subjects will be required to complete a 30-day safety follow-up period (including Visits 6 and 7 for Group A and Visits 7 and 8 for Group B in the dose expansion phase).

Subjects in the dose expansion phase continuing to an additional 28 days of treatment (or 56 treatment days) will proceed to Treatment B Visit 5 procedures:

- Application of SOR007;
- Adverse events review;
- Subject will be supplied with the appropriate number of tubes of SOR007 for treatment until the next visit.

Group B Visit 6 (Day 57 + 2 Days)

- Subject will self-apply the last dose of SOR007 the evening prior to the visit;
- Day 57 PK sample collection;
- Blood samples will be collected for routine hematology and serum chemistry, as per Section 6.4.1;
- Review and documentation of concomitant prescription and non-prescription medications;
- A problem-oriented physical examination; only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Pain assessment of the treatment area with the Numeric Rating Scale (NRS-11);
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;
- Subject will return SOR007 ointment tube for dosing compliance (Section 5.1.10) and study drug accountability (Section 5.2) purposes;
- Adverse events review;

- Subject diary from Visit 5 will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff.
- A new Visit 6 diary to be provided to the subject for daily completion.

This visit will constitute the End-of-Treatment visit for Group B subjects. All subjects will be required to complete a 30-day safety follow-up period (including Visits 7 and 8).

6.5.4 Follow up and End-of-Study Evaluations: Group A

Visit 6 (Day 43 ± 2 Days) End-of-Study Evaluations

- Day 43 PK sample collection at any time during the visit;
- Review and documentation of concomitant prescription and non-prescription medications;
- Problem-oriented physical examination only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Pain assessment of the treatment area;
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;
- Blood samples will be taken for routine hematology and serum chemistry;
- Urinalysis by dipstick;
- Adverse events review;
- Subject diary from Visit 5 will be collected and reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff.

Visit 7 (Day 59 + 2 Days) - Final Visit

Thirty days following the last study drug application all subjects must complete a final visit. The visit may be conducted at the Investigator's discretion as a clinic/office visit or by phone. During this visit the site will follow up on any existing adverse events and record any new adverse events. If the visit is conducted in the clinic/office, a physical exam may be conducted, only if deemed necessary by the Investigator. If the visit is conducted by phone, all phone call details must be recorded in the subject source.

6.5.5 Follow up and End-of-Study Evaluations: Group B

Visit 7 (Day 70 ± 2 Days) End-of-Study Evaluations

- Day 70 PK sample collection;

- Review and documentation of concomitant prescription and non-prescription medications;
- Problem-oriented physical examination only if determined necessary by Investigator;
- Vital signs (blood pressure, heart rate, respiration rate, temperature);
- Pain assessment of the treatment area;
- Photography of the treatment area and eligible lesions, incorporating a ruler for size evaluation;
- Blood samples will be taken for routine hematology and serum chemistry;
- Urinalysis by dipstick;
- Adverse events review;
- Subject diary from Visit 6 will be collected and reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff.

Visit 8 (Day 86 + 2 Days) - Final Visit

Thirty days following the last study drug application all subjects must complete a final visit. The visit may be conducted at the Investigator's discretion as a clinic/office visit or by phone. During this visit the site will follow up on any existing adverse events and record any new adverse events. If the visit is conducted in the clinic/office, a physical exam may be conducted, only if deemed necessary by the Investigator. If the visit is conducted by phone, all phone call details must be recorded in the subject source.

6.5.6 Early Termination Visit

In the event a subject, from either group is withdrawn they would, at minimum, undergo the End-of-Study (Visit 6 or 7) evaluations. If a subject is withdrawn at a routine study visit, all evaluations that would have been done at that study visit should be completed as well as all End-of-Study evaluations. If a subject received any study drug application, an additional safety assessment must be completed thirty days (+ 2 days) following the last study drug application (see 6.5.4/Visit 7 or 6.5.5/Visit 8).

6.5.7 UNSCHEDULED VISIT

Any unscheduled visits will be documented in the subject source notes/clinic or hospital chart and any assessments and/or evaluations performed will be noted and reviewed. The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject's well-being. If the Investigator deems it necessary to perform additional evaluations outside the scope of this study, this information will be documented in the subject source documents and collected for study purposes.

6.5.8 Schedule of Events Table 1: Treatment Group A: 28 Days

Timepoint/Study Visit	Screening (≤ 14 days)	Baseline	Treatment			Follow up	
	Visit 1 (Days -13 to Day 0)	Day 1 / Visit 2	Day 8 / Visit 3 (+/- 1 d)	Day 15 / Visit 4 (+/- 1 d)	Day 29 / Visit 5 (+ 2 d)	Day 43 / Visit 6 (+/- 2 d)	Day 59 / Visit 7 (+ 2 d)
Informed Consent	X						
History and Demographics[1]	X						
Inclusion/Exclusion	X	X[2]					
Height and Weight	X						
Physical Examination[3]	X	X	X	X	X	X	
Vital Signs[4]	X	X	X	X	X	X	
ECOG Performance Status	X						
Hematology and Chemistry	X		X	X	X	X	
Urinalysis	X					X	
Pregnancy Test	X						
Pharmacokinetic (PK) Assay[5]		X	X	X	X	X	
Pain Assessment	X	X	X	X	X	X	
Tumor Measurements[6]	X	X					
Tumor Assessment[7]			X	X	X	X	
Photography		X	X	X	X	X	
Distribute SOR007 Tube(s)		X	X	X			
Collect SOR007 Tube(s)			X	X	X		
SOR007 Application Training[7]		X	X	X			
SOR007 Application[7]		X	X	X			
Adverse Events[8]	X	X	X	X	X	X	X[10]

Concomitant Therapy	X	X	X	X	X	X	
Diary Distribution[9]		X	X	X	X		
Diary Collection			X	X	X	X	

1 History includes all medical and surgical events prior to SOR007 treatment application.
2 Final determination of study eligibility to be confirmed prior to first study drug application.
3 A comprehensive physical examination to be completed at the screening visit only; problem-oriented physical exam to be completed at all other visits, as needed.
4 Vital signs include: blood pressure, heart rate, respiration rate and temperature.
5. PK samples will be collected 24 hours (+/- 2 hours) post the first study drug application; at Visits 3 and 4 (prior to the first daily application); at Visit 5 and Visit 6 (at any time during the visit).
6 Cutaneous metastatic lesions will be measured with calipers at Screening to determine eligibility and at Baseline to document the 'starting dimensions' if different from screening. Eligible lesions will be determined by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter).
7 Lesions identified at Baseline, will be observed, tracked and documented for changes on a Lesion tracking log by the investigator at each visit.
8 SOR007 will be administered by topical application to metastatic lesions by the Subject following training by the Investigator or delegated study staff. Assigned SOR007 cohort dose will be applied daily on Day 1 to Day 28.
9 All adverse events and treatment emergent adverse event (TEAE) determination will start immediately following initiation of study treatment.
10 Subject Diary to be completed daily as an ointment dose application self-reminder and to record all ointment dose applications, record AEs and CMs.
11 The final safety assessment to be performed 30 days (+ 2 days) after last study drug dose application. The decision to conduct the visit in clinic or by phone is at the investigator discretion.

6.5.9 Schedule of Events Table 2: Treatment Group B: 56 Days

Timepoint/Study Visit	Screening (≤ 14 days)	Baseline	Treatment				Follow up	
	Visit 1 (Days -13 - 0)	Day 1 / Visit 2	Day 8 / Visit 3 (+/- 1 d)	Day 15 / Visit 4 (+/- 1 d)	Day 29 / Visit 5 (+/- 2 d)	Day 57 / Visit 6 (+/- 2 d)	Day 70 / Visit 7 (+/- 2 d)	Day 86 / Visit 8 (+ 2 d)
Informed Consent	X							
History and Demographics[1]	X							
Inclusion/Exclusion	X	X[2]						
Height and Weight	X							
Physical Examination[3]	X	X	X	X	X	X	X	
Vital Signs[4]	X	X	X	X	X	X	X	
ECOG Performance Status	X							
Hematology and Chemistry	X	X	X	X	X	X	X	
Urinalysis	X						X	
Pregnancy Test	X							
Pharmacokinetic (PK) Assay		X[5]	X	X	X	X	X	
Pain Assessment	X	X	X	X	X	X	X	
Tumor Measurements[6]	X	X						
Tumor Assessment[7]			X	X	X	X	X	
Photography		X	X	X	X	X	X	
Distribute SOR007 Tube(s)		X	X	X	X			
Collect SOR007 Tube(s)			X	X	X	X		
SOR007 Application Training[8]		X	X	X	X			
SOR007 Application[8]		X	X	X	X			
Adverse Events[9]	X	X	X	X	X	X	X	X[11]

Concomitant Therapy	X	X	X	X	X	X	X	
Diary Distribution[10]		X	X	X	X	X		
Diary Collection			X	X	X	X	X	

1 History includes all medical and surgical events prior to SOR007 treatment application.
2 Final determination of study eligibility to be confirmed prior to first study drug application.
3 A comprehensive physical examination to be completed at the screening visit; problem-oriented physical exam to be completed at all other visits as needed;
4 Vital signs include: blood pressure, heart rate, respiration rate and temperature.
5. PK samples will be collected 24 hours (+/- 2 hours) post the first study drug application; at Visits 3, 4 and 5 (prior to the first daily application, at Visits 6 and 7 at any time during the visit.
6 Cutaneous metastatic lesions will be measured with calipers at Screening to determine eligibility and at Baseline to document the 'starting dimensions' if different from screening. Eligible lesions will be determined by the RECIST (version 1.1) definition of measurable tumors (≥ 10mm in its longest diameter).
7 Lesions identified at Baseline, will be observed, tracked and documented for changes on a Lesion tracking log by the investigator at each visit.
8 SOR007 will be administered by topical application to metastatic lesions by the Subject following training by the Investigator or delegated study staff. Assigned SOR007 cohort dose will be applied daily on Day 1 to Day 56.
9 All adverse events and treatment emergent adverse event (TEAE) determination will start immediately following initiation of study treatment.
10 Subject Diary to be completed daily as an ointment dose application self-reminder and to record all ointment dose applications, record AEs and CMs.
11 The final safety assessment to be performed 30 days (+ 2 days) after last study drug dose application. The decision to conduct the visit in clinic or by phone is at the investigator discretion.

6.6 Concomitant Medications, Treatments, and Procedures

Any medication ongoing at the time of the first study drug application will be collected and recorded for study purposes. These will be considered baseline medications. Any new medication started after the first study drug application, or medication changed from baseline will be collected and recorded on the electronic case report forms (eCRF). Following Visit 2/Day 1, if disease progression requires chemotherapy treatment, any treatment can be administered at the discretion of the Investigator. If a taxane treatment is indicated, the subject will be withdrawn from the study (See 6.1.2, 6.5.5).

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications and/or treatments to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

6.6.1 Precautionary Medications, Treatments, and Procedures

No precautionary medications, treatments, or procedures are included in this protocol; they may, however, be administered at the discretion of the Investigator or the subject's primary care provider or oncologist unless a prohibited medication (See 6.6.2); all medications will be recorded.

6.6.2 Prohibited Medications, Treatments, and Procedures

Systemic treatment or treatment to the target area with radiotherapy, intralesional therapy; laser therapy surgery other than biopsy, local hyperthermia, levulinic acid, 5-fluorouracil, high potency corticosteroids (including systemic steroids), retinoids, diclofenac, hyaluronic acid, imiquimod within the 4 weeks prior to the screening visit are prohibited. Subjects should not be scheduled to receive any systemic taxane cytotoxic chemotherapy, or topical or direct lesional therapy (e.g. intralesional injections, laser, hyperthermia, and steroids to within 2 inches (5 cm) of the 50 cm^2 treatment area) within 2 weeks prior to the first study drug application or during the study. Following Visit 2/Day 1, if disease progression requires taxane chemotherapy treatment, the subject will be removed from the study (i.e.: study drug treatments to be discontinued). All early termination assessments (Visit 6 or 7) as well as the 30 days post last study drug dose application contact will be required to be completed.

If the Investigator determines that any prohibited medications or procedures are required in the best interests of the subject, the subject will receive the treatment or procedure. When this occurs, discussion with the Medical Monitor is required, the subject is to discontinue further treatment with SOR007, and complete Visit 6 or 7 and 30 days post last study drug dose application call or visit, per protocol.

6.6.3 Prophylactic Medications, Treatments, and Procedures

No specific prophylactic medications are required for this study. While prophylaxis is commonly administered to subjects receiving intravenous paclitaxel, clinically significant systemic exposure

is not expected with topical administration of SOR007 under the conditions of this study. Routine prophylaxes may be instituted if signs and symptoms suggest the need, provided these are not prohibited medications, treatments or procedures (see Section 6.6.2).

7 ASSESSMENT OF SAFETY

7.1 Specification of Safety Parameters

Safety assessments being conducted in this study include:

- Laboratory assessments;
- Adverse events and TEAE, collected at all study visits from the time of initial dosing;
- Changes in concomitant medications and;
- Findings from physical examinations.

Safety will be reviewed by the Medical Monitor in an ongoing manner via the EDC system, and details will be confirmed at routine on-site monitoring visits.

7.1.1 Definition of Adverse Events (AE) and Adverse Drug Reaction (ADR)

An AE is any untoward medical occurrence (whether or not considered to have a causal relationship to the study drug) in a study subject administered the study drug. Therefore, an AE can be any unfavorable and unintended sign (including a clinically significant laboratory finding), symptom, or disease temporally associated with the use of an study drug, whether or not related to the study drug. For the purposes of this protocol, all AE occurring during the study are considered treatment-emergent AE (TEAE) associated with the use of the product), whether or not the AE is determined to be product related.

According to the FDA *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (January 2006)*, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.

7.1.2 Definition of Serious Adverse Events (SAE)

All AE must be evaluated as potential serious adverse events (SAE). An SAE is any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening (i.e., the subject 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 subject who was exposed to the study drug); or
- Is a medically important event or reaction:

Events that do not result in death or hospitalization but may, based on appropriate medical judgment, jeopardize the subject or require intervention to prevent one of the outcomes in the definition of SAE listed above, should also be considered SAE.

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

The Investigator will assess the severity of AE according to the criteria below:

- **Mild:** The AE is transient and does not interfere significantly with the subject's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention.
- **Moderate:** The AE produces limited functional impairment and may require therapeutic intervention. The AE produces no sequelae.
- **Severe:** The AE results in significant impairment of function and may lead to temporary inability to resume the subject's normal life pattern. The AE produces sequelae which require prolonged therapeutic intervention.
- **Life Threatening:** The AE results in life-threatening consequences, urgent intervention is indicated, urgent operative intervention is indicated or the patient is at risk of death at the time of the event if immediate intervention is not undertaken.
- **Fatal:** The AE results in death.

Further, toxicities will be evaluated according to the current NCI CTCAE (version 4.0) criteria.

7.2.2 Relationship to Study Agent

The following five-point scale will be used by the Investigator to rate the relationship of the AE to the study product:

- **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 disease or other drugs or chemicals. The response to withdrawal of the drug

(de-challenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory re-challenge procedure, if necessary.

- **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 disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **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 disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Unlikely to be related:** A clinical event (including laboratory test abnormality) whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the study drug. An alternative definitive etiology should be documented by the Investigator.

Causality will be assessed as follows:

The Investigators will assign causality at their respective sites during the study. The SMC will review the assigned causality for all AE and SAE prior to database lock. This assignment will be included in the study database and final study report. As noted in the FDA *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, decisions on whether there is some basis to believe there is a causal relationship will be based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and de-challenge experience, and (7) whether the adverse event is known to be caused by related drugs.

7.2.3 Expectedness

Expected adverse reactions are AE that are common and known to occur for the study agent being studied. Expectedness refers to the awareness of AE previously observed, not on the basis of what might be anticipated from the properties of the study agent.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or

elsewhere in the protocol, as amended. "Unexpected," as used in this definition, also refers to AE or suspected adverse reactions that are mentioned in the IB as occurring with the class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The Medical Monitor and sponsor's Medical Director will be responsible for determining whether an AE is expected or unexpected.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The Investigator will record all reportable events with start dates occurring any time after first study drug dose application until 30 days after the last study drug application for AE or, in the case of an SAE, at least 30 days after onset, whichever is later. At each study visit, the investigator will inquire about the occurrence of AE/SAE since the last visit. Events will be followed for outcome until resolution or stabilization.

7.4 Reporting Procedures

7.4.1 Adverse Event Reporting

AE will be captured from first study drug dose application until 30 days after the last treatment application. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AE including local and systemic reactions not meeting the criteria for SAE will be captured on the appropriate eCRF. If the subject reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the eCRF.

Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AE occurring while on study must be documented appropriately regardless of relationship. All AE will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened until just prior to the first study drug application will be considered as baseline medical history condition and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AE characterized as intermittent require documentation of onset and duration of each episode.

Clinically significant laboratory abnormalities will be recorded as adverse events. Clinically significant laboratory abnormalities are those that are changed compared to baseline and require intervention, whether or not they are associated with signs or symptoms.

7.4.2 Serious Adverse Event Reporting

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the Sponsor within 24 hours of site awareness.
- Other SAE regardless of relationship, will be submitted to the Sponsor within 72 hours of site awareness.

All SAE will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or stable. Other supporting documentation of the event should be provided as soon as possible. The Sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case, later than 7 calendar days after the sponsor's initial receipt of the information.

All SAE, including death, due to any cause which occurs during this study between the period of dose administration and last study visit, whether or not expected and regardless of relationship to study drug, must be reported to the Medical Monitor immediately upon discovery of the event, using the SAE reporting form, scanned and sent by email. Additionally, the SAE report form may also be submitted to the sponsor by fax. SAE reports should be sent to:

Dr. Tony Verco
Medical Monitor
Email: tony.verco@usbiotest.com
Phone: 805-235-9193
Fax: 805-980-4897

Rose Marie Cavanna-Mast
Director, Clinical Trials
Email: rosemarie.cavanna@usbiotest.com
Phone: 281-685-6092
Fax: 805-980-4897

24-hour Emergency Contacts:	Gere diZerega, MD Medical Director 805-630-2800	or	Tony Verco, MD Medical Monitor 805-235-9193

The sponsor will advise the Investigator regarding the nature of any further information or documentation that is required. The Investigator should provide the following documentation at the time of SAE reporting if available:

- SAE Report Form;
- Concomitant and support medication pages;
- Relevant diagnostic reports;
- Relevant laboratory reports;
- Admission Notes;
- Hospital discharge summary (when available).

7.4.3 Events of Special Interest

Events of Special Interest will be defined and reported to the authorities by the sponsor as signs of local effect and toxicity e.g. odor, purulence, new ulceration at the treatment site, and bleeding. Adverse events of special interest usually attributed to paclitaxel include infusion reactions, vital signs, and bone marrow depression. Additionally, systemic toxicity due to paclitaxel exposure such as reduction in neutrophils (absolute and relative) and thrombocytopenia will be monitored by the sponsor. Due to the low total dose administered, very low surface area of cutaneous metastases surface exposed relative to body weight and size, and expected absorption rate of SOR007, it is unlikely that detectable and clinically relevant systemic levels of SOR007 will occur.

7.4.4 Reporting of Pregnancy

A female subject is considered to be of childbearing potential unless she has had a hysterectomy, is at least one year postmenopausal or has undergone tubal ligation. Male patients whose vasectomy has been confirmed by negative semen analysis at least 3 months after the vasectomy are exempt from using contraceptives. For the purposes of this study, male or female subjects must use at least one medically approved and highly effective birth control method (low failure rate (i.e. < 1% per year when used consistently and correctly) to include hormonal methods, barrier methods, IUD or abstinence. Any contraceptive method or justification for lack of method must be recorded in the subject source.

If any subject becomes pregnant during the study, the subject must be followed up until birth or termination of pregnancy. The pregnancy is to be immediately reported to US Biotest on the Pregnancy Report form. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report. The outcome of the pregnancy should be reported to US Biotest as soon as it is known on the Pregnancy Report form. If the pregnancy ends for any reason before the anticipated date initially reported the Investigator must notify US Biotest the following working day.

If the outcome of the pregnancy meets any criteria for classification as a SAE (including stillbirth, neonatal death, spontaneous abortion, or congenital anomaly - including that in an aborted fetus) the Investigator must follow the procedures outlined in protocol Section 7.4.2. for reporting SAE. Any neonatal death occurring ≤ 30 days after birth will be reported as a SAE.

7.5 Study Halting Rules

This study is a Phase 1/2 dose escalation study, and dose escalation will be determined following review of all safety and tolerability data of a cohort by the Medical Monitor in conjunction with the SMC.

The Sponsor is responsible for notifying the FDA of any temporary halts to the study or when a study is terminated; the Investigator will be required to notify the IRB accordingly.

The severity of toxicity will be classified according to CTCAE criteria (version 4.0). Any adverse event that is considered related or possibly related to SOR007 is potentially a DLT. The definition of a DLT will be made by consensus by the SMC.

Dose escalation of SOR007 will be halted when ≥ 2 grade 3 AEs (CTCAE version 4.0), occur in any single cohort/dose level and are determined to be "probably related" to SOR007 (See Figure 2). Further enrollment will be temporarily halted until the safety review has been conducted. The Medical Monitor, in conjunction with the SMC will determine next steps per the Safety Monitoring Plan. The final decision for dose escalation and/or premature study drug discontinuation is the responsibility of the Medical Monitor.

7.6 Dose Escalation and Dose Limiting Toxicity

During the dose escalation phase, the study will follow a standard 3+3 dose-ascending design, with the first cohort of three subjects commencing treatment with 0.15% SOR007. The SMC will review all available data on a monthly basis and after the last subject in each cohort of three subjects completes 15 days of treatment to determine whether dose escalation may continue, per the Safety Monitoring Plan. If no DLTs are identified in any of the first 3 subjects in a cohort, dose escalation may proceed. If a single dose limiting toxicity (DLT) is identified in one of three subjects in the cohort, a further three subjects will be enrolled at the same dose level. If one or more DLT occur in the three additional subjects enrolled in the cohort, dose escalation will stop and the prior dose level will be regarded as the Maximum Tolerated Dose (MTD) and taken forward into the dose expansion phase. If no further DLTs are identified, dose escalation will continue, until either a DLT is identified at a higher dose or the top dose of 2.0% SOR007 is reached. During the dose expansion phase the SMC will review all available data on a monthly basis until the study is complete.

If it is determined that a DLT has been reached, the prior dose level will be defined as the highest dose with an acceptable safety and tolerability level.

Figure 2. Dose Escalation and Study Stop Algorithm – Step-by-Step Procedure

Step	Regimen	Outcome	Outcome 2	Next Step
1 (n=3)	0.15% BID	2 DLT		STOP STUDY
		1 DLT – add 3 subjects	If 1 further DLT	STOP STUDY
			If no DLT	Go to Step **2** (1% BID)
		0 DLT		Go to Step **2** (1% BID)
2 (n=3)	1% BID	2 DLT		Go to Step **4** (0.15% BID)
		1 DLT – add 3 subjects	If 1 further DLT	Go to Step **4** (0.15% BID)
			If no DLT	Go to Step **3** (2% BID)
		0 DLT		Go to Step **3** (2% BID)
3 (n=3)	2% BID	2 DLT		Go to Step **5** (1% BID)
		1 DLT – add 3 subjects	If 1 further DLT	Go to Step **5** (1% BID)
			If no DLT	Go to Step **6** (2% BID)
		0 DLT		Go to Step **6** (2% BID)

Step	Regimen	Outcome	Outcome 2	Next Step
4	0.15% BID	≥ 3 DLT		STOP STUDY
5	1% BID	≥ 3 DLT		STOP STUDY
6	2% BID	≥ 3 DLT		STOP STUDY

Dose Limiting Toxicity will be defined as:

Non-Hematologic:

- ≥ Grade 3 non-hematological toxicity, excluding nausea, vomiting, diarrhea;
- ≥ Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/ antidiarrheal therapy ≥72 hours;
- Any toxicity which in the judgment of the Medical Monitor, Principal Investigator and Sponsor Medical Director is considered a DLT;
- Hypersensitivity reactions to SOR007 that cannot be controlled with standard treatment;
- New ulceration within the treatment area;
- ALT or AST >3x ULN and total bilirubin > 2x ULN.
- Any death not clearly due to the underlying disease or extraneous cause.

Hematologic:

- ≥ Grade 3 anemia and/or neutropenia;
- Neutropenic fever;
- Thrombocytopenia of any Grade if associated with clinically significant bleeding (clinically significant as determined by the Investigator, or results in a transfusion of red blood cells.),
- Grade 4 thrombocytopenia without bleeding.

Study Halt Rules:

- New ulceration within the treatment area occurring in ≥ 2 of 6 subjects in each dose escalating cohort, or ≥ 3 of 9 subjects in the dose expansion cohort.
- Any Grade 4 dermal toxicity
- ≥ 3 Grade 3 AE occurring in the cohort of 9 subjects, and which are determined to be "probably related" to SOR007 (in the dose expansion phase only).

Dose Expansion Phase:

In the dose expansion phase, additional subjects will be enrolled to reach a maximum of 16 total subjects at the dose level determined to be the MTD in the dose escalation phase. Subjects in the dose expansion phase will attend the clinic on the same visit days and receive the same evaluations as the dose escalation phase above.

7.7 Safety Oversight

Safety will be overseen by the SMC, in conjunction with the Medical Monitor. In the event the Medical Monitor has any concerns or identifies any safety trends emerging during ongoing reviews it will be brought to the immediate attention of the Sponsor Medical Director and the Principal Investigator for further discussion and action as required.

All subject study data will be captured in an EDC system, allowing real-time access to ongoing safety and tolerability data. The SMC and the Medical Monitor will review all data for each subject entered to the database on a regular basis (in both dose escalation and dose expansion), and upon completion of the Day 15 visit of the last subject in a cohort and prior to dose escalation proceeding, the Medical Monitor will review the cohort data, and a report will be generated outlining any safety concerns from the data available for review in the EDC. This report will be shared with the Sponsor Medical Director and Principal Investigator and will take place prior to proceeding with dose escalation.

8 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

US Biotest monitors, or monitors designated by US Biotest, will conduct scheduled site visits to the investigational centers for the purposes of monitoring the study. The Investigator agrees to allow these monitors, and other authorized sponsor personnel or designees, access to the subject's medical records, Investigator Site File (ISF), eCRF, and any other source documents as needed to assure the conduct of the study is within compliance. In addition, the FDA or other government agencies may request an inspection following notification to the site. In such an event, the Investigator agrees to notify the sponsor immediately of the request, and will allow sponsor and inspectors to review records.

US Biotest will conduct a Site Initiation Visit to provide the Investigator and their staff with a comprehensive overview of the protocol and study procedures and to review mutual obligations and requirements of regulatory authorities prior to any subjects being consented. The Investigator Site File (ISF) or regulatory file containing essential and non-essential documentation will be kept at the site for reference and inspection.

Routine monitoring visits will be conducted by the sponsor to assure compliance with the study protocol, to review and verify all study documentation is properly maintained to include, but not limited to: the subject's source documents, the eCRF, clinical supplies, all investigational product receipt, accountability, storage and disposition records are maintained and to assess the continued suitability of the investigational site.

Upon completion of the study, the monitor will make a final close out visit to the site to assess final conduct of the study, complete a final regulatory review and inventory all clinical drug and non-drug supplies for disposition or return to US Biotest or designee.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical and Analytical Plans

A formal Statistical Analysis Plan (SAP) will be prepared for this trial, and the SAP will be signed off prior to study database lock.

