PHASE 1/2 CLINICAL TRIAL OF A TOPICAL SUBMICRON PARTICLE PACLITAXEL (SOR007) FOR THE TREATMENT OF CUTANEOUS METASTASES

ClinicalTrials.gov Identifier: NCT03101358

Mario E Lacouture[1], Julie E. Lang[2], Sant Chawla[3], Shari Goldfarb[1], Alina Markova[1], Alexander Pan[1], Rose Marie Cavanna-Mast[4], Peter Mast[4], Christopher Savoie[4], Gere diZerega[4].
[1]Memorial Sloan-Kettering Cancer Center, New York, NY, [2]USC Norris Comprehensive Cancer Center, Los Angeles, CA, [3]Sarcoma Oncology Research Center, Santa Monica, CA, [4]US Biotest, Inc. for NanOlogy, LLC.

Background

Cutaneous Metastases (CM) are progressive malignant skin lesions of advanced solid tumors and are usually associated with pain, pruritus, ulceration, discharge, malodor, and additional morbidities like secondary infections, all negatively affecting quality of life. Lesion-directed therapies including advanced wound care, topical agents, cryo-, electro-, photodynamic-, laser and intralesional therapies have been limited by inconsistent efficacy, inconvenience, or toxicity. [1,2] In this open-label trial, submicron particle paclitaxel in an anhydrous base (SOR007) was evaluated for topical treatment of CM from breast cancer (n=21), leiomyosarcoma (n=1) and Paget's disease (n=1). Previous preclinical and clinical studies with topical SOR007 demonstrated penetration of paclitaxel into the dermis with minimal local skin reactions and negligible systemic absorption.

Trial Design

The study followed a standard 3+3 dose-rising design, with SOR007 formulated at 0.15%, 1.0%, and 2.0% concentrations. During the dose-escalation phase, subjects self-applied SOR007 ointment twice daily for 28 days to a 50 cm^2 area containing at least one eligible lesion (≥ 10 mm longest diameter under RECIST 1.1) selected by the Investigator. Ten subjects were enrolled in dose-escalation: 0.15% (n=4), 1.0% (n=3) and 2.0% (n=3). While dose escalating the Safety Monitoring Committee (SMC) reviewed all available safety data after the last subject in each cohort of three, completed 15 days of SOR007 applications, or after Visit 4 to determine whether to dose escalate, add to the current dose, or expand the previous dose. This was repeated for each escalated dose until all dose levels were enrolled. No dose limiting toxicities (DLT) were identified in any subject allowing the 2.0% concentration to carry-over to dose expansion.

Primary Objective/Endpoint:

- Determine safety and tolerability, as assessed by AEs, changes in laboratory assessments, physical examination findings and vital signs.

Secondary Objective/Endpoint:

- Determine preliminary efficacy: objective tumor response (OTR), best overall response (BOR) and complete clinical response (CR).
- Assess potential reduction in pain at the treatment area by Numeric Rating Scale (NRS-11).
- Describe the paclitaxel pharmacokinetics (systemic exposure) post-topical application.

Inclusion Criteria

- Signed informed consent
- Age ≥18 years
- Malignancies resulting in cutaneous metastasis originating from a solid tumor
- Diagnosis confirmed prior to consent by preferred institutional method
- ECOG Grade 0-2, with minimum life expectancy of at least 3 months
- At least one baseline eligible lesion, ≥ 10mm in the longest diameter
- Willing to refrain from using lotions, creams, etc. during treatment
- Adequate organ and bone marrow function: ANC ≥1500/µl, Hemoglobin ≥ 9.5 grams/dL, AST/ALT ≤ 3.0xULN, bilirubin ≤2.0xULN, Creatinine ≤ 1.5xULN
- Systemic chemo ended before Day 1, systemic taxane chemo ended 4 weeks before Day 1
- Willing to use appropriate birth control for patients of child-bearing potential
- Refrain from touching treatment area during study

Exclusion Criteria

- Open / ulcerated wound extending through the dermis in treatment area
- Colorectal, hepatocellular, gallbladder, cholangiocarcinoma, neuroendocrine, melanomas, hematological and CNS malignancies
- Active viral Hepatitis A, B, or C or liver disease
- Systemic or localized treatment to target area within 4 weeks prior to Day 1
- Elective surgery for treatment of the treatment area during the study and up to 4 weeks post-study
- Known allergic reactions to SOR007 active ingredients or components
- Significant illness that may place subject at risk by participating
- Participation in another trial
- Investigator's opinion of subject noncompliance/ inability to consent
- Current chronic alcohol / drug abuse
- Pregnancy and/or lactating

Methods & Results

Four US sites were initiated and qualified based on Investigator experience in CM and availability of appropriate population. One site was closed early due to lack of enrollment; total enrollment was completed in 24 months.

