

# **Phase 2 Dose-Rising Study of SOR007 Ointment for Actinic Keratosis**

**Protocol Identifying Number: SOR007-2017-04**

**Principal Investigator: Reginold Simmons, MD**

**IND Number: 126915**

**IND Sponsor: DFB Soria, LLC**

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## LIST OF ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
FDA	The U.S. Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
LSR	Local Skin Reaction
NCI	National Cancer Institute
NDA	New Drug Application
PCA	Precipitation with Compressed Antisolvents
PK	Pharmacokinetics
SAE	Serious Adverse Event
SOC	System Organ Class
UP	Unanticipated Problem
WBC	White blood cell

**SPONSOR SIGNATURE PAGE**

**Protocol Title:** Phase 2 Dose-Rising Study of SOR007 Ointment for Actinic Keratosis  
**Protocol Number:** SOR007-2017-04  
**Version Number:** 2  
**Date:** 20 April 2017  
**IND Number:** 126915  
**Investigational Product:** SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment  
**Sponsor:** DFB Soria, LLC  
231 Bonetti Dr., Suite 240  
San Luis Obispo, CA 93401-7310  
805-595-1300

The Sponsor for IND 126915, DFB Soria, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to the IND; 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  
President & CEO, US Biotest, Inc.



Signature of Sponsor's Representative

24 April 2017

Date

## STATEMENT OF COMPLIANCE

I have read the attached protocol number SOR007-2017-04 entitled, *Phase 2 Dose-Rising Study of SOR007 Ointment for Actinic Keratosis*, Version 2.0 dated 20 April 2017 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 DFB Soria, LLC. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of DFB Soria, LLC. 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.

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Signature of Principal Investigator	Date
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Reginold Simmons, MD  
Printed Name of Principal Investigator

## PROTOCOL SUMMARY

**Title:** Phase 2 Dose-Rising Study of SOR007 for Actinic Keratosis

**Précis:** This is a Phase 2, randomized, double-blind, dose rising study to determine the safety, tolerability, and preliminary efficacy of four concentrations of SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment (SOR007) applied to actinic keratosis (AK) lesions twice daily for up to 28 days, compared to SOR007 Ointment Vehicle.

Subjects with AK will be enrolled in four dose-escalating cohorts of eight subjects assigned consecutively. Each cohort will be randomized to SOR007 or Ointment Vehicle in a ratio of 3:1. Dose escalation will be as follows:

- Cohort 1: Six subjects with 0.15% SOR007 Ointment topically applied to lesions;  
Two subjects with Ointment Vehicle topically applied to lesions;
- Cohort 2: Six subjects with 0.3% SOR007 Ointment topically applied to lesions;  
Two subjects with Ointment Vehicle topically applied to lesions;
- Cohort 3: Six subjects with 1% SOR007 Ointment topically applied to lesions;  
Two subjects with Ointment Vehicle topically applied to lesions;
- Cohort 4: Six subjects with 2% SOR007 Ointment topically applied to lesions;  
Two subjects with Ointment Vehicle topically applied to lesions;

Investigational product will be applied topically to a target AK lesion test field, a 25 cm<sup>2</sup> area on the face which contains 4-8 AK lesions, twice daily for up to 28 days, or until all lesions resolve. Investigational product will be applied with a gloved finger. The maximum total amount of investigational product that will be applied daily will be 1 finger-tip unit (FTU), approximately 0.5g. No more than 25cm<sup>2</sup>, approximately 0.15% of the total body surface area, will be treated.

Safety will be assessed in an ongoing manner and formal safety reviews will be conducted four times for each cohort: at Day 8, at Day 15, at Day 21 and at Day 28 for the last subject enrolled in each cohort. The next dose level cohort will enroll upon a finding of safety and tolerability at the previous cohort's second safety review.

Visit Schedule:

Screening visit: Within 14 days prior to the first application of investigational product the subject will have hematology and biochemistry laboratory samples taken and be assessed against enrollment criteria.

Day 1: Target AK lesion test field will be identified, assessed by the physician, and documented photographically. Suitability for enrollment will be confirmed. Study area will be photographed and mapped on a transparency. The subject will be randomized to treatment and have first application of investigational product. **The tube of IP will be weighed prior to dispensing.** Blood samples for pharmacokinetic (PK) analysis of paclitaxel plasma levels will be collected at 1 h, 2 h, 4 h, and 6 h post-first daily application. The subject will receive training on application and handling of investigational product which they will take home for self-application later that day and on subsequent days. The subject will maintain an application diary throughout the treatment period of the study.



Days 8, 15, 21: The subject will return to the clinic for assessment and documentation of target AK lesion test field and a single PK sample collection prior to first daily application of investigational product. A photograph will be taken and any changes on the transparency mappings will be recorded. The tubes of IP will be weighed.

Day 28: The subject will return to the clinic for assessment and documentation of the target AK lesion test field, PK sample collection, and application of investigational product. PK samples will be collected prior to first daily application and 1 h, 2 h, 4 h, 6 h, and 12 h post-first daily application. Hematology and biochemistry laboratory samples will be collected. A photograph will be taken and any changes on the transparency mappings will be recorded. The last application will occur following the 12 h PK sample collection. The tubes of IP will be weighed.

Day 43: The subject will return to the clinic for assessment and documentation of target AK lesion test field and a single PK sample collection. Hematology and biochemistry laboratory samples will be collected. A photograph will be taken and any changes on the transparency mappings will be recorded.

Day 56: The subject will return to the clinic for assessment and documentation of target AK lesion test field and a single PK sample collection. A photograph will be taken and any changes on the transparency mappings will be recorded.

Once the last cohort has completed the study, all available data, including safety, PK, and preliminary efficacy, will be analyzed. The PK blood samples will be analyzed per cohort when the last subject of each cohort completes Day 28.

**Objectives:**

Primary objective:

- To determine the safety and tolerability of topical SOR007 Ointment applied to AK lesions

Secondary objectives:

- To obtain preliminary determination of the efficacy of topical SOR007 Ointment applied to AK lesions
- To describe the pharmacokinetics of topical SOR007 Ointment applied to AK lesions

**Endpoints:**

Primary endpoint: Safety and tolerability as demonstrated by:

- Local toxicity
- Adverse events
- Laboratory assessments
- Vital signs
- Local skin reactions (LSR)

Secondary endpoints:

- Preliminary Efficacy: reduction in number of AK lesions and lesion size
- Systemic Exposure as determined by:  $T_{max}$ ,  $C_{max}$ , AUC

**Population:**

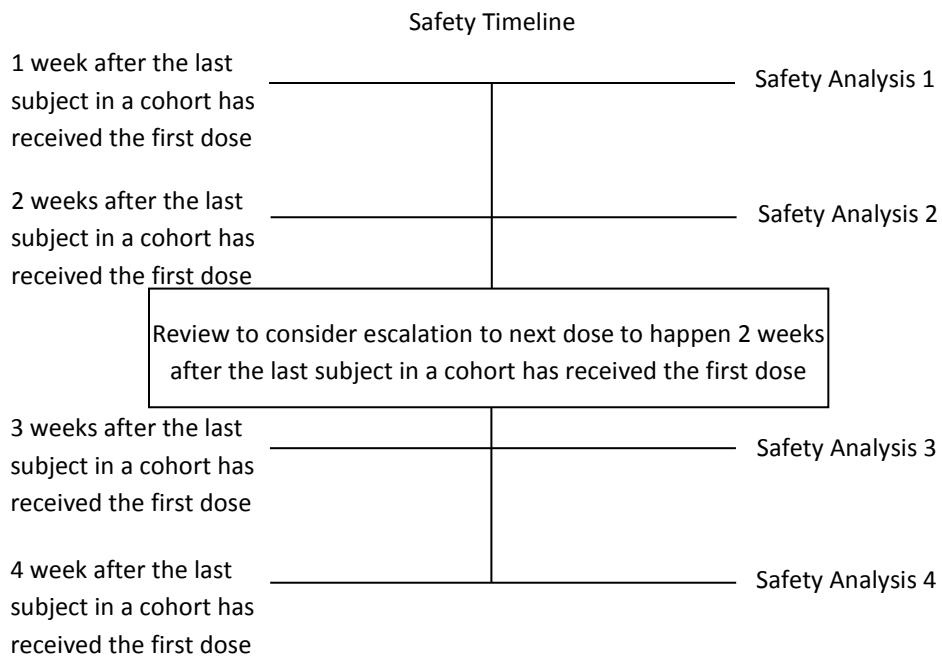
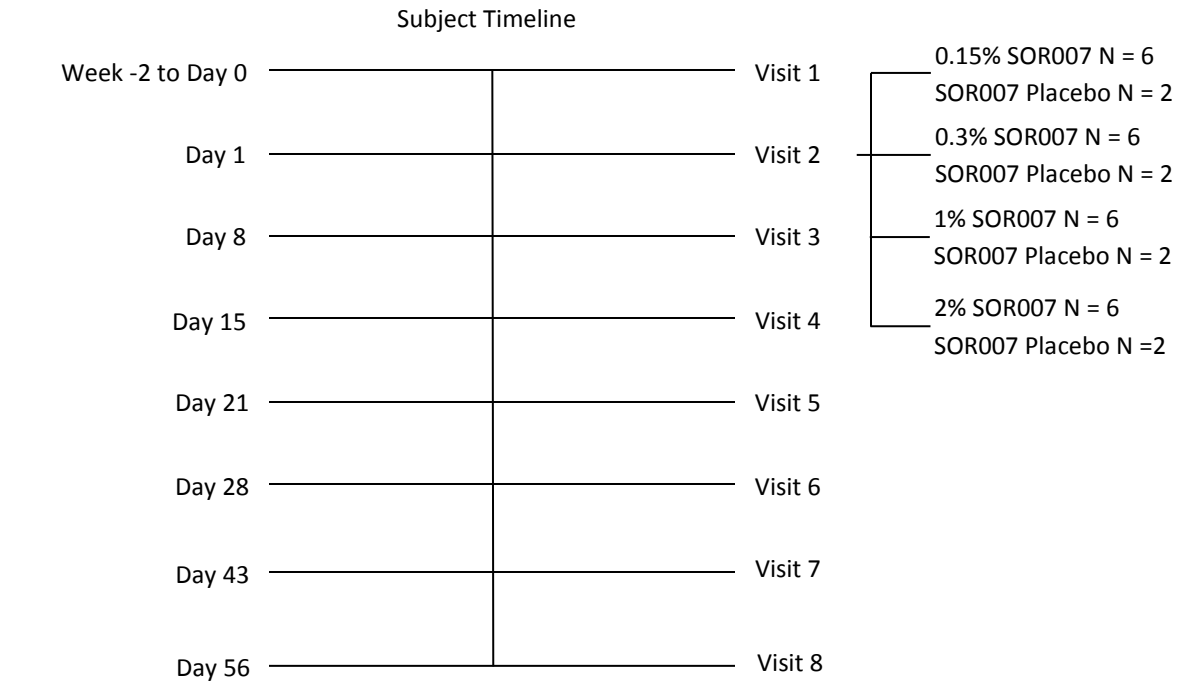
Up to 32 subjects with AK lesions.

**Phase:**

Phase 2

<b>Number of Sites enrolling participants:</b>	1
<b>Description of Study Agent:</b>	SOR007 Ointment Vehicle (active ingredient-free)  SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment 0.15 % (1.5 mg/g, 1.23 mg/mL paclitaxel, USP)  SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment 0.3 % (3 mg/g, 2.47 mg/mL paclitaxel, USP)  SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment 1.0 % (10 mg/g, 8.23 mg/mL paclitaxel, USP)  SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment 2.0 % (20 mg/g, 16.46 mg/mL paclitaxel, USP)
<b>Study Duration:</b>	The study duration will be up to approximately 10 months.
<b>Participant Duration:</b>	The participant duration is estimated to be 8 weeks for each subject.

**SCHEMATIC OF STUDY DESIGN**



## 1 KEY ROLES

### **Medical Director**

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## 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

The Sponsor for IND 126915, DFB Soria, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to the IND. In accordance with 21 CFR Part 312, US Biotest, Inc., shall be considered the sponsor with regard to all activities related to the IND. Therefore, references to “Sponsor” hereafter in this protocol refer to US Biotest, Inc.

### 2.1 BACKGROUND INFORMATION

**Name and description of study agent:**

Investigational drug product SOR007 (Uncoated Nanoparticle Paclitaxel) Ointment (SOR007) is being developed by US Biotest, Inc. ("US Biotest") for the topical treatment of actinic keratosis (AK). SOR007 is also being investigated for the topical treatment of moderate to severe plaque psoriasis in a Phase I clinical trial under IND 126915, Protocol SOR007-2016-01.

SOR007 contains a nanoparticulated uncoated paclitaxel powder (NanoPac®) created using a Precipitation with Compressed Antisolvent (PCA) technique that employs supercritical carbon dioxide and acetone to generate paclitaxel nanoparticles within a well-characterized particle-size distribution. SOR007 consists of this NanoPac suspended in an ointment vehicle (13% cyclomethicone 5, 5% mineral oil, and 5% paraffin wax in a white petrolatum base) that facilitates dermal absorption from topical application while maintaining particle size stability. 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.

**Nonclinical Summary:**

Nonclinical studies of SOR007 in animal models of AK have not yet been completed. The safety of NanoPac and SOR007 have been investigated in other nonclinical models and are presented in the SOR007 Investigator's Brochure. Numerous nonclinical studies were performed to establish the safety of paclitaxel formulated as Taxol® (see Taxol Package Insert).

Daily topical administration of SOR007 to Göttingen minipigs for 28 days applied at the maximal feasible volume of 2 mL/kg, at dose concentrations of 0.0, 0.3, 1.0, and 3% (0, 4.9, 16.5, and 49.9 mg/kg/day, respectively) was well tolerated (S07-TP-02-2015). There were no SOR007-related effects on survival, clinical signs, dermal irritation, body weights, body weight gains, food consumption, ophthalmic findings, or cardiology parameters. Dermal irritation was observed in all groups during the dosing phase and was considered vehicle or procedurally related as the frequency and severity of the findings were comparable between the placebo controls and SOR007-treated groups. SOR007-related effects on hematology parameters were limited to nonadverse, minimally to mildly lower RBC mass parameters, and reticulocytes on Day 29/30 that showed recovery during the 2-week reversal period. There were no SOR007-related changes in coagulation, clinical chemistry, or urinalysis parameters in main study phase or recovery animals. There were no gross or microscopic findings or differences in organ weights in the terminal or recovery groups that were attributed to administration of SOR007. 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. Day 28 combined-sex  $AUC_{0-24}$  values were 36.0, 85.5, and 149 ng·hr/mL at 4.9, 16.5, and 49.9 mg/kg/day, respectively. Based on these findings, the NOAEL was the high dose of 49.9 mg/kg/day.

**Clinical Summary:**

SOR007 has not been administered to humans for topical treatment of AK. A Phase 1 clinical trial, Protocol SOR007-2016-01, in plaque psoriasis has recently completed subject participation with no treatment related adverse events (AE) reported by the 13 subjects who had SOR007 applied topically under occlusion for up to 10 applications. The Phase I psoriasis plaque clinical trial is evaluating the anti-inflammatory efficacy of SOR007 in subjects with psoriasis vulgaris. 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<sup>2</sup>, or 0.03% total body surface area of a 1.6 m<sup>2</sup> 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<sup>2</sup> basis, the paclitaxel applied

topically over the 12-day study would be approximately 0.1 mg/kg (3.8 mg/m<sup>2</sup>) per day, or 1.0 mg/kg (38 mg/m<sup>2</sup>) total exposure for a 60-kg subject. The primary endpoint will be 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.