9.2 Statistical Hypotheses

No formal statistical inference (i.e. "p-values") will be applied. The results of this trial will be based on descriptive statistics only.

9.3 Analysis Datasets

In this safety and tolerability trial, all subjects who are enrolled and receive at least one dose of study drug will be included in the descriptive analysis.

9.3.1 Missing Data

Data will be presented as observed and no missing data imputation will be performed.

9.4 Description of Statistical Methods

9.4.1 General Approach

The focus of the trial will be on the safety and tolerability of the dose escalated treatments. The general approach will be to highlight any trends that cause concern for the reviewing medical monitoring team (i.e. dose limiting toxicities (DLT)).

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Not applicable. The primary objective is to evaluate the safety and tolerability as demonstrated by TEAE, changes in laboratory assessments, physical examination findings and vital signs.

9.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints will be summarized descriptively. These will include supportive information to provide context for the dose(s) chosen to move forward for future study.

- Objective tumor response, defined as the difference in the sum of the tumor diameter/s between baseline and Visit 6; i.e. 14 days after the last dose in the dose escalation and expansion phases depending on dose regimen. Tumor surface area and response will be

assessed at all visits. Change in surface area will be assessed using ImageJ freeware provided by the NIH.

- Objective Clinical Response is defined as subjects with Complete Clinical Response (CR) + Partial Response (PR), further defined as the percentage of subjects who achieve complete clinical response or partial response 14 days after the last treatment with SOR007, measured as change in the sum of the longest diameter/s of the target lesion/s 14 days after last treatment. The response to treatment is then evaluated as a function of post-treatment total diameter divided by pretreatment total diameter.
- Best overall response is defined as the best response recorded from the start of study treatment until the end of the study i.e. Visit 6/Day 43 or Visit 7/Day 70.
- The definition of eligible cutaneous tumors is based on the (version 1.1) definition of measurable tumors (superficial and ≥ 10mm in its longest diameter). Complete clinical response (CR) is defined as absence of any detectable residual disease in the target lesion/s; partial response (PR) as at least a 30% decrease in the sum of the diameters of the target lesion/s compared to baseline (Visit 2); and progressive disease (PD) as at least a 20% increase in the sum of diameters of target lesion/s, taking as reference the smallest sum on study. In addition, the sum must also demonstrate an absolute increase of at least 5 mm. Stable disease (SD) is defined as the sum of target lesion diameters between that defined as PR or PD.
- The appearance of new non-target lesions during participation in this study does NOT constitute progressive disease.
- Change in pain (NRS-11) score from baseline to any post-baseline time point that the pain scale captures.
- The concentration of paclitaxel in the systemic circulation post-topical application, will be measured by pharmacokinetic (PK) sampling for Group A Subjects on Days 1 (24 hours post-application), 8, 15, 29 and 43 or for Group B Subjects Days 1 (24 hours post-application), 8, 15, 29, 57 and 70. If some concentration data is above the detectable limit and can be reported numerically, this data will be tabulated and graphed for individuals and by dose group.

9.4.4 Safety Analyses

9.4.4.1 Adverse Events

Adverse events (AE) recorded during the trial will capture medically relevant changes found during the physical exam, and medically relevant changes in vital signs and laboratory analytes found during the course of the trial. In addition, spontaneously reported or observed events will be recorded

Events reported at or after the application of SOR007 will be considered Treatment Emergent Adverse Events (TEAE). All reported events will be listed by subject number and assigned treatment, investigator term, MedDRA coded term, date/study day (from initial treatment) for

onset and cessation, severity (using the NCIC severity grading), relationship to study medication and but only the TEAE will be tabulated.

Safety analysis for dose escalation will be based on the review of the data from the first 15 days of treatment, when a decision is made to proceed to increase the dose or not.

Adverse event reports will be coded using the most recent version of MedDRA, signed off by the Medical Monitor and presented by System Organ Class (SOC) and preferred term. All AE and abnormal laboratory variables will be assessed according to the NCI-CTCAE (version 4.0) grading system. The number of subjects and number of events reported will be presented in frequency tables (overall, by intensity, by relationship and by outcome) for each dose cohort. Adverse events of special interest (e.g., AE leading to study drug discontinuation, SAE, DLT, deaths) will be presented separately.

9.4.4.2 Laboratory Analytes

Quantitative laboratory data will be summarized as mean values and change from baseline scores (change = baseline-visit) presented by dose level for each sampling time point. For tests with normal ranges provided, the clinical status and its change from baseline (Normal/High Abnormal/Low Abnormal) will be summarized using shift tables for each dose group. Analytes of particular interest (e.g., hematological tests) may be graphed by subject with the dose indicated; these special analytes will be confirmed in the SAP.

9.4.4.3 Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiration rate and temperature) will be tabulated and mean raw values and changes from baseline scores (change = baseline-visit) where baseline is the last measurement prior to the study drug application, for each treatment group.

9.4.5 Adherence and Retention Analyses

All subjects who enter the trial will be accounted for and any reasons for early termination noted – including disease progression and AE.

9.4.6 Baseline Descriptive Statistics

Complete demographic and baseline data will be tabulated. The medical history, which will be coded in MedDRA, will be presented. The disease history data, with a focus on the previous treatment and current staging, will be presented in by-subject listing. Categorical results will be summarized.

9.4.7 Planned Interim Analyses

9.4.7.1 Safety Review

See Section 7.6.

9.4.7.2 Efficacy Review

Not applicable.

9.4.7.3 Additional Sub-Group Analyses

Not applicable.

9.4.8 Multiple Comparison/Multiplicity

Not applicable, as no inferential analyses will be employed.

9.4.9 Tabulation of Individual Response Data

All data collected in the eCRF will at a minimum be listed; listings will support the tabulated data/outcomes.

9.4.10 Concomitant Medication

All medication taken during the trial will be, at a minimum, listed with the start and stop dates. For this small clinical trial, the medications will not be coded using the WHO Drug Dictionary. Although no interaction studies have been conducted using SOR007, paclitaxel is metabolized by cytochrome P450 isozymes CYP2C8 and CYP3A4 (Taxol Package Insert). Thus, there is a potential for drug interactions with concomitantly administered substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8. There is also the potential for paclitaxel to interact pharmacokinetically with CYP3A4 substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine).

9.5 Safety Monitoring Committee (SMC)

The Safety Monitoring Committee (SMC) will draft and agree to a Charter which outlines the criteria to be applied to the subjects in the trial as well as the final choice of dose groups to be studied further, prior to the first subject being enrolled in the trial. The trial statistician will work with the SMC to produce specific data driven reports to support their decision making.

Subject safety will be the primary driver in all decision making.

9.6 Sample Size

As there are no formal inferential statistical analyses planned, the sample size estimates below are provided for informational purposes only to help with decision-making around the cohort size and the rarity of events that could be detected.

Defining the primary endpoint explicitly requires understanding the primary purpose of the study. If, as in this case, the primary purpose of the study is dose-finding, then the incidence of DLT would be an appropriate endpoint. When choosing events that will qualify as DLT, it's important to consider the rarity of events given the small number of subjects. For example, if a particular adverse event is known to occur in only 5% of subjects, there is a 26.5% chance it will appear in a particular cohort of 6 subjects, and a 60.3% chance it will occur during the study of 22 subjects. If the event only occurs in 1% of patients, there is only a 6% chance it will appear in a given 6-subject cohort, and a 16.5% chance it will be observed in the entire study. So rarity is a factor that should be considered when deciding which adverse reactions to include as part of the endpoint. Estimates were obtained using the "confidence interval for probability of observing a rare event" calculation in nQuery 6.01.

The rationale to expand the final cohort in the Dose Expansion Phase to 16 subjects, from either 3 or 6 subjects, was based on the "reasonable gain" in detection rate that each additional subject would provide in this early phase exploratory trial. The calculations were performed using nQuery Advisor 6.01 "confidence interval for probability of observing a rare event". With 16 subjects the probability of detecting the 0.1 event rate is 71.8% as well as some probability of detecting much rarer events (11.4% probability of detecting an event with a base rate of 0.01, and 46% probability of detecting an event with a 0.5 base rate).

9.7 Measures to Minimize Bias

9.7.1 Enrollment/ Randomization/ Masking Procedures

Not applicable.

9.7.2 Evaluation of Success of Blinding

Not applicable.

9.7.3 Breaking the Study Blind/Participant Code

Not applicable.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the Sponsor and Regulatory Agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

An eCRF is required and must be completed for each consenting and enrolled subject by qualified and authorized study site personnel.

Subjects who fail the Screening assessments will have demographics and reason for screen fail collected.

Subjects meeting all inclusion/exclusion criteria will have all data entered in an eCRF. All data in the eCRF must reflect the corresponding source document. Any corrections to entries made on the eCRF must be documented in a valid audit trail. Only data required by the protocol for the purposes of the study should be collected within the EDC.

The Investigator must maintain adequate and accurate source documents on which the eCRF for each subject are based. They will be separate and distinct from the eCRF. These records should include detailed notes on:

- The medical history prior to the subject's involvement in the study;
- Date of informed consent;
- The basic identifying information that links the subject's medical record with the eCRF;
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject;
- The medical condition during the subject's involvement in the study;
- All AE;
- The subject's exposure to the study medication;
- The subject's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the subject throughout the trial;
- Justification for all entries in the subject's eCRF.

11 QUALITY ASSURANCE AND QUALITY CONTROL

Data required by the protocol will be collected and entered into a validated data management system that is compliant with all regulatory requirements. The eCRF is an electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data recording must follow the instructions described in the eCRF Completion Guidelines. The PI has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The PI, as identified on Form FDA 1572, must electronically sign the completed eCRF for each participating subject to attest to their accuracy, authenticity, and completeness.

The EDC application being used in this study is OpenClinica, an open source application which has been installed and validated by McDougall Scientific Ltd., following SOPs based on the

Systems Development Life Cycle (SDLC) methodology. All personnel using the system will be trained and the training documented. All changes to the database are recorded in an audit trail. The database will be locked when all open queries have been addressed, all agreed to data is marked as source verified, and the PI has signed off on the eCRF contents.

All software applications used in the collection of data will be properly validated following standard computer system validation methods compliant with all regulatory requirements

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. The Sponsor and Investigator will comply with their responsibilities as defined in 21 CFR 312.50-312.70.

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval, in accordance with local legal requirements. It is the responsibility of the Investigator to assure that all aspects of the IRB review are conducted in accordance with current regulations. US Biotest and the Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented at the study site. All changes to the consent form will be IRB approved; a determination will be made by the IRB regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent and Other Informational Documents Provided to Participants

Subjects being considered for participation in this study will be provided an Informed Consent Form (ICF) to read and sign before being permitted to participate. The ICF will describe the study agent and any prior findings from previous studies, it will describe the study procedures including the timing of study clinic visits and their responsibilities to adhere to those timelines, any risks which may be associated with the study agent or the procedures being carried out in the study, and all other items required under 21 CFR part 50.25.

Subjects will be required to provide signed consent prior to any study-related procedures being carried out. The Investigator is required to document the process for obtaining informed consent in the source notes and according to institutional consenting requirements.

12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the study subject's participation. Extensive discussion of risks and possible benefits of participation will be provided to the patients and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the patient and answer any questions that may arise. All patients will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The Investigator will obtain informed consent from each subject enrolled in the study, in accordance with the U.S. Food and Drug Administration (FDA) regulations 21 CFR 50.20 - 50.27 and the laws and regulations of the state in which the investigation is being conducted. The IRB must approve ICF to be used by the Investigator. The Investigator will provide the sponsor with a copy of the written approval generated by the IRB or Ethics Committee before the Investigator will be permitted to enroll subjects into the study.

It is the responsibility of the Investigator to ensure that informed consent is obtained from the subject before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of study medication. Any draft version of the informed consent document modified by each site and must be reviewed and approved in writing by US Biotest prior to submission to the IRB.

Should a protocol amendment be made, the subject consent form may be revised to reflect the changes of the protocol. If the consent form is revised, it is the responsibility of the Investigator to ensure that an amended consent is approved by the IRB and if required by the IRB, signed by all subjects currently on study as well as those subsequently entered in the study.

The Investigator will not perform any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF. The original, signed informed consent document must be

maintained on file at the study site and be made available for review during monitoring visits and site audits.

12.4 Study Subject and Data Confidentiality

Study subject's confidentiality is strictly held in trust by the participating Investigators, their staff, the Sponsor, and their agents. This confidentiality includes the testing of study subjects' biological samples (and genetic tests where applicable) in addition to their clinical information relating to study participation. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, authorized representatives of the Sponsor, representatives of the IRB and applicable government agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for any study subject. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study subjects research data, for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at McDougall Scientific. This will not include the subject's contact or identifying information. Individual study subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by McDougall Scientific research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at US Biotest.

All local legal requirements regarding data protection will be enforced. The anonymity of study subjects must be maintained to the extent required by law. Throughout documentation collection and evaluation, subjects will be identified on eCRF and other documents submitted to US Biotest and McDougall Scientific by their initials, and birth date (if allowed by local institution requirements), and their subject number. Subjects will be advised that all study findings will be stored and handled in strictest confidence, according to legal requirements, but will be informed that authorized research Investigators and agents of the FDA, the NCI, and authorized personnel of US Biotest have the right to inspect their medical records.

12.4.1 Research Use of Stored Human Samples, Specimens or Data

Samples and data collected under this protocol are specifically for use in the evaluation and analyses being conducted in the study. Samples will not be available for purposes other than indicated within this protocol, and no genetic testing will be performed.

Access to stored samples will be limited to personnel authorized to have access at the site prior to shipping to the laboratories for analysis/assessment. Samples will be stored using codes assigned by the Sponsor or as required by the clinical laboratories.

Samples will only be retained until analysis is complete, following which samples will be disposed of according to the laboratory SOP. No samples will be retained for any future use.

Data will be kept in password-protected computers. Only Investigators and those delegated on the Delegation of Authority Log will have access to the samples and data.

12.5 Future Use of Stored Specimens

Not applicable

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, the original entry should be crossed out with a single line to not obscure the original entry and all changes should be initialed and dated. No source data is to be erased, overwritten. Correction fluid or correction tape must not be used on any source documentation.

Source documents will be maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AE, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OpenClinica, a 21 CFR Part 11-compliant data capture system provided by MacDougall Scientific. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Data recording must follow the instructions described in the eCRF Completion Guidelines. The PI has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF.

The database will be locked when all outstanding queries have been addressed, all agreed to data is marked as source verified, and the PI has signed off on the eCRF contents.

13.2 Study Records Retention

The Investigator must retain a copy of all study documents in accordance with the FDA or local regulations, whichever are the more stringent.

The Investigator must maintain study documents:

- For a minimum of two years following the date the marketing application (NDA) is approved for the indication for which the drug was investigated for;
- For a minimum of two years following the release date of the final report, if no marketing application is to be filed, or if the marketing application is not approved for the indication of which the drug was investigated or is discontinued and the FDA has been notified; or,
- For a minimum of 15 years after the completion or discontinuation of the study to be filed in support of the registration in the European Union.
- The Investigator, or designee will notify the sponsor in writing if the study records are moved or transferred to another responsible individual.

These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), FDA or IRB requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as possible after occurrence and identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the Sponsor and to the data Management group.

Protocol deviations must be reported to the local IRB as per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Serious non-compliance on the part of the site, and an inability of the Sponsor to bring the site back into compliance, will be reported to the FDA in accordance with their requirements.

13.4 Publication and Data Sharing Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The sponsor will prepare an integrated clinical/statistical report. Publication/presentation of data is not allowed without explicit permission from US Biotest. Submission of data for publication/presentation will be coordinated and approved by US Biotest in collaboration with the Investigator.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in subjects or participants, including pharmacokinetic measures and AE. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Data entered to the ClinicalTrials.gov website will be in accordance with the FDA requirements for this registration and for publication of study results on that site.

14 STUDY ADMINISTRATION

14.1 Study Leadership

The study will be overseen by the Study Manager or designee who will be responsible, together with the Investigator, for tracking enrollment, timelines, and deliverables, and other study-related performance.

All questions regarding the enrollment of subjects, regulatory requirements for the conduct of the study, safety reporting, or study conduct should be addressed to the Study Manager or Site Monitor designated by the sponsor.

15 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical and therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. As required by the FDA, a Financial Disclosure Form will be completed by each person noted on the

Form FDA 1572 for this study at the site, the original will be filed in the TMF and a copy will remain in the site's regulatory binder.

16 LIABILITY AND INSURANCE

The sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. This insurance will cover all parties involved in the trial including, but not necessarily limited to, the principal Investigator, clinical trial site, and subjects.

17 LITERATURE REFERENCES

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