STATISTICAL ANALYSIS PLAN (SAP)

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

Protocol Number:	**SOR007-2017-04**	**Study Phase**	**II**
Trial Design	Randomized, double-blind, dose rising, single-center study to determine the safety, tolerability, and preliminary efficacy of four concentrations of SOR007 (Uncoated Nanoparticulate Paclitaxel) Ointment compared to SOR007 ointment vehicle for actinic keratosis (AK) lesions on the face		
Study Treatment	SOR007 (Uncoated Nanoparticulate Paclitaxel) Ointment (SOR007) of four concentrations: 1.5 mg/g, 3 mg/g, 10 mg/g, 20 mg/g, or SOR007 Ointment Vehicle, twice daily for up to 28 days		
Subjects	Up to 32 subjects, aged 45-85 years, male or female, with actinic keratosis (AK) lesions on the face		
Treatment Period	Study drug will be topically applied to actinic keratosis (AK) lesions on the face, twice daily for up to 28 days The participant duration is estimated to be 8 weeks for each subject.		
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Plan Status	Final		
Plan Date	April 3, 2018		

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

1 of 2

Date of Final Protocol (including all amendments)	27-April-2017 (version 2) 10-March-2017 (version 1)

Date of Final Plan: 03-April-2018

I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

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Reviewed by:

Leanne Drummond Director, Oncology US Biotest, Inc.	Date (dd-mmm-yyyy)
Dr. Gere diZerega President and CEO US Biotest, Inc.	Date (dd-mmm-yyyy)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AK	Actinic Keratosis
APR	Analysis Programming Requirements
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantitation
CRF	Case Report Form
CRO	Contract Research Organization
DLC	Data Logic Checks
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
EDC	Electronic Data Capture System
LSR	Local Skin Reaction
McDougall	McDougall Scientific Ltd – CRO contracted to perform the statistical programming and analysis functions
MedDRA	Medical Dictionary for Regulatory Affairs
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SAS	Statistical Analysis System
SOC	System Organ Class
SDLC	Systems Development Lifecycle
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionary

1 BACKGROUND

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).

AK is a pre-cancerous skin disease that affecting approximately 58 million Americans. 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. SOR007 is being developed as an alternative to existing treatments for AK.

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. It is expected 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.

2 OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives are:

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

3 STUDY DESIGN

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 on the face twice daily for up to 28 days, compared to SOR007 Ointment Vehicle.

Subjects with AK on the face 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 (1.5 mg/g, 1.23 mg/mL paclitaxel, USP) topically applied to lesions; Two subjects with Ointment Vehicle (active ingredient-free) topically applied to lesions;
- Cohort 2: Six subjects with 0.3% SOR007 Ointment (3 mg/g, 2.47 mg/mL paclitaxel, USP) topically applied to lesions; Two subjects with Ointment Vehicle (active ingredient-free) topically applied to lesions;
- Cohort 3: Six subjects with 1% SOR007 Ointment (10 mg/g, 8.23 mg/mL paclitaxel, USP) topically applied to lesions; Two subjects with Ointment Vehicle (active ingredient-free) topically applied to lesions;
- Cohort 4: Six subjects with 2% SOR007 Ointment (20 mg/g, 16.46 mg/mL paclitaxel, USP) topically applied to lesions; Two subjects with Ointment Vehicle (active ingredient-free) topically applied to lesions.

Safety will be assessed in an ongoing manner and formal safety reviews will be conducted four times for each cohort: at Day 8, Day 15, Day 21, and 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.

Once the last cohort has completed the study, all available data, including safety, pharmacokinetics, 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.

3.1 Overview of Study Procedures

3.1.1 Screening

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.

3.1.2 Treatment Period

At Day 1, prior to the first application of investigational product, target AK lesion test field will be identified, assessed by the physician, and documented photographically. Blood

samples for PK analysis of paclitaxel plasma levels will be collected at 1 h, 2 h, 4 h, and 6 h post-first daily application.

Investigational product will be applied topically to a target AK lesion test field, a 25 cm^2 area on the face which contains 4-8 AK lesions, twice daily for up to 28 days, or until all lesions resolve. 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^2, approximately 0.15% of the total body surface area, will be treated.

On Days 8, 15, and 21, 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.

At Day 28, subject will return to the clinic for assessment and documentation of target AK lesion test field and PK samples will be collected at pre-first daily application, 1 h, 2 h, 4 h, 6 h and 12 h post-first daily application. The last study drug application will occur following the 12 h PK sample collection.

3.1.3 Follow-up Period

After completing the Treatment Period, subjects will return to the clinic on Days 28 and 56 for assessment and documentation of target AK lesion test field and a single PK sample collection.

3.2 Schedule of Events

	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)
Informed Consent	X							
History[1]	X							
Physical Examination	X							
Inclusion/Exclusion	X	X						
Concomitant Therapy	X	X	X	X	X	X	X	X
CBC, Liver Function, BUN & Creatinine, Prothrombin	X					X	X	
Vital Signs	X	X	X	X	X	X	X	X
Assessment of LSRs	X	X	X	X	X	X	X	X
AK Lesion Count in Treatment Field		X	X	X	X	X	X	X
PK Samples[2]		X	X	X	X	X	X	X
Pregnancy Test for Female Subjects	X	X				X		X
Photographs	X	X	X	X	X	X	X	X
Transparency Mapping		X	X	X	X	X	X	X
Examination of AK	X	X	X	X	X	X	X	X
Adverse Events[3]		X	X	X	X	X	X	X
End of Study								X[4]

1 History includes all events before initiation of SOR007 treatment.
2 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.
3 Adverse event determination will start immediately following initiation of study treatment.
4 AEs and concomitant medications at the Week 4 follow-up that are still active will be followed.

4 DATA MANAGEMENT METHODS

4.1 Data Collection and Database Construction

Data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall. All clinical research staff will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data has been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor, or the Sponsor delegate, and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at McDougall and are identified by the project code US19SOG.

All data activities will be performed on validated computer systems as per 21CRF11 and kept under control, according to McDougall's SOPs. All programming will be performed in SAS version 9.4 or higher under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in Toronto, Canada.

4.2 Coding

Adverse Events (AEs) and Medical History will be coded using MedDRA (version 20.0 or higher). Concomitant medications will be coded using WHODD version 2016.

All coding will be approved by the sponsor prior to data base lock.

5 STATISTICAL METHODS

5.1 Changes from the Protocol

None.

5.2 Analysis Dataset

There is only one analysis dataset for all statistical analysis. All subjects who received at least one dose of study treatment will be included in the analysis dataset.

5.3 Missing Data

Missing values will not be imputed.

5.4 Interim Analysis

No interim analysis is planned in this study.

5.5 Calculated Outcomes

The following are the key endpoints derived from the study data for analysis. Complete documentation of the calculations and data manipulation required to go from the clinical database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Age (yr) = year of consent date – birth year, if consent day is after or the same as birthday, or

= year of consent date – birth year – 1, if consent day is before birthday.

BMI (kg/cm^2) = 10000*weight (kg) / [Height (cm)]^2

Study Day 1 = Date of first study treatment

Study day of an event = Date of that event – Study Day 1 + 1, if it occurs on or after the first study treatment, or

= Date of that event – Study Day 1, if it occurs before the first study treatment.

Time in Trial (days) = Date of study completion or discontinuation – Informed consent date

Time on Treatment (days) = Last dosing day – First dosing day = Last dosing day – Study Day 1

Change of Assessment = Assessment at Visit – Assessment at Baseline, where “Assessment” is the measurement or assessment of study endpoints (e.g. AK size, AK count, vital signs, lab results, etc.). Baseline is the last non-missing assessment prior to first study treatment.

Compliance of study treatment (%) = 100 x (Actual Doses / Expected Doses). It will be calculated by visit from Visit 2 (Day 1) to Visit 6 (Day 28), and overall.

5.6 Analysis Methods

All calculations described in this SAP will be performed using SAS version 9.4 or higher resident on the Windows 2012R2 server at McDougall in Toronto, Canada.

No inferential analyses are proposed. Safety and efficacy endpoints will be descriptively summarized. Continuous data will be summarized via PROC MEANS – number of subjects, mean, standard deviation, median and range, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

6 RESULTS

All data collected in the clinical database, include data captured via EDC and data from external source (e.g. PK concentration), will be listed by subject and treatment group in data listings. The organization of the Tables and Listings will be guided by the ICH E3 – Structure and Content of Clinical Study Reports.

6.1 Study Subjects

6.1.1 Subject Disposition

Each Subject enrolled into the trial will be accounted for. The early terminators will be summarized by the primary reason for early withdrawal. Data listings for subject disposition and end of study information, including any additional textual reasons where applicable, will be provided.

6.1.2 Subject Characteristics

6.1.2.1 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed for all enrolled subjects using standard summary statistics. The summary will include age (years), sex, race, ethnicity, height (cm), weight (kg), the calculated BMI, and baseline vital signs (i.e. assessments of Baseline Visit, or assessments of Screening Visit if Baseline assessments are missing). These variables will be summarized by treatment group.

6.1.2.2 AK Diagnosis and Previous Treatment

Date of AK diagnosis and previous treatment of AK will be listed in by-subject data listing.

6.1.2.3 Medical History

Medical history will be summarized by MedDRA SOC and PT and will be listed by subject.