#### **Importance of the study:**

AK is a pre-cancerous skin disease that affecting approximately 58 million Americans (Lewin Group 2005). The progression of AKs occurs due to chronic sun exposure. Most AKs are found on places of the body that experience the most sun exposure (i.e. face, neck, back of hands). If left untreated, an estimated 10% of AKs will develop into squamous cell carcinoma (Fuchs 2007). SOR007 is being developed as an alternative to existing treatments for AK.

## **2.2 RATIONALE**

This Phase 2 study will include subjects with AK. The study design allows for a safety evaluation of topical application of SOR007 onto the face as topical therapy for AK. We hypothesize that topical application of SOR007 onto the face will result in limited, if any, systemic exposure to paclitaxel and should therefore result in only low-grade and transitory AEs. Birth control and abstinence from sexual contact requirements in the proposed study will protect participants and their partners.

## **2.3 POTENTIAL RISKS AND BENEFITS**

### **2.3.1 KNOWN POTENTIAL RISKS**

There is no known risk of SOR007 applied topically to AK.

### **2.3.2 KNOWN POTENTIAL BENEFITS**

There is no known benefit of SOR007 applied topically to AK.

## **3 OBJECTIVES AND PURPOSE**

The primary objective of this study is to evaluate the safety and tolerability of topical SOR007 ointment applied to the face in subjects with actinic keratosis (AK). Secondary objectives are (a) to determine preliminary efficacy of topical SOR007 ointment applied to AK; and (b) to determine the concentration of paclitaxel in the systemic circulation post-topical application.

## **4 STUDY DESIGN AND ENDPOINTS**

### **4.1 DESCRIPTION OF THE STUDY DESIGN**

The proposed study is a Phase 2, dose-rising, safety, and preliminary efficacy study. Subjects will have SOR007 topically applied to AK lesions.

Subjects will enroll in four dose-escalating cohorts of eight subjects each. Each cohort will be randomized to SOR007 or Ointment Vehicle in a ratio of 3:1. Safety will be assessed in an ongoing manner and formal safety

reviews will be conducted four times for each cohort: at Day 8, at Day 15, at Day 21 and at Day 28 for the last subject enrolled in each cohort. The next dose level cohort will enroll upon a finding of safety and tolerability at the previous cohort's second safety review. Any symptoms of systemic toxicity will be reviewed along with the routine safety assessments. In addition, special attention will be given to the onset of ulceration within the AK test field. Significant ulceration in more than 33% of the subjects in a cohort will be considered a dose limiting toxicity (DLT) and dose escalation will not be permitted.

- Cohort 1: Six subjects with 0.15% SOR007 ointment topically applied to lesions  
Two subjects with SOR007 vehicle topically applied to lesions
- Cohort 2: Six subjects with 0.3% SOR007 ointment topically applied to lesions  
Two subjects with SOR007 vehicle topically applied to lesions
- Cohort 3: Six subjects with 1% SOR007 ointment topically applied to lesions  
Two subjects with SOR007 vehicle topically applied to lesions
- Cohort 4: Six subjects with 2% SOR007 ointment topically applied to lesions  
Two subjects with SOR007 vehicle topically applied to lesions

Once the last cohort has completed the study, all available data, including safety, PK, and preliminary efficacy, will be analyzed. The PK blood samples will be analyzed per cohort when the last subject of each cohort completes Day 28.

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#### 4.2.1 PRIMARY ENDPOINT

The primary endpoint will be safety and tolerability, as assessed by adverse events, changes in vital signs, laboratory results, and physical examination of the test field for local skin reactions (LSR).

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#### 4.2.2 SECONDARY ENDPOINTS

The secondary endpoints will be:

- Preliminary efficacy of topical SOR007 ointment applied to AK by change in number and size of AK lesions.
- Concentration of paclitaxel in the systemic circulation post-topical application.

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#### 4.2.3 EXPLORATORY ENDPOINTS

Not applicable.

## 5 STUDY ENROLLMENT AND WITHDRAWAL

### 5.1 PARTICIPANT INCLUSION CRITERIA

Subjects who meet the following criteria will be considered eligible for participation in the study:

- Signed informed consent.

- Men and women with presence of actinic keratosis.
- Age 45-85 years, inclusive.
- Women who have had surgical sterilization or are post-menopausal (absence of menses for at least one year) are eligible. Women of child-bearing potential who are non-pregnant and non-nursing, and willing to avoid pregnancy during the course of the study and during the menstrual cycle following completion of their participation in the study are eligible. (Adequate contraception is defined as regular use of diaphragm with condoms, IUD with condoms, or systemic contraceptives – if used for at least three months prior to enrollment in the study). A negative pregnancy test is required as an entry criteria. Women must continue to use the method of contraceptive for 30 days after the last study drug administration.
- Male subjects must agree to sexual abstinence or use adequate contraception when sexually active in combination with their female partners, if they are of childbearing potential. That means the volunteer must be vasectomized or use a condom and his female partner must either be surgically sterile (hysterectomy or tubal ligation) or agree to use a reliable method of contraception with a failure rate of less than 1 % per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, or non-Dalkon Shield intra uterine devices [IUDs]. This applies from signing of the informed consent form until 90 days after the last study drug administration. Methods of contraception must have been effective for at least 30 days on the day of signing the informed consent form. Male volunteers must also refrain from sperm donation from signing of the informed consent form until 90 days after the last study drug administration.
- Presence of 4-8 AK lesions total in a 25 cm<sup>2</sup> area identified on the face through transparency mapping and photographs. The face area will be defined from hair line to jaw line. The scalp will not be included. An imaginary normal hair line will be the upper boundary for bald men. Lesions that are thicker than 1 mm (a piece of paper) or larger than 9 mm will not be included in lesion counts. Lesions suspicious for squamous cell carcinoma, basal cell carcinoma, or melanoma will not be included in lesion counts and cannot be in the 25 cm<sup>2</sup> area of treatment.
- Able to refrain from the use of all other topical medications to the facial area during the treatment period.
- Considered reliable and capable of understanding their responsibility and role in the study.

## 5.2 PARTICIPANT EXCLUSION CRITERIA

If a subject meets any of the following criteria, they must be excluded from the study:

- History of allergy or hypersensitivity to paclitaxel.
- Abnormal pre-existing dermatologic condition which might affect the normal course of the disease (e.g., albinism, or chronic vesiculobullous disorders).
- Positive urine pregnancy test in women of child-bearing potential.
- Inability to use adequate birth control measures for men or women of child-bearing potential, as defined above.
- Serious psychological illness.
- Significant history (within the past year) of alcohol or drug abuse.
- During the 30 day period preceding study entry:
  - Participating in any clinical research
  - Using topical paclitaxel as treatment for AK



- Using any other topical agents including but not limited to actinex, glycolic acid products, alpha-hydroxy acid products, and chemical peeling agents for treatment of AK
- Using any systemic steroids or topical corticosteroids
- Having cryosurgery (cryotherapy on extremities is acceptable)
- Use of sun lamps or sun tanning beds or booths during the 2 weeks prior to first application until final visit.
- Prior treatment with systemic paclitaxel or systemic cancer therapy within 6 months of study entry.
- Medical history which, based on the clinical judgement of the Investigator, implies an unlikelihood of successful completion of the study.

### 5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Sufficient subjects will be screened to allow for up to 32 subjects to be enrolled in the Phase 2 study. Subjects will be recruited from the Principal Investigator's clinic. Advertising may be required for recruiting to the study. Subjects will be recruited and screened for eligibility and will proceed to treatment.