Following consent, the 14-day screening assessments (medical history, concomitant medication review, CM diagnosis, physical examination, vital signs, ECOG, CBC, chemistry, urinalysis collection, pregnancy test) were completed and eligibility was confirmed prior to Baseline/Day 1 SOR007 ointment application. Eligible lesions were determined by the RECIST (version 1.1) criteria for measurable tumors (≥ 10mm longest diameter). A 50 cm^2 treatment (target) area, containing at least one eligible lesion, was selected by the Investigator at baseline, outlined with a permanent marker, photographed, caliper-measured and tracked at each visit: Days 1, 8, 15, and 29; Day 43 (Group A) or Days 57 and 70 (Group B) or early termination. One last safety visit was conducted 28 days after the last SOR007 application.

Responses (primary efficacy and pain) were assessed as changes from baseline to Day 43 (Group A) or Day 70 (Group B) or to early termination. Tumor response (OTR), (BOR) and (CR) was assessed by photographic analysis of lesion dimension and area using ImageJ, a JAVA image processing program. Pain (best and worst (24-hours prior to visit) and current) was captured on a 0 – 10-point rating scale. PK analysis was conducted on samples collected starting 24-hours after the 1st SOR007 application and continued at each study visit, until the end of study.

Subjects self-applied 1 (0.5 g) fingertip unit (FTU) BID to the gently-cleansed, 'marker-outlined' CM area. SOR007 ointment tubes were supplied at each visit and returned when empty. Instruction cards and diaries were provided to capture dosing, adverse events and concomitant medications.

Of 23 subjects, 12 (Group A n= 6, Group B n= 6) were experiencing pain at baseline (n=1[A], n=3[B], n=8[C]). At Day 29, 1[C] Group A subject pain intensity had not changed, 1[C] worsened, 3 (n=2[B], n=1[C]) improved, and 1 completely resolved through the end of study; by the end of study 3[C] worsened and 3[B] improved. At Day 29, 1 Group B[C] subject pain intensity had worsened, 2 improved and 1 completely resolved through the end of study; 1 subjects' pain was not reported; by the end of study 2 worsened and 3 completely resolved. One subject first experienced mild pain at Day 8, which completely resolved at the next scheduled visit, through the end of study. Two subjects were not assessed due to early termination.

Footnote: [A] = 0.15%, [B] = 1.0%, [C] = 2.0%

Negligible systemic uptake was observed with plasma paclitaxel concentrations below the limit of quantitation (LLOQ = 25 pg/mL) in all but 2 subjects (0215 Day 8= 35.8 pg/mL; 0219 Day 2 =31.4 pg/mL; Day 8=78.4pg/mL; Day15=59.7pg/mL;, and Day 29= 103pg/mL.

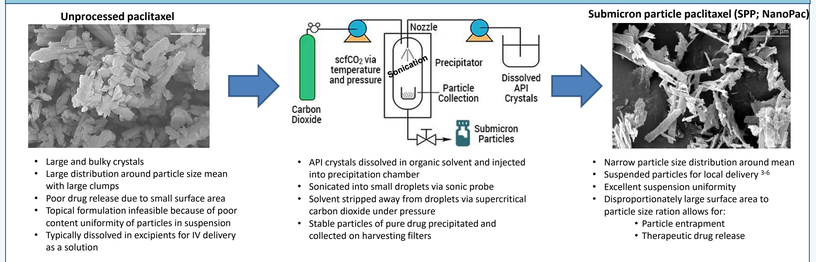
There were 8 SAEs in 7 subjects, of which 1 (Mediport infection) was deemed possibly-related by the Medical Monitor. All other SAEs were unrelated. There were no toxicities assessed as definitely-related. There were 14 'SOR007 application-area AEs' identified as possibly-related (pruritis, burning sensation, pain, soreness, decrease in lymphocytes, irritation from dressing and nausea) and probably-related (burning, tingling, discomfort (started after drug-application was discontinued), muscle tightness and stinging). There were no definitely-related systemic toxicities identified. One subject was withdrawn at Day 8 due to AE of excessive bleeding in the treatment area [8/16 applications; enrolled with lesion area drainage and bacterial infection].

Preliminary efficacy, per BOR (n=22/sum of area of all lesions) at 28 days (n=11) with 55% SD, 18% PD, 27% showing PR and no complete responders. The 56-day treatment group (n=11) showed 45% with SD, 0% PD; 45% PR and 9% with a complete response. BOR (n=22/sum of longest diameter of all lesions) showed at 28 days with 73% SD, 18% PD, 9% showing PR and no complete responders. The 56-day treatment group showed 91% with SD, 0% PD; 0% PR and 9% with a complete response.

Clinical tumor response (CTR) (n=22/area of primary lesion) at 28 days (n=11) showed 45% SD, 36% PD, 18% PR and no complete responders. The 56-day treatment group (n=11) showed 73% SD, 9% PD, 9% PR, and 9% CR. Both the 28-day and 56-day treatment groups had an OTR (n=22/area of primary lesion) of 18%.

CTR (n=22/longest diameter of primary lesion) at 28 days (n=11) showed 55% SD, 36% PD, 9% PR and no complete responders. The 56-day treatment group (n=11) showed 91% SD, 0% PD, 0% PR, and 9% CR. Both the 28-day and 56-day treatment groups had an OTR (n=22/longest diameter of primary lesion) of 9%.

Submicron Particle Production Technology



- Large and bulky crystals
- Large distribution around particle size mean with large clumps
- Poor drug release due to small surface area
- Topical formulation infeasible because of poor content uniformity of particles in suspension
- Typically dissolved in excipients for IV delivery as a solution

- API crystals dissolved in organic solvent and injected into precipitation chamber
- Sonicated into small droplets via sonic probe
- Solvent stripped away from droplets via supercritical carbon dioxide under pressure
- Stable particles of pure drug precipitated and collected on harvesting filters

- Narrow particle size distribution around mean
- Suspended particles for local delivery [3-6]
- Excellent suspension uniformity
- Disproportionately large surface area to particle size ration allows for:
  - Particle entrapment
  - Therapeutic drug release

Fingertip Unit (FTU) Application

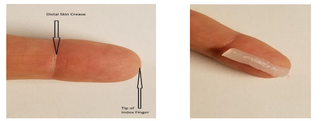
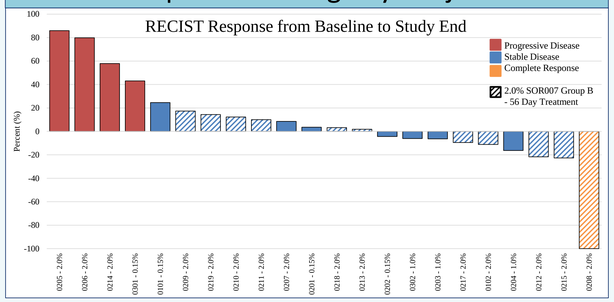


Figure 1. Fingertip Unit (FTU) - the amount of ointment expressed from a tube with a 5mm diameter nozzle, applied from the distal skin-crease to the tip of the index finger of an adult. One FTU or approximately 0.5g covered the 50 cm^2 area.

Graph 1. % Change by Subject



Primary Lesion Photos

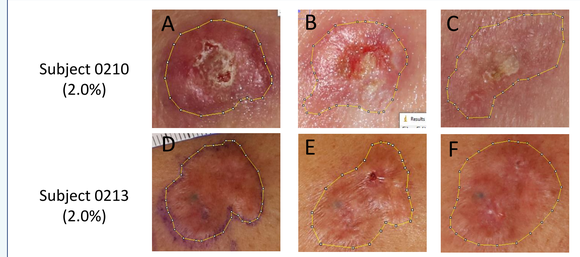


Figure 2. 0210 Day 1 (A), Day 29 (B), Day 70 (C). 0213 Day 1 (D), Day 29 (E), Day 70 (F).

Graph 2. % Change by Lesion

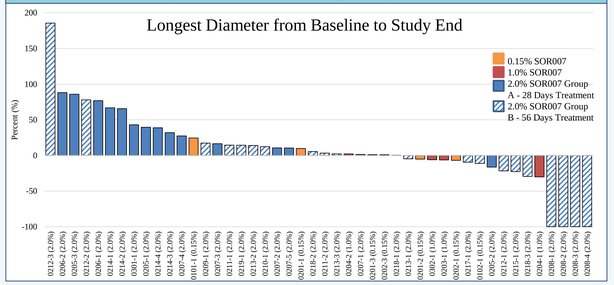


Table 1. Safety

Cohort Dose	Events	TEAEs by Relationship					TEAEs by Severity				
		Not Related	Unlikely to be Related	Possibly Related	Probably Related	Definitely Related	Mild	Moderate	Severe	Life Threatening	Fatal
0.15% SOR007 (n=4)	25	22 (88.0%)	0 (0.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	15 (60.0%)	7 (28.0%)	2 (8.0%)	0 (0.0%)	1 (4.0%)
1.0% SOR007 (n=3)	15	9 (60.0%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	7 (46.7%)	7 (46.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
2.0% SOR007 Group A (n=5)	45	28 (62.2%)	10 (22.2%)	5 (11.1%)	2 (4.4%)	0 (0.0%)	21 (46.7%)	15 (33.3%)	9 (20.0%)	0 (0.0%)	0 (0.0%)
2.0% SOR007 Group B (n=11)	129	103 (79.8%)	19 (14.7%)	2 (1.6%)	5 (3.9%)	0 (0.0%)	73 (56.6%)	33 (25.6%)	22 (17.1%)	1 (0.9%)	0 (0.0%)

Conclusion

SOR007 was determined to be safe and well-tolerated when applied to CM lesions with no significