STATISTICAL ANALYSIS PLAN (SAP)

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

Protocol Number:	SOR007-2017-01	**Study Phase**	1/2
Trial Design	Open-label, multi-center, dose-rising study to evaluate the safety, tolerability and preliminary efficacy of three concentrations of SOR007 Ointment applied topically twice daily for up to 28 days or with the option of extending treatment an additional 28 days to total up to 56 days to non-melanoma cutaneous metastases.		
Study Treatment	SOR007 (Uncoated Nanoparticulate Paclitaxel) Ointment of three concentrations: 0.15%, 1%, and 2%		
Subjects	Up to 28 subjects, ≥ 18 years of age, with non-melanoma cutaneous metastases, from up to 4 sites		
Treatment Period and Study Duration	SOR007 ointment (IP) will be applied topically twice daily in Group A subjects for up to 28 days and Group B subjects for up to 56 days. Follow-up will continue for 30 days after last IP application. The participant duration is estimated to be 75 (Group A) or 102 (Group B) days for each subject, including the screening period.		
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Plan Status	Final		
Plan Date	Aug 31, 2020		

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

1 of 2

Date of Final Protocol (including all amendments)	28-December-2018 (version 7.0) 05-March-2018 (version 6.0) 03-October-2017 (version 5.0) 12-September-2017 (version 4.0) 10-August-2017 (version 3.0) 01-August-2017 (version 2.0) 26-June-2017 (version 1.1) 21-March-2017 (version 1.0)

Date of Final Plan: 31-Aug-2020

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

2 of 2

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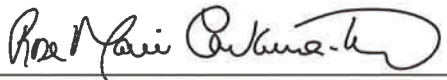

24-Aug-2020

Rose Marie Cavanna-Mast
Director, Clinical Trials
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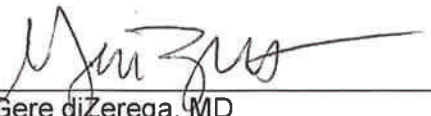
Date (**24-Aug-2020**)



24 Aug 2020

Gere diZerega, MD
Vice President for Medical Affairs
NanOlogy, LLC

Date (**24-Aug-2020**)

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
APR	Analysis Programming Requirements
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantitation
BOR	Best Overall Response
CR	Complete Clinical Response
CRF	Case Report Form
CRO	Contract Research Organization
DLC	Data Logic Checks
DLT	Dose Limiting Toxicity
EDC	Electronic Data Capture System
LSR	Local Skin Reaction
IP	Investigational Product (SOR007 ointment / Study drug)

Abbreviation	Definition
McDougall	McDougall Scientific Ltd – CRO contracted to perform the statistical programming and analysis functions
MedDRA	Medical Dictionary for Regulatory Affairs
NIH	National Institutes of Health
NRS	Numeric Rating Scale
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
PD	Progressive Disease
OCR	Objective Clinical Response
OTR	Objective Tumor Response
QOL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SDLC	Systems Development Lifecycle
SOP	Standard Operating Procedure

Abbreviation	Definition
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 NanOlogy, LLC (NanOlogy) for the topical treatment of non-melanoma cutaneous metastases.

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

Despite the prevalence and impact of cutaneous metastases, a standard of care remains elusive. Treatment is complicated by underlying disease, poor patient performance, previous radiation therapy and short duration of overall survival. These factors make surgery and radiation unfeasible in most patients. Systemic chemotherapy has negligible impact on most cutaneous metastases. Additional therapies for cutaneous metastases include electrochemotherapy, photodynamic therapy, intralesional therapy, and topical therapy.

SOR007 is being developed as an alternative to existing treatments for cutaneous metastases. This Phase 1/2 study will include subjects with non-melanoma cutaneous metastases. The study design allows for a safety evaluation of topical application of SOR007 as topical therapy for cutaneous metastases. It is expected that topical application of SOR007 onto the diseased skin will result in limited systemic exposure. It is also anticipated that topical treatment of cutaneous metastases with SOR007 will be well tolerated, allowing for repeat administration if necessary.

2 OBJECTIVES

2.1 Primary Objective

To determine the preliminary safety and tolerability of topical SOR007 Ointment.

2.2 Secondary Objectives

- To determine preliminary efficacy of topical SOR007;
- To study potential reduction in pain at the treatment area.;
- To describe the pharmacokinetics of topical SOR007 Ointment applied to metastatic lesions.

3 STUDY DESIGN

3.1 Primary Endpoint

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

3.2 Secondary Endpoints

- Objective Tumor Response (OTR) - the difference in the lesion size within the treatment area between baseline and 14 days after the last dose in the dose group i.e. Day 43 for dose escalation subjects, and dose expansion Group A subjects; Day 70 for dose expansion Group B subjects; or between baseline and last timor assessment for early terminators. Four OTRs will be calculated based on different definitions of “lesion size”: 1) Area of the primary eligible lesion, 2) Sum of area of all eligible lesions, 3) Longest diameter of the primary eligible lesion, and 4) Sum of longest diameter of all eligible lesions.

- Objective Clinical Response (OCR) - subjects with Complete Clinical Response (Clinical Response (CR) – the absence of any detectable residual disease in eligible lesion(s) within the treatment area) + Partial Response (PR) - at least a 30% decrease in the lesion size compared to baseline), within 14 days after the last treatment with SOR007 or at the last tumor assessment for early terminators. Similar to OTR, four OCRs will be calculated based on different definitions of “lesion size”.

- Best Overall Response (BOR) - the best response recorded from the start of study treatment until the end of the study (i.e. Day 43 of dose escalation phase subjects and dose expansion Group A subjects; Day 70 of dose expansion Group B subjects, or early termination visit).

- Change in Pain - Change in pain at the treatment area between Baseline and Day 43, Day 70 or early termination visit, as measured on the 11-point Numeric Rating Scale (NRS).

3.3 Exploratory Endpoint

Appearance of new lesions within the treatment area.

3.4 Description of the Study Design

This is a phase I/II, open-label, dose-rising study evaluating the safety, tolerability, and preliminary efficacy of three concentrations of SOR007 Ointment (0.15%, 1.0%, and 2.0%) applied topically to non-melanoma cutaneous metastatic lesions, twice daily for up to 28 or 56 days.

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

In the dose escalation phase, subjects with non-melanoma cutaneous metastases will be enrolled in three dose-escalating cohorts consecutively as follows:

- Cohort 1: 0.15% SOR007 (1.23 mg/mL paclitaxel);
- Cohort 2: 1.0% SOR007 (8.2 mg/mL paclitaxel);
- Cohort 3: 2.0% SOR007 (16.4 mg/mL paclitaxel).

Cohorts will be enrolled sequentially starting at the lowest concentration, i.e. Cohort 1. In each cohort, all subjects will be monitored for safety and tolerability. Safety will be assessed in an ongoing manner and a Safety Monitoring Committee (SMC) will review all available data after the last subject in each cohort of three subjects completes 15 days of treatment to determine whether dose escalation may continue.

Any AE that is considered related or possibly related to SOR007 is potentially a Dose Limiting Toxicity (DLT). Specific DLT are described in Section 7.6 of the Protocol. Any potential DLT will be discussed and dose escalation will be determined following review of all safety and tolerability data of a cohort by the Medical Monitor in conjunction with the SMC. The final decision for dose escalation and/or premature termination of the study is the responsibility of the Medical Monitor.

Dose-escalation is applied by using the standard 3+3 dose-ascending method. For each cohort, three subjects are enrolled and are monitored for safety and tolerability after the 3rd subject in the cohort completes 15 days of treatment:

- If no DLT is found in the three subjects, dose-escalation will continue.
- If one DLT is found in the three subjects, an additional three subjects will be enrolled in that cohort.
    - If no additional DLT is found, dose-escalation will continue.
    - If one or more DLTs are found in the three additional subjects, the dose-escalation will be halted. The dose level of previous cohort will be the Maximum Tolerated Dose (MTD) and taken forward into the dose expansion phase.
- If two or more DLTs are found in the first three subjects, dose-escalation will be halted. The dose level of previous cohort will be the MTD and taken forward into the dose expansion phase.
- The dose-escalation will continue, until either halt rule described above is met or the top dose of 2% (i.e. Cohort 3) is reached.
- If no DLT is found in the first three subjects of Cohort 3, or in the additional subjects. Dose level 2.0% (of Cohort 3) will be the MTD.

- If dose-escalation is halted at Cohort 1, the study is terminated without the finding of MTD.

In the dose expansion phase, additional subjects will be enrolled to reach a maximum of 16 total subjects at the MTD found in the dose escalation phase. Subjects in the dose expansion phase will receive 28 days (Group A) or 56 days (Group B) of treatment per investigator's decision, subject consent, disease progression, additional systemic chemotherapy or other metastatic treatment requirements.

Group A subjects will attend the clinic on the same visit days and receive the same evaluations as the dose escalation phase subjects. Group B subjects will be treated 28 more days than Group A subjects. Both groups will be followed for 30 days after the last IP application. .

3.5 Overview of Study Procedures

3.5.1 Screening

Within 14 days prior to the first application of investigational product the subject will have a medical history and concomitant medication review, demographics, vital signs, pain, and cutaneous metastatic lesions assessed and/or measured. Laboratory samples for hematology, biochemistry, and urinalysis will be taken and be assessed against enrollment criteria.

All measurable lesions will be measured by caliper and determined to be eligible (RECIST criteria $\geqslant$ 10mm in its longest diameter) within the 50 cm^2 treatment area selected by the Investigator. There will be at least one eligible lesion within the treatment area of 50 cm^2 for a patient to qualify for the study.The investigator may measure and track more than one eligible and/or non-eligible lesion within the 50 cm^2 treatment area during the study.

3.5.2 Baseline (Day 1)

At Day 1, prior to the first application of SOR007, hematology, biochemistry, and urinalysis results will be reviewed and lesion eligibility will be confirmed (≥ 10mm in its longest diameter at baseline).

All measurable lesions in the 50 cm^2 treatment area will be measured by caliper and documented for size prior to lesion area cleaning. A subject may have multiple eligible lesions (≥ 10 mm) and multiple non-eligible lesions (< 10 mm) at baseline. Only one eligible lesion is required for study eligibility. The eligible lesion with the largest demension at baseline will be selected as the primary eligible lesion.

Medical and concomitant medication history will be reviewed/updated, vitals will be measured, photos will be taken of the lesion area and lesion area pain will be assessed,

SOR007 will be applied topically to a 50 cm^2 treatment area (identified by the Investigator). The amount of SOR007 that will be applied will be 1 finger-tip unit (FTU), approximately 0.5g. The subject will be instructed to self-apply SOR007 twice daily for up to 28 days during dose-escalation and for up to 28 days (Group A) or up to 56 days (Group B) during dose-expansion. The subject will be given a diary for daily completion to document IP application, AE and concomitant medication and will be supplied with the appropriate number of tubes until the next study visit. Subjects will return to the clinic 24-hours post the first IP application for a PK blood draw.

3.5.3 Treatment Visits (Days 8, 16, 29, 57)

On Days 8, 15, and 29, subjects will return to the clinic for targeted physical exam, documentation and photography of lesions, pain assessment, blood sample collection for hematology, biochemistry and PK. There will also be a review for changes in medication and physical status including possible adverse experiences from the diary review and interview. For dose expansion Group B, subjects will return to clinic for treatment and assessment on Day 57.

At each visit, the subject will return the daily diary for dosing compliance review and IP accountability purposes, will be given sufficient SOR007 for daily treatment until the next visit. The subject will be instructed to return SOR007 ointment tubes when empty or per institution requirements. At returns, SOR007 ointment tubes will be weighed to assess proper and sufficient IP usage. At each visit, the application area will be verified and outlined in permanent marker, if necessary. SOR007 ointment application will be supervised by study staff to ensure adequate FTU is appied and is within the 50 cm^2-marked area. Subjects will self-apply the last dose of SOR007 at home the evening of Day 28 or Day 56.

The subject will be given a diary for daily completion to document AE and concomitant medication at visit 5/Day 29 (Group A) and visit 6/Day 57 (Group B) for return at the end of study visits (Days 43/70 respectively).

3.5.4 End of Study (Day 43/Day 70)

After completing the Treatment Period, subjects will enter a 14 day follow-up period and return to the clinic on Day 43 (Group A) or Day 70 (Group B) to complete the end-of-study evaluations which will include documentation and photography of lesions, targeted physical exam, pain assessment, blood sample collection for hematology, biochemistry,

PK and urinalysis collection. There will also be a review for changes in medication and physical status including possible adverse experiences.

The subject will return all treatment diaries (if not already done so) and the Day 29-43 (Group A) or Day 57-70 (Group B) AE diaries and any remaining SOR007 ointment tubes (if not previously done so).

3.5.5 Safety Follow-up (Final Visit)

A safety visit or phone call will be completed 30 days after the last IP application to review AE; the investigator will determine whether this final safety visit is conducted at the clinic or over the phone.

3.6 Schedule of Events

3.6.1 Schedule of Events Table 1: Dose Escalation and Dose Expansion Group A: 28 Days Treatment

Timepoint/Study Visit	Screening (≤ 14 days)	Baseline	Treatment			Follow up	
	Visit 1 (Days -13 to Day 0)	Day 1 / Visit 2	Day 8 /Visit 3 (+/- 1 d)	Day 15 / Visit 4 (+/- 1 d)	Day 29 / Visit 5 (+ 2 d)	Day 43 / Visit 6 (+/- 2 d)	Day 59 / Visit 7 (+ 2 d)
Informed Consent	X						
History and Demographics[1]	X						
Inclusion/Exclusion	X	X[2]					
Height and Weight	X						
Physical Examination[3]	X	X	X	X	X	X	
Vital Signs[4]	X	X	X	X	X	X	
ECOG Performance Status	X						
Hematology and Chemistry	X		X	X	X	X	
Urinalysis	X					X	
Pregnancy Test	X						
Pharmacokinetic (PK) Assay[5]		X	X	X	X	X	
Pain Assessment (NRS-11)	X	X	X	X	X	X	
Tumor Measurements[6]	X	X					
Tumor Assessments[7]			X	X	X	X	
Photography		X	X	X	X	X	
Distribute SOR007 Tube(s)		X	X	X			
Collect SOR007 Tube(s)			X	X	X		
SOR007 Application Training[8]		X	X	X			
SOR007 Application[8]		X	X	X			
Adverse Events[9]	X	X	X	X	X	X	X[11]
Concomitant Therapy	X	X	X	X	X	X	
Diary Distribution[10]		X	X	X	X		
Diary Collection			X	X	X	X	