Following successful screening, the eight subjects of the first cohort will be treated (at the lowest dose or vehicle) daily for a total of 56 treatments (twice daily for 28 days) per subject. Subjects will be followed for four weeks after their last application. During the study, the subjects will be monitored for safety and tolerability. Safety will be assessed in an ongoing manner and formal safety reviews will be conducted four times for each cohort: at Day 8, at Day 15, at Day 21 and at Day 28 for the last subject enrolled in each cohort.

- If the Medical Monitor concludes it is acceptable to proceed to the next cohort, the next cohort will begin screening.
- If the preceding dose elicits an unfavorable safety and/or tolerability profile in a subject, as determined by the Medical Monitor, the escalation to the next dose is not permitted at that time.

Escalation of dosing to the highest concentration in the study (2% SOR007) will proceed as described above in groups of eight subjects. Once the last cohort has completed the study, all available data, including safety, PK, and preliminary efficacy, will be reviewed.

Accrual of subjects will occur over a period of 10 months.

### 5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

#### 5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. Their reason for wanting to withdraw will be documented in the source notes and in the Electronic Data Capture system (EDC).

A subject who is not suitable to be treated will be withdrawn prior to Day 1 (Baseline/Treatment), and therefore in all study documentation this subject would be considered a Screenfail Subject.

- Clinical AE, laboratory abnormalities, or other medical conditions/situations may occur which would usually require withdrawal from a study. In this instance it is very important that all of these events be

captured, followed, and documented, and therefore a subject would be withdrawn from treatment but would continue through the follow up period and completion.

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

Subjects that miss more than 2 consecutive days of ointment application should be considered non-compliant and be withdrawn from the study.

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#### 5.4.2 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, as 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 (End-of-Study evaluations) which include vital signs, AE collection and concomitant medication updates.

In the event a subject does not attend a visit/visits and is unable to be contacted, then they should be considered lost-to-follow-up. Reasonable and diligent attempts such as dates and content of phone calls, emails and registered mail should be recorded in the subject's record.

If a subject repeatedly misses study visits or remains non-compliant between the time of topical SOR007 ointment application and the end of study visit, 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 will still be used in the safety evaluations in this study. A new subject will be enrolled into the study and the withdrawn subject will not be included in the cohort number count.

Treatment compliance will be verified by use of the subject diaries and by IP tube weights pre- and post-dose. Subjects must apply SOR007 for at least 75% (11 doses) and not more than 125% (17 doses) of expected doses per week to be considered compliant with the treatment regimen. Anyone who missed the prescribed applications for more than 2 consecutive days should be considered non-compliant and withdrawn.

#### 5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is 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.

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

## 6 STUDY AGENT

### 6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

#### 6.1.1 ACQUISITION

SOR007 will be manufactured by Dow Development Laboratories (DDL) and provided for use in this study. Study agent will not be shipped to the study site until all Regulatory Documentation has been provided by the site, at which time the study agent 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 Site Initiation. Study Agent will be shipped to the on-site Pharmacy where it will be stored according to the conditions required (see 6.1.3)

#### 6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

SOR007 is presented as an off-white ointment, provided in a sealed, 15 g laminate tube.

The tube label will at a minimum include:

Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).

For Topical Dermatological Use Only. 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, Suite 240, San Luis Obispo, CA 93401

#### 6.1.3 PRODUCT STORAGE AND STABILITY

Prior to administration at the hospital/clinic, the SOR007 tubes will be stored at the Pharmacy, temperature controlled at 68° to 77°F (20° to 25°C).

#### 6.1.4 PREPARATION

Not applicable.

#### 6.1.5 DOSING AND ADMINISTRATION

Treatment will be applied to the lesions twice daily for up to 28 days. A maximum of 1/2 finger-tip unit (FTU) of ointment will be applied for each application. 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. A FTU will cover up to 50 cm<sup>2</sup> of body surface area.

#### 6.1.6 ROUTE OF ADMINISTRATION

SOR007 will be applied topically to the target AK lesion test field.

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### 6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

SOR007 concentrations of 0.15% (1.23 mg/mL), 0.3% (2.47 mg/mL), 1% (8.23 mg/mL), and 2% (16.46 mg/mL), or ointment vehicle will be administered. Each application will be 0.5 g (1/2 FTU). Cohorts will be enrolled sequentially starting at the lowest concentration. Each cohort will start with a planned minimum of eight subjects, each receiving the SOR007 or vehicle ointment. Dose escalation to the next cohort will proceed following review of data by the Medical Monitor as appropriate. Special attention will be given to the onset of ulceration within the AK test field. Significant ulceration in more than 33% of the subjects in a cohort will be considered a DLT and dose escalation will not be permitted.

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### 6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

The decision to make dose adjustments to a subject's treatment schedule will only be made after consultation with the medical monitor and as agreed upon with the medical monitor. Any symptoms of systemic toxicity will be reviewed along with the routine safety assessments.

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### 6.1.9 DURATION OF THERAPY

Fifty-six applications of SOR007 will be administered over four weeks. Subjects will then be followed for four weeks after last application.

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### 6.1.10 TRACKING OF DOSE

The subject will maintain an application diary and ointment tubes will be weighed at each applicable visit.

On Day 1, the subject will receive two tubes of ointment. The tubes will be weighed before being dispensed. One tube will be opened and used for the first application and the subject will be instructed to continue using the open tube for the ointment applications. If the open tube is finished prior to the next visit, the subject can use the second (back up) tube until the next visit. The subject will bring in both tubes for the next visit and both tubes will be weighed.

- If only one tube has been used it will be replaced with a new tube (weighed prior to dispensing) for the following week, and the first application from the new tube will be made at the site. The subject will still have the back-up tube to take home again in case the first tube is emptied prior to the next visit.
- If one tube was emptied and the second tube opened and used during the week, the empty tube will be retained at the site. The subject will be dispensed a replacement back-up tube (weighed prior to dispensing) and instructed to continue using the tube which has already been opened and used before using the newly provided back-up tube.

This process will be repeated at each study visit until the visit on Day 28.

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### 6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

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## 6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The Investigator will maintain adequate records showing the receipt, dispensing, return, or other disposition of the investigational drug, including the date, quantity, batch or code number, and identification of subjects (number, initials) who received study medication.

Accountability will be conducted on the individual tubes.

The used tubes will be retained in the Pharmacy for accountability purposes, and will not be disposed of until confirmation is received from the Sponsor that accountability is completed. Tubes will be weighed pre- and post-dose at each visit.

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 the consent of the sponsor.

## 7 STUDY PROCEDURES AND SCHEDULE

### 7.1 STUDY PROCEDURES/EVALUATIONS

#### 7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures and evaluations will be done as part of this study.

- Complete medical history to be completed, documented, and reviewed by the Investigator within 14 days prior to SOR007 administration, including review of previous medical records, demographics, and parity;
- Review and documentation of concomitant prescription and non-prescription medications;
- Review and documentation of diagnosis of AK and previous treatments;
- Female subjects will be required to take a pregnancy test at screening and on Days 1, 28, and 56;
- Comprehensive physical examination and vital signs (blood pressure, heart rate, temperature);
- Blood samples will be taken during the Screening Visit and on Days 28 and 43 to measure white blood cell (WBC), hemoglobin, platelet count, liver function (total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and prothrombin);
- PK blood samples will be taken on Days 1, 8, 15, 21, 28, 43, and 56. For Day 1, blood will be taken at 1 h, 2 h, 4h, and 6 h post initial application of SOR007. For Days 8, 15, and 21, blood will be taken prior to first daily application of SOR007. For Day 28, blood will be taken prior to first daily application and 1 h, 2 h, 4 h, 6 h and 12 h post first daily application of SOR007. For Days 43 and 56, blood will be taken at the beginning of the follow-up visit. PK samples within the first 4 hours on days 1 and 28 will allow for a 10-minute window around the samples. The remaining samples within the first 24 hours will allow for a 30-minute window;
- LSR evaluation will be performed by the evaluator. LSR will be performed to monitor the AK lesions in the test field as a whole through the evaluation of erythema, crusting, swelling, vesiculation/postulation, erosion/ulceration, hyperpigmentation, and hypopigmentation;
- SOR007 or vehicle ointment to be applied topically to the target AK lesion test field. twice daily for up to 28 days. Subjects will be assessed using a 25 cm<sup>2</sup> treatment area containing 4-8 AK lesions. AK lesions will be notated on a transparency along with landmarks to help the investigator distinguish old and new AK's throughout the subject's participation in the trial. Photographs of the treatment area will also be used to help the investigator in distinguishing between different AK lesions and the status of these lesions

throughout the study subjects' participation. The investigator will monitor the status of these AK lesions to ensure that the subject is safe to continue participation in the trial.