6.1.2.4 Physical Examination

Physical examination data: performed /not performed, and date physical exam performed will be listed by subject.

6.1.2.5 Eligibility

The eligibility criteria failed and waiver information, if any, will be listed by subject.

6.1.3 Treatment Exposure and Compliance

Time in trial and time on treatment will be summarized by treatment.

Study drug application information, both at clinical visits and at home via diary, will be listed.

Study drug usage data, including dispensed, returned, and used weight, will be listed by tube. Total used amount and amount per dose will be summarized by treatment.

Treatment compliance, both weekly and overall, will be tabulated by treatment group.

All exposure and compliance data will be listed. The records that had ≥ 4 missing doses in a week, and weekly compliance rate out of range 75% to 125% will be flagged.

6.2 Primary Endpoints

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.

All primary endpoints will be summarized by treatment group.

6.2.1 Adverse Events

All Treatment Emergent Adverse Events (TEAEs) will be summarized according to primary SOC and PT based on MedDRA coding. The summaries will focus on the counts of subjects and also the number of events, for each SOC and PT, presented for whole study period, and by treatment period (Day 1 to Day 28) and follow-up period (Day 29 onward).

The summaries for TEAEs will be:

1. the number and percent of subjects/events for all TEAEs;
2. the number and percent of subjects/events for all TEAEs by severity of event;

3. the number and percent of subjects/events for all TEAEs by relationship to study drug;
4. the number and percent of subjects/events for all SAEs;
5. the number and percent of subjects/events for all TEAEs with death as outcome;
6. the number and percent of subjects/events for all TEAEs with CTCAE toxicity grade 3 or greater;
7. the number and percent of subjects/events for all TEAEs leading to early withdrawal.

All AEs will be listed by subject. SAEs will be listed separately.

6.2.2 Vital Signs

Vital signs (blood pressures, heart rate, and body temperature) data at each visit and change from baseline will be summarized for each time point using standard summary statistics. Baseline is defined as the last non-missing assessments prior to the start of the first study treatment.

All vital signs data will be listed by subject and time point.

All vital signs will also be visually presented in by-subject graphs.

6.2.3 Clinical Laboratory Measurements

All laboratory test results (quantitative results, abnormal status, clinically significant status) of blood chemistry, hematology, and urinalysis will be summarized by visit of assessment using standard summary statistics.

For quantitative laboratory measurements after the study treatment, the laboratory measurement summarization will also include the change from Baseline.

For tests with normal range provided, the clinical status (Normal /High Abnormal /Low Abnormal) and its change from baseline will be summarized using a shift table.

All laboratory data will be listed by subject and visit. The laboratory abnormalities will be listed separately.

6.2.4 Local Skin Reaction (LSR)

At each visit, the results (severity, or present /not present) of each Local Skin Reaction (LSR) evaluation category (erythema, crusting, swelling, vesiculation/postulation, erosion/ulceration, hyperpigmentation, and hypopigmentation) will be summarized.

6.3 Secondary Endpoints

6.3.1 AK Lesions

The number of AK lesions will be summarized by visit.

The size of AK lesion will be summarized by visit and by lesion ID.

All AK lesion information will be presented in by-subject data listing.

6.3.2 PK Analysis

The concentration of paclitaxel in the systemic circulation post-topical application will be assessed on Days 1 (post first study dose 1 h, 2 h, 4 h, and 6 h), 8 (pre first daily dose), 15 (pre first daily dose), 21 (pre first daily dose), 28 (pre first daily dose, and 1 h, 2 h, 4 h, 6 h and 12 h post first daily dose), 43 (single sample), and 56 (single sample).

Given SOR007 is administered topically in this study, it is not expected that paclitaxel will be present in the systemic circulation at quantifiable concentrations over the PK sampling intervals on Days 1 and 28. As such, characterization of paclitaxel pharmacokinetics or determination of trough plasma concentrations from plasma samples collected prior to the first dose on Days 15 and 21, as well as on Post-Treatment Days 43 and 56, will be unlikely. However, for those PK samples that exhibit concentrations above the lower limit of quantitation, the results will be tabulated by sampling day, time point, and treatment group. Concentration values that are below the limit of quantitation (BLQ) concentration data will be treated as zero.

6.4 Safety Endpoints

In this study, all safety analyses will be presented as part of the primary endpoint analysis.

6.5 Other Analyses

6.5.1 Concomitant Medications

All concomitant medications collected in EDC will be coded based on WHODD, and will be tabulated by the therapeutic class (ATC level 2) and chemical subgroup (ATC level 4). The number and percentage of coded medications and subjects who used medications will be presented.

All medications will be listed.

6.5.2 Pregnancy Test

For female subjects, the urine pregnancy test information: performed /not performed, date, and result, will be listed.