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

3.6.2 Schedule of Events Table 2: Dose Expansion Group B: 56 Days Treatment

Timepoint/Study Visit	Screening (≤ 14 days)	Baseline	Treatment				Follow up	
	Visit 1 (Days -13 to 0)	Day 1 / Visit 2	Day 8 /Visit 3 (+/- 1 d)	Day 15 / Visit 4 (+/- 1 d)	Day 29 / Visit 5 (+/- 2 d)	Day 57 / Visit 6 (+ 2/- d)	Day 70 / Visit 7 (+/- 2 d)	Day 86 / Visit 8 (+ 2 d)
Informed Consent	X							
History and Demographics[1]	X							
Inclusion/Exclusion	X	X[2]						
Height and Weight	X							
Physical Examination[3]	X	X	X	X	X	X	X	
Vital Signs[4]	X	X	X	X	X	X	X	
ECOG Performance Status	X							
Hematology and Chemistry	X		X	X	X	X	X	
Urinalysis	X						X	
Pregnancy Test	X							
Pharmacokinetic (PK) Assay[5]		X[5]	X	X	X	X	X	
Pain Assessment (NRS-11)	X	X	X	X	X	X	X	
Tumor Measurements[6]	X	X						
Tumor Assessments[7]			X	X	X	X	X	
Photography		X	X	X	X	X	X	
Distribute SOR007 Tube(s)		X	X	X	X			
Collect SOR007 Tube(s)			X	X	X	X		
SOR007 Application Training[8]		X	X	X	X			
SOR007 Application[8]		X	X	X	X			
Adverse Events[9]	X	X	X	X	X	X	X	X[11]
Concomitant Therapy	X	X	X	X	X	X	X	
Diary Distribution[10]		X	X	X	X	X		
Diary Collection			X	X	X	X	X	

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

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 enrolling the first subject.

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 have 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 responsible Data Manager will lock each subject's data files when all the criteria noted above are satisfied for that subject.

The data management processes are outlined in the project specific Data Management Plan; this and all related documentation are on file at McDougall and are identified by the project code US20SOG.

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 Statistical Analysis System (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 Medical Dictionary for Regulatory Affairs (MedDRA) version 20.1.

Concomitant medications will be coded using the most current version of WHODD at the beginning of coding, version 2017.

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

4.3 Pharmacokinetic (PK) Data

PK analysis will be performed by Covance Laboratories, Inc. Madison, Wisconsin, and will be reported separately by a third party and will not be described in this Statistical Analysis Plan (SAP).

4.4 Lesion Measurements

At screening and baseline (prior to treatment), all measurable lesions' longest diameter within the treatment area are captured by EDC database.

The following lesion measurements are recorded by investigators and will be provided to McDougall in Excel data sheet:

- Lesion length and width – all visits
- Lesion status change from baseline
- Lesion status change from previous visit

4.5 Tumor Surface Area

Tumor surface area will be assessed using a calibrated grid measurement system (ImageJ, freeware) provided by the NIH. US Biotest will provide McDougall with calculated tumor surface area and tumor dimensions in excel data sheet before database lock.

At each visit, lesions may be measured multiple times (area and/or dimensions) and verified in duplicate. The average value will be used in the calculation of tumor responses: OTR, OCR, and BOR.

4.6 Protocol Deviations

Protocol deviations will be provided in Excel data sheet by US Biotest before database lock.

5 STATISTICAL METHODS

5.1 Changes from the Protocol

5.1.1 PK analysis.

PK parameters Cmax, Tmax and AUC was described in the Protocol Section 3.3. According to Sponsor's decision, PK analysis will be performed and reported separately by a third party and will not be covered in this SAP.

All concentrations of paclitaxel will be listed.

5.1.2 Tumor Response

In the Protocol, OTR was defined as the difference in the sum of eligible tumor diameter(s) between baseline and Day 43 or 70 (i.e. 14 days after the last dose in the dose escalation and expansion phases depending on dose regimen).

As requested by the Sponsor, OTR will be calcualted based on four lesion measurements: 1) Area of the primary eligible lesion, 2) Sum of area of all eligible lesions, 3) Longest diameter of the primary eligible lesion, and 4) Sum of longest diameter of all eligible lesions.

To be consistent to OTR, the tumor response CR, PR, Stable disease (SD), or Progressive disease (PD) at each visit will also be determined based on these four tumor measurements.

Because of the four types of tumor response at each visit, the OCR and BCR will also be calculated using four methods.

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 = Date of Visit 2

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 + 1

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

Dosing Compliance (%) of a period = 100 * Actual Doses / Expected Doses, where Expected Doses = 2 x Days of the Period.

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

OTR will be assessed using following four methods:

- The difference of the area of the primary eligible lesion between baseline and last measurement
- The difference of the sum of area of all eligible lesions between baseline and last measurement
- The difference of the longest diameter of the primary eligible lesion between baseline and last measurement
- The difference of the sum of the longest diameter of all eligible lesions between baseline and last measurement

The last measurement is 14 days after the last application in the dose group *(i.e. Day 43 for dose escalation subjects, and dose expansion Group A subjects; Day 70 for dose expansion Group B subjects)* or the last non-missing assessment for the early terminators. Eligible lesions are determined at baseline by the

RECIST (Vn 1.1) definition of measurable tumors (≥ 10mm in its longest diameter). The eligible lesion with longest dimension at baseline is selected as the primary eligible lesion.

CTR is assessed according to tumor size change in the treatment area:

CR = Absence of any detectable residual disease in the treatment area;

PR = at least a 30% decrease in lesion size between baseline and visit. Same as OTR, PR will be determined from following four methods:

- At least a 30% decrease in the area of the primary eligible lesion compared to baseline
- At least a 30% decrease in the sum of area of all eligible lesions within the treatment area compared to baseline
- At least a 30% decrease in the longest dimension of the primary eligible lesion compared to baseline
- At least a 30% decrease in the sum of the longest dimension of all eligible lesions within the treatment area compared to baseline

Progressive Disease (PD) = at least a 20% increase in the lesion size. Similar to PR, PD will also be determined from four “lesion size” definitions:

- At least a 20% increase in the area of the primary eligible lesion compared to baseline, and with an absolute increase of at least 25 mm^2.
- At least a 20% increase in the sum of area of all eligible lesions within the trestmenat area compared to baseline, and with an absolute increase of at least 25 mm^2.
- At least a 20% increase in the longest dimension of the primary eligible lesion compared to baseline, and with an absolute increase of at least 5 mm
- At least a 20% increase in the sum of the longest dimension of all eligible lesions within the trestmenat area compared to baseline, and with an absolute increase of at least 5 mm.

SD = tumor size change between PR and PD.

Note: for the purpose of this study, and as described in the Protocol, the appearance of new non-target lesions does NOT constitute progressive disease.

OCR = Yes, if CR or PR

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 will be listed by subject and treatment group in data listings; the dose escalation and dose expansion phases will be differentiated in the listings. The dose expansion Group A and Group B will also be separated because of the different treatment/visit structures. The organization of the Tables and Listings will be guided by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use or 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.

Throughout the trial summarization, the dose escalation subjects, dose expansion Group A subjects, and dose expansion Group B subjects will be presented separately and also be combined into the designated dose groups to provide an overall view of any dose response criteria.

Protocol deviations will be presented in by-subject data listing.

6.1.2 Eligibility

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

6.1.3 Subject Characteristics

6.1.3.1 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.

6.1.3.2 Cutaneous Metastases Diagnosis and Previous Treatment

Cutaneous metastases diagnosis are reported in medical history dataset. No separate analysis will be provided.

Previous treatment of cutaneous metastases are captured in the Prior and Concomitant Medications form. No separate table or listing will be provided.

6.1.3.3 Medical History

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

6.1.3.4 Physical Examination

Clinically relevant results from the physical examination will be recorded in Medical History at screening and baseline and as an adverse experience post the first application of the study treatment.

6.1.4 Treatment Exposure

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

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 will be summarized by treatment.

Dosing compliance of each visit and for whole treatment period will be summarized by treatment group.

6.2 Primary Endpoints

The primary objective of this study is to evaluate the safety and tolerability of three doses of topical SOR007 ointment (0.15%, 1.0% and 2.0%) applied to metastatic lesions on subjects diagnosed with non-melanoma cutaneous metastases. The primary endpoints include AEs, vital signs, and clinical laboratory results. The focus will be on the AEs as

these will capture the clinically relevant changes in the vital signs and/or laboratory values. The vital signs and laboratory analytes will also be summarized in tables and listings as part of the complete Clinical Summary Report.

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. The presentations will separate out and highlight any SAEs (including deaths), and AEs leading to the discontinuation of study treatment.

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 Common Terminology Criteria for Adverse Events - CTCAE (version 4.0) toxicity grade;
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 TEAEs by outcome;
5. the number and percent of subjects/events for all SAEs;
6. the number and percent of subjects/events for all TEAEs with death as outcome;
7. the number and percent of subjects/events for all TEAEs leading to drug withdrawal;
8. the number and percent of subjects/events for all AEs of Specific Interest. The AEs of specific interest include the following:
    a. clinically significant laboratory results as determined by the Investigator
    b. peripheral neuropathy
    c. neutropenia, anemia, thrombocytopenia
    d. any infection, local or systemic
    e. anaphylaxis
    f. cardiovascular AEs
    g. hepatoxicity (AST, ALT, GGT, ALP, bilirubin)

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

6.2.2 Vital Signs

Vital signs (blood pressures, heart rate, respiration rate, and body temperature) 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. Change from Baseline is defined as baseline value minus value at visit.

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

6.2.3 Clinical Laboratory Measurements

All laboratory test results (quantitative results, abnormal status, and 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. Change from Baseline is defined as baseline value minus value at visit.

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

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

6.3 Secondary Endpoints

To determine the primary efficacy and potential pain reduction, the difference between baseline (i.e. last non-missing value prior to first SOR007 treatment) and 14 days after last treatment (i.e., Day 43 for dose escalation subjects and dose expansion Group A subjects, or Day 70 for dose expansion Group B subjects) or the last assessment of early teminators of following secondary endpoints will be analyzed.

6.3.1 Objective Tumor Response

Eligible lesion is defined as a lesion within treatment area, with its longest diameter ≥ 10 mm at baseline.

The sizes (longest diameter and lesion area) of the Primary elgible lesion, as well as its change from baseline, will be summarized by visit.

The sum of longest diameter and tumor surface area of all eligible lesions, as well as the change from baseline, will be summarized by visit.

OTR, i.e., the change of lesion size from baseline to End of Study (i.e. Day 43 for dose escalation subjects, and dose expansion Group A subjects; Day 70 for dose expansion Group B subjects, or last assessment for early terminators) will be summarized separately. Please see Section 5.5 regarding the four types of OTRs based on different definitions of "lesion size".

All measurements of individual lesions, including longest diameter, length, width, tumor surface area, status change from baseline, and status change from previous visit, will be listed.

6.3.2 Objective Clinical Response

At each visit, four types of clinical tumor response (CR, PR, SD, or PD) will be assessed and summarized. The frequency of OCR at each visit, i.e. subject with CR or PR, will be summarized by treatment group.

The CTR and OCR of whole study, i.e. at End of Study (Day 43 visit for dose escalation subjects and dose expansion Group A subjects; or Day 70 visit for dose expansion Group B subjects, or the last assessment of early terminotors), will be summarized separately.

6.3.3 Best Overall Response

The best response recorded from the start of study treatment until the end of the study will be summarized.

6.3.4 Pain Score

The pain scores as assessed on the 11-point numerical scale (from 0 – no pain to 10 – greatest pain imaginable), i.e. NRS-11, will be summarized as raw values and changes from baseline in tables and listings at each visit for each dose group.

6.3.5 PK Analysis

The concentrations of paclitaxel will be presented in data listing.

PK parameters calculation and analysis will be conducted and reported separately by a third party.

6.4 Exploratory Endpoints

6.4.1 Non-eligible and New Lesions

Non-eligible lesions within the treatment area (<10 mm in diameter) identified at baseline and new measured lesions which develop during the trial will be evaluated as exploratory endpoints. Each category will be listed separately.

6.5 Safety Endpoints

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

6.6 Other Analyses

6.6.1 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.

6.6.2 Pregnancy Test

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