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### 7.1.2 STANDARD OF CARE STUDY PROCEDURES

For any treatment of AK outside the treatment field, the subject will be referred to their primary care provider. Should a lesion in the treatment field progress to a more serious lesion, i.e. squamous cell carcinoma or basal cell carcinoma, the subject will be withdrawn from the study and referred to their primary care provider for course of treatment. All attempts will be made to follow-up with the subject and to get a resolution for the lesion.

## 7.2 LABORATORY PROCEDURES/EVALUATIONS

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### 7.2.1 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory assessments performed at screening/baseline, Day 28, and Day 43 are noted in Section 7.1.1 and all of these tests will be conducted at the local CLIA certified laboratory routinely used by the Investigator.

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### 7.2.2 OTHER ASSAYS OR PROCEDURES

PK samples will be taken on Days 1, 8, 15, 21, 28, 43, and 56. For Day 1, blood will be taken at 1 h, 2 h, 4 h, and 6 h post initial application of SOR007. For Days 8, 15, and 21, blood will be taken prior to daily application of SOR007. For Day 28, blood will be taken prior to daily application and 1 h, 2 h, 4 h, 6 h, and 12 h post first initial application of SOR007. For Days 43 and 56, blood will be taken at the beginning of the follow-up visit. Subjects will return for a final visit on Day 56. PK samples within the first 4 hours on days 1 and 28 will allow for a 10-minute window around the samples. The remaining samples within the first 24 hours will allow for a 30-minute window.

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### 7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

PK samples will be drawn at the specified time/visit and stored frozen on-site until a cohort has completed all day 28 draws for analysis, at which time each cohort blood samples will be batch-shipped to Covance Laboratories for analysis. Procedures for processing for storage will be provided prior to study initiation. PK samples from days 43 and 56 will be sent with the next cohort PK samples. For the last cohort all samples will be shipped after the day 56 samples are collected.

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### 7.2.4 SPECIMEN SHIPMENT

Not applicable.

## 7.3 STUDY SCHEDULE

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### 7.3.1 VISIT 1/SCREENING

The following procedures and assessments must be completed, documented and reviewed by the Investigator during the screening period, within 14 days prior to the application of investigational product:

- Written informed consent including comprehensive discussion of the study schedule, procedures and subject protocol requirements.
- Complete medical history, including review of previous medical records, demographics and parity.
- Complete physical examination.
- Vitals will be collected.
- Review and documentation of AK diagnosis and previous treatments. If the site is unable to retrieve the past medical records containing a confirmed diagnosis for facial AK, it is acceptable for the site to document patient self-reporting with the Investigator making the diagnosis for facial AK at screening.
- LSR performed by the evaluator. LSRs will be performed to monitor the AK lesions in the test field as a whole through the evaluation of erythema, crusting, swelling, vesiculation/postulation, erosion/ulceration, hyperpigmentation, and hypopigmentation as seen in the table below:

Local Skin Response	Grading Criteria				
	0	1	2	3	4
Erythema	Not present	Slightly pink < 50%	Pink or light red > 50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking / Scaling	Not present	Isolated scale, specific to lesion	Scale < 50%	Scale > 50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting < 50%	Crusting > 50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	Marked swelling extending outside treatment area
Vesiculation / Pustulation	Not present	Vesicles only	Transudate or pustules, with or without vesicles < 50%	Transudate or pustules, with or without vesicles > 50%	Transudate or pustules with or without vesicles extending outside treatment area
Erosion / Ulceration	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion > 50%	Black eschar or ulceration
Hyperpigmentation		Present	Not Present		
Hypopigmentation		Present	Not Present		

- If applicable, a copy of the histology report confirming the diagnosis must be filed in the subject's study record.
- Blood samples for WBC, hemoglobin, platelet count, total bilirubin, AST, ALT, BUN, creatinine, and prothrombin.
- Review and documentation of all concomitant prescription and non-prescription medications.
- Female subjects of child bearing potential will take a urine pregnancy test.
- Review of inclusion and exclusion criteria and determination of eligibility.

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### 7.3.2 ENROLLMENT/BASELINE

#### **Day 1/Visit 2 – Baseline and Treatment – Day of 1<sup>st</sup> SOR007 Ointment Treatment**

Following review of all test results from the Screening Visit, the following will be conducted:

- Review of inclusion and exclusion criteria and determination of eligibility to proceed to treatment.
- Female subjects of child bearing potential will take a urine pregnancy test prior to treatment.
- The target AK lesion test field on the face will be identified. A 25 cm<sup>2</sup> area of skin mapped by transparency tracing and photos with 4-8 AK lesions will be the application field. A copy of the photograph will be given to the subject to help identify where to apply the medication as instructed by the Investigator. The baseline photograph will be used at the final visit to allow the Investigator to accurately compare exactly all the keratosis recorded if they are clear, or still present. The transparency will be photocopied for records.
- All AKs in the application field will be counted by the Investigator at baseline.
- LSR performed by the evaluator.
- Vitals will be collected.
- The subject will be randomized to treatment and have first daily application of investigational product.
- Two tubes will be weighed before being dispensed. One tube will be opened and used for the first application and the subject will be instructed to continue using the open tube for the ointment applications.
- PK samples will be collected at 1 h, 2 h, 4 h, and 6 h after initial application.
- Concomitant medication will be reviewed and updated as necessary.
- AEs prior to this visit will be considered as medical history; from this visit forward will be collected and recorded in the AE forms.
- Subjects will be given the following instructions for investigational product application:
  - Subject will wash their application test field every morning and night, wait 10 minutes and then lightly apply the given test medication to the application field for 28 days.
  - Subject will continue to use the open tube for ointment applications. If the open tube is finished prior to the next visit, the subject can use the second (back-up) tube until the next visit. The subject will bring both tubes for the next visit.
  - Subject will apply the medication cream with a gloved finger and must wash their hands thoroughly after each application. The gloves can be discarded in regular trash.
  - Subject will be instructed to apply a maximum of 1/2 finger-tip unit (FTU) of ointment for each application. 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. A FTU will cover up to 50 cm<sup>2</sup> of body surface area (Finlay 1989; Long 1992).

- Subject will avoid contact with the eyes, eyelids, nostrils, and mouth. If there is contact with the specified areas, the subject should wash the area of contact with cold water.
- Subjects may use their own moisturizer to areas not treated and use make-up on areas not treated.
- Subject will be advised that some subjects using active ingredient may develop skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of the skin), and swelling. If irritation occurs at the application site, it may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy. The subject is allowed to cover the area with loose, light dressing while in public.
- Subject will be instructed to not apply any other prescription medication or moisturizer to the treatment area during the study.
- Subject will be instructed to keep a careful diary of the number of applications during the study.
- Subject will be advised that if at any point the lesion begins to ulcerate to stop application of SOR007 on that lesion and to schedule a visit with the Investigator immediately.
- Subjects will be given the following instructions for storage and handling of SOR007:
  - Store at 20-25°C (68-77°F); excursions permitted between 15-30°C (59-86°F).
  - For Topical Dermatological Use Only. Keep out of the reach of children.

#### **Day 8/Visit 3; Day 15/Visit 4; Day 21/Visit 5**

Subjects will return to the clinic for the following evaluations and procedures:

- All AKs in the application field will be counted by the Investigator.
- LSR performed by the evaluator.
- Vitals will be collected.
- Treatment compliance will be verified by use of the subject diaries. Subjects must apply SOR007 for at least 75% (11 doses) and not more than 125% (17 doses) of expected doses per week to be considered compliant with the treatment regimen. Anyone who missed the prescribed application for more than 2 consecutive days should be considered non-compliant and withdrawn.
- A photograph will be taken and any changes on the transparency mappings will be recorded. The transparency will be photocopied for records.
- Both tubes will be collected and weighed. If only one tube has been used it will be replaced with a new tube (weighed prior to dispensing) for the following week, and the first application from the new tube will be made at the site. The subject will still have the back-up tube to take home again in case the in use tube is emptied prior to the next visit. If one tube was emptied and the second tube opened and used during the week, the empty tube will be retained at the site. The subject will be dispensed a replacement back-up tube (weighed prior to dispensing) and instructed to continue using the tube which has already been opened and used before using the newly provided back-up tube. A tube can be reissued if sufficient ointment remains to treat for 1 week, approximately 4 g of ointment.
- Concomitant medication will be reviewed and updated as necessary.
- A single PK sample will be collected prior to first daily application of investigational product.

- Subject will receive first daily application of investigational product.
- AEs will be reviewed and updated as necessary.

The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject well-being.

#### **Day 28/Visit 6 – End of Treatment**

Subjects will return to the clinic for the following evaluations and procedures:

- Female subjects of child bearing potential will take a urine pregnancy test prior to treatment.
- All AKs in the application field will be counted by the Investigator.
- LSR performed by the evaluator.
- Vitals will be collected.
- Treatment compliance will be verified by use of the subject diaries. Subjects must apply SOR007 for at least 75% (11 doses) and not more than 125% (17 doses) of expected doses per week to be considered compliant with the treatment regimen. Anyone who missed the prescribed application for more than 2 consecutive days should be considered non-compliant and excluded from analysis.
- A photograph will be taken and any changes on the transparency mappings will be recorded. The transparency will be photocopied for records.
- The tubes of investigational product will be weighed and collected.
- Concomitant medication will be reviewed and updated as necessary.
- Subject will receive application of investigational product.
- PK samples will be collected prior to first daily application and 1 h, 2 h, 4 h, 6 h, and 12 h post first daily application of investigational product.
- The last application will occur following the 12 h PK sample collection.
- Blood samples for WBC, hemoglobin, platelet count, total bilirubin, AST, ALT, BUN, creatinine, and prothrombin.
- AEs will be reviewed and updated as necessary.

The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject well-being.

#### **Day 43/Visit 7**

Subjects will return to the clinic for the following evaluations and procedures:

- A single PK sample will be collected at the beginning of the visit.
- All AKs in the application field will be counted by the Investigator.
- LSR performed by the evaluator.
- Vitals will be collected.
- The baseline photograph will be used at the visit to allow the Investigator to accurately compare all the keratosis recorded if they are clear, or still present.
- A photograph will be taken and any changes on the transparency mappings will be recorded. The transparency will be photocopied for records.

- The percent of lesions cleared will be determined. (Change in lesion counts will be determined by subtracting the final counts from the initial counts i.e.  $7(\text{initial}) - 4(\text{final}) = 3$ ). Partially cleared lesions are counted as still present in final count. A cleared actinic keratosis lesion is defined as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin.
- Blood samples for WBC, hemoglobin, platelet count, total bilirubin, AST, ALT, BUN, creatinine, and prothrombin.
- Concomitant medication will be reviewed and updated as necessary.
- AEs will be reviewed and updated as necessary.

The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject well-being.

#### **Day 56/Visit 8 – Final Visit**

Subjects will return to the clinic for the following evaluations and procedures:

- Female subjects of child bearing potential will take a pregnancy test.
- A single PK sample will be collected at the beginning of the visit.
- All AKs in the application field will be counted by the Investigator at final visit.
- LSR performed by the evaluator.
- Vitals will be collected.
- The baseline photograph will be used at the visit to allow the Investigator to accurately compare all the keratosis recorded if they are clear, or still present.
- A photograph will be taken and any changes on the transparency mappings will be recorded. The transparency will be photocopied for records.
- The percent of lesions cleared will be determined. (Change in lesion counts will be determined by subtracting the final counts from the initial counts i.e.  $7(\text{initial}) - 4(\text{final}) = 3$ ). Proportion of subjects who have 100% clearance will be the primary efficacy endpoint. Partially cleared lesions are counted as still present in final count. A cleared actinic keratosis lesion is defined as either no evidence of the lesion, or only residual smooth flat redness present without elevation above the skin.
- Concomitant medication will be reviewed and updated as necessary
- AEs will be reviewed and updated as necessary.

The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject well-being.

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#### **7.3.3 FOLLOW-UP**

The subject's participation in the study will end following their final study visit. Subjects who have lesions that are still present at the last visit will be advised to see a dermatologist or their general medical doctor for further evaluation.

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#### **7.3.4 FINAL STUDY VISIT**

The final study visit will occur four weeks following the last application of SOR007. At this time the subject will exit the study with no further follow-up requirements unless there are ongoing and study related AEs (see Section 8.3).

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#### 7.3.5 EARLY TERMINATION VISIT

In the event a subject is withdrawn they would, at minimum, undergo End of Treatment visit evaluations, which include vital signs, AE collection, concomitant medication updates, LSR evaluations, and blood samples. 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 far as possible, and the least amount of information that would be captured are the vitals, AEs, concomitant medications, LSR evaluations, and blood samples. Blood samples will be sent to the local laboratory to test for WBC, hemoglobin, platelet count, total bilirubin, AST, ALTL, BUN, creatinine, and prothrombin.

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#### 7.3.6 UNSCHEDULED VISITS

Any unscheduled visits will be documented in the source, and any assessments and/or evaluations performed will be noted and reviewed. If the unscheduled visit occurs between the time of dosing but prior to end of study, the following assessments should be conducted and entered into the EDC to monitor the ongoing safety of the subject:

- Vital signs will be obtained;
- AE will be recorded;
- Concomitant medication will be reviewed and updated as necessary.

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 for blood work to be done this information will be filed in the source and be available if required at a later date, but laboratory results will not be transcribed into the EDC.

7.3.7 SCHEDULE OF EVENTS TABLE

	Screening Clinic Visit	Day 1	Day 8 (±2 days)	Day 15 (±2 days)	Day 21 (±2 days)	Day 28 (±2 days)	Day 43 (±2 days)	Day 56 (±2 days)
<b>Informed Consent</b>	X							
<b>History<sup>1</sup></b>	X							
<b>Physical Examination</b>	X							
<b>Inclusion/Exclusion</b>	X	X						
<b>Concomitant Therapy</b>	X	X	X	X	X	X	X	X
<b>Blood Samples</b>	X					X	X	
<b>Vital Signs</b>	X	X	X	X	X	X	X	X
<b>Assessment of LSRs</b>	X	X	X	X	X	X	X	X
<b>AK Lesion Count in Treatment Field</b>		X	X	X	X	X	X	X
<b>PK Samples<sup>2</sup></b>		X	X	X	X	X	X	X
<b>Pregnancy Test for Female Subjects</b>	X	X				X		X
<b>Photographs</b>	X	X	X	X	X	X	X	X
<b>Transparency Mapping</b>		X	X	X	X	X	X	X
<b>Examination of AK</b>	X	X	X	X	X	X	X	X
<b>Adverse Events<sup>3</sup></b>		X	X	X	X	X	X	X
<b>End of Study</b>								X <sup>4</sup>

<sup>1</sup> History includes all events before initiation of SOR007 treatment.

<sup>2</sup> For Day 1, PK samples will be collected at 1 h, 2 h, 4 h, and 6 h post application first daily application. For Days 8, 15, and 21, PK samples will be collected prior to daily application. For Day 28, PK samples will be collected prior to final application and 1 h, 2 h, 4 h, 6 h and 12 h post first daily application. For Days 43 and 56, PK samples will be collected at the beginning of the visit. PK samples within the first 4 hours will allow for a 10-minute window around the samples. The remaining samples within the first 24 hours will allow for a 30-minute window.

<sup>3</sup> Adverse event determination will start immediately following initiation of study treatment.

<sup>4</sup> AEs and concomitant medications at the Week 4 follow-up that are still active will be followed.

#### 7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not applicable.

#### 7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (eCRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

#### 7.6 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

#### 7.7 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Use of concomitant chemotherapy (other than the protocol specified agents), immunotherapy, or radiation therapy, at any time prior to end of study is prohibited.

Although no interaction studies have been conducted using SOR007, according to the [Taxol Package Insert](#), paclitaxel is metabolized by cytochrome P450 isozymes CYP2C8 and CYP3A4. 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). Use of prohibited medication is only of concern in the target AK lesion field.

#### 7.8 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

#### 7.9 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Not applicable.

#### 7.10 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable.

### 8 ASSESSMENT OF SAFETY

## 8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety assessments being conducted in this study include:

- AE, collected at all study visits from the time of dosing
- Laboratory findings
- Changes in concomitant medications and
- Findings from dermatological 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.

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### 8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended change in structure, function, signs, or symptoms temporally associated with the use of a medicinal product, whether or not related to the product. Undesirable changes in laboratory values should not be considered AEs unless they are considered symptomatic of a clinical condition or diagnosis, are evaluated as clinically significant or require therapy. Worsening of a pre-existing condition is also considered an AE as is the discovery of an abnormal finding during physical exam that was not included in the medical history. Clinical conditions attributable to disease progression will be considered AEs and reported on the eCRF.

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### 8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event (SAE) is any adverse event that meets at least one of following criteria:

- Is fatal;
- Is life threatening, meaning the subject was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
- Is a persistent or significant disability or incapacity;
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization that is longer than 24 hours, or a hospitalization that requires an intervention to treat emergent symptomatology (non-diagnostic);
- Is a congenital anomaly or birth defect;
- Other important medical events may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes as listed in this definition.

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### 8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

As this is a Phase 2 study all unanticipated problems will be captured as either AEs or SAEs and will be defined and reported accordingly.

## 8.2 CLASSIFICATION OF AN ADVERSE EVENT

### 8.2.1 SEVERITY OF EVENT

Signs and symptoms will be graded by the Investigator as mild, moderate, severe, or life threatening according to the following definitions:

- **Mild:** Causing no limitation of usual activity
- **Moderate:** Causing some limitations of usual activities
- **Severe:** Causing inability to carry out usual activities
- **Life Threatening:** Subject was at immediate risk of death from the event
- **Fatal:** Death related to the event.

Toxicities should be evaluated according to the NCI CTCAE, version 4.0.

[https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

Toxicity grades should be recorded as: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life Threatening, 5 = Fatal.

### 8.2.2 RELATIONSHIP TO STUDY AGENT

Events will be considered drug-related if classified by the Investigator as possible, probable, or definite.

Association of events to the study drug will be made using the following definitions:

- No relationship to study drug: the event is not associated with study drug.
- Possibly related to study drug: the event follows a reasonable temporal association with the study drug administration, however could have been produced by the subject's clinical condition or other therapy.
- Probably related to study drug: the event follows a) a reasonable temporal association with the study drug administration, but b) abates upon discontinuation of study drug and c) cannot be explained by the subject's clinical condition or other therapy.
- Definitely related to study drug: the event: a) follows a reasonable temporal association with the study drug administration, but b) abates upon discontinuation of study drug, c) cannot be explained by the subject's clinical condition or other therapy, and d) reappears on re-exposure to study drug.

### 8.2.3 EXPECTEDNESS

Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent, in the protocol and within the Investigator's Brochure.



### 8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

AE should be followed until resolved, stabilized or, if ongoing at End-of-Study (study-related AEs only), for a minimum of 30 days following the termination of the subject's participation from the study for any reason. Subjects will be required to spontaneously report any AE. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented.

All AEs and SAEs must be followed until the event resolves or, in the opinion of the Investigator, becomes stable.

The sponsor will report any serious, unexpected and drug-related AE to applicable regulatory agencies and make these reports available to the investigative sites. The Investigator must promptly inform the IRB of such events and retain a copy of the notification in the site's regulatory binder.

### 8.4 REPORTING PROCEDURES

#### 8.4.1 ADVERSE EVENT REPORTING

All AE (whether or not attributable to the investigational agent) occurring during the study observed by the Investigator or reported by the subject will be recorded on the eCRF. The following information will be recorded for all AE:

- Name of condition/diagnosis/description
- Onset and resolution dates
- Severity
- Relationship to Investigational Agent
- Action taken
- Seriousness

#### 8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs, including death, due to any cause which occurs during this study between the period of dose administration and end of study (occurring 28 days after last application), 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, by fax and, if necessary, by phone to:

Antony Verco, MD  
Medical Monitor  
Email: [tony.verco@usbiotest.com](mailto:tony.verco@usbiotest.com)  
Phone: 805-762-4615  
Fax: 805-980-4196

24-hour Emergency Contacts:      Gere diZerega, MD                  or      Antony Verco, MD  
   Medical Director                  Medical Monitor  
   805-630-2800                  805-762-4615

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 notification if available:

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

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#### 8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that occur during the conduct of the study, meeting the criteria for an AE or SAE, will be captured in the source documents and in the EDC, and in the case of an SAE also on the formal reporting form designed to capture the required information. Reporting of these events will be in accordance with the rules around AE and SAE reporting described in the protocol, including notification of the IRB and/or the FDA as required.

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#### 8.4.4 EVENTS OF SPECIAL INTEREST

Of particular interest will be signs of local toxicity; persistent erythema, ulceration, excessive pruritus. Additionally, systemic toxicity (i.e. peripheral neuropathy, neutropenic fever, excessive bleeding) due to paclitaxel exposure will be monitored; this is not expected and is unlikely due to the mode of administration and dose levels.

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#### 8.4.5 REPORTING OF PREGNANCY

Any pregnancy occurring in a subject during the study duration must be reported to US Biotest as soon as the Investigator is aware of it. The pregnancy will not be considered an SAE; however, information on these pregnancies will be collected and followed for the outcome of the pregnancy and the health of the newborn.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 8.4.2. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to the exposure to the study treatment should also be reported.

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### 8.5 STUDY HALTING RULES

This study is a dose escalation study, and dose escalation will be determined following review of all safety and tolerability data of a cohort by the Medical Monitor. Following review, the study may be terminated.

The Medical Monitor may determine if it is acceptable to proceed with an increased dose in the eight subjects of the next cohort; or they may determine that the safety and tolerability profiles are not acceptable and may stop the study.

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.

## 8.6 SAFETY OVERSIGHT

Safety will be overseen by the Medical Monitor.

All subject study data will be captured in an EDC system, allowing real-time access to ongoing safety and tolerability data. Summary tables of safety information will be reviewed by the Medical Monitor prior to dose escalation in a new cohort. A report will be generated outlining any safety concerns from the data available for review in the EDC.

In the event the Medical Monitor has any concerns or sees any safety trends emerging during his ongoing reviews he will bring it to the immediate attention of the Medical Director and the Principal Investigator.

## 9 CLINICAL MONITORING

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, regulatory binder, study binder, eCRFs, and source documents as needed to assure the conduct of the study was 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. A regulatory file or binder containing required documentation will be kept at the site for reference and inspection.

Routine monitoring visits will be made to assure compliance with the study protocol, to review and collect the subject's eCRF and compare with source documents, to ensure adequate records of clinical supplies are maintained, and to assess the continued suitability of the investigational site. On completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to US Biotest.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 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.

## 10.2 STATISTICAL HYPOTHESES

No inferential analyses are proposed; thus, no hypotheses are stated.

## 10.3 ANALYSIS DATASETS

All subjects who receive treatment will be included in the outcome presentations.

## 10.4 DESCRIPTION OF STATISTICAL METHODS

### 10.4.1 GENERAL APPROACH

In this Phase 2 dose escalation trial, the focus will be on providing descriptive statistical summaries including tables and graphs for each of the dose groups. The clinical/medical review of these data will determine if there are any issues with toxicity that could be associated with dose and if there is any effect of the treatments on the AK lesions.

### 10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary objective of this study is to evaluate the safety and tolerability of four doses of topical SOR007 ointment (concentrations of 1.23, 2.47, 8.23, and 16.46 mg/mL) applied to target AK lesion test field on subjects diagnosed with AK.

The adverse events reported will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) for each of the dose groups. Where possible and relevant, these will also be subset temporally by date and time of onset (e.g. first 24 hours, up to Day 7); the details of the timeframes will be established medically and presented in the SAP. Events reported as Grade 3 or greater on the CTCAE v4.0 (Appendix A) and those that lead to trial discontinuation will be noted. Any serious AEs and any deaths will be summarized separately.

The laboratory analyses will be presented in summary tables with changes from screening. By applying the normal ranges (high, normal and low) shift tables will be generated. Values which are noted by the investigator to be abnormal and clinically relevant will be summarized separately as will any analytes where the shift in category is greater than two (e.g. high to low or low to high). The SAP may capture medically relevant changes (e.g. 3 x the normal range) and analytes which meet this criterion will also be presented separately.

Vital signs (blood pressure, heart rate, temperature), as well as changes from screening, will be summarized for each visit. Graphical displays may be generated to illustrate the changes.

LSR results (Grade 0-4, or Present/Not Present) will be summarized and presented by visit for each evaluation category (erythema, crusting, swelling, vesiculation/postulation, erosion/ulceration, hyperpigmentation, and hypopigmentation).

### 10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

To evaluate the preliminary efficacy of SOR007 on AK lesions. This will be reported from data collected from the number and sizes of AK lesions, and will be summarized by visit and dose group

To address the secondary objective of the concentration of paclitaxel in the systemic circulation post-topical application, the pharmacokinetic (PK) samples taken on Days 1, 8, 15, 21, 28, 43, and 56. 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.

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#### 10.4.4 SAFETY ANALYSES

All safety analyses will be presented as part of the primary endpoint analysis.

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#### 10.4.5 ADHERENCE AND RETENTION ANALYSES

All subjects who are enrolled and treated in the trial will be accounted for. Subjects terminating early will be noted and the reasons provided.

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#### 10.4.6 BASELINE DESCRIPTIVE STATISTICS

Complete demographic, medical history (coded in MedDRA) and disease history will be summarized for each of the dose groups.

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#### 10.4.7 PLANNED INTERIM ANALYSES

An interim analysis is not planned

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##### 10.4.7.1 SAFETY REVIEW

Not applicable.

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##### 10.4.7.2 EFFICACY REVIEW

Assessment will be conducted to provide preliminary determination of the efficacy of topical SOR007 Ointment applied to AK lesions. Details are included in 10.4.3 above.

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#### 10.4.7 ADDITIONAL SUB-GROUP ANALYSES

Not applicable.

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#### 10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

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#### 10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

All data collected in the trial and any calculated outcomes derived from this data will, at a minimum, be listed with the dose group, subject identifier and a timepoint, if relevant. The organization of the listings will support the writing of the Clinical Study Report (CSR) as outlined in the ICH E3 guidelines.

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#### 10.4.11 EXPLORATORY ANALYSES

Not applicable.

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#### 10.4.12 CONCOMITANT MEDICATION

All medication taken during the trial will be, at a minimum, listed with the study date start and stop. For this small clinical trial, the medications will not be coded using the WHO Drug Dictionary.

#### 10.5 SAMPLE SIZE

Up to 32 subjects

#### 10.6 MEASURES TO MINIMIZE BIAS

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##### 10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Within each cohort (dose group), subjects will be randomized to receive either SOR007 or vehicle, in a 3:1 ratio. SOR007 is presented as an off-white ointment, provided in a sealed, 15 g laminate tube. The SOR007 and vehicle tubes will be identical in appearance.

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##### 10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

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##### 10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Study blind will not be broken until the database has been locked for final data analysis, unless in the case of medical emergency. Tamper evident sealed envelopes with code break information will be included with the product shipment. These envelopes should be filed securely and only accessed in an emergency situation.

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## 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

An eCRF is required and must be completed for each consenting and enrolled subject by qualified and authorized personnel. Subjects who fail the Screening assessments will not have 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 eCRFs for each subject are based. They will be separate and distinct from the eCRFs. 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 eCRFs;
- 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 AEs;

- 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.

## 12 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 CRF Completion Guidelines. The PI has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The PI or designee, as identified on Form FDA 1572, must electronically sign the completed eCRF for each participating subject to attest to their accuracy, authenticity, and completeness.

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

## 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

### 13.1 ETHICAL STANDARD

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

### 13.2 INSTITUTIONAL REVIEW BOARD

Before the start of the study, the study protocol, informed consent form and/or other appropriate documents will be submitted to the IRB and/or the authorities, 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.

Amendments to the protocol will be subject to the same requirements as the original protocol. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

### 13.3 INFORMED CONSENT PROCESS

#### 13.3.1 CONSENT/ASSENT 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 are carried out. The Investigator is required to document the process for obtaining informed consent in the source notes.

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### 13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

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 or his/her guardian or legal representative 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. The draft version of the informed consent document will be modified by each site and 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 signed by all subjects currently on study as well as those subsequently entered in the study.

The Investigator will not undertake 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.

## 13.4 PARTICIPANT AND DATA CONFIDENTIALITY

All local legal requirements regarding data protection will be enforced. All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from US Biotest.

The anonymity of participating subjects must be maintained to the extent required by law. Throughout documentation and evaluation, the subjects will be identified on eCRFs and other documents submitted to US Biotest by their initials, birth date, and their subject number. The subjects will be told 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.

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### 13.4.1 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 personal 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 SOPs. No samples will be retained for any future use.

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

### 13.5 FUTURE USE OF STORED SPECIMENS

Not applicable.

## 14 DATA HANDLING AND RECORD KEEPING

### 14.1 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 ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. **DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.**

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.

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 or designee, as identified on the Delegation of Responsibilities Log (and included on Form FDA 1572), must electronically sign the completed eCRF to attest to their accuracy, authenticity, and completeness.

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.

## 14.2 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.

If the Investigator relocates, retires or withdraws from the study for any reason, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or the sponsor. The Investigator must obtain the sponsor's written permission before transferring or disposing of any records.

## 14.3 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.

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.

Protocol deviations must be sent to the local IRB 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.

## 14.4 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 patients 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.

## 15 STUDY ADMINISTRATION

### 15.1 STUDY LEADERSHIP

The study will be overseen by the Study Manager who will be responsible, together with the Investigator, for tracking enrolment, 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. Contact information for the sponsor is provided near the beginning of this protocol and will be provided to the Investigator in separate study documents.

## 16 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 FDA Form 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.

## 17 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.

## 18 LITERATURE REFERENCES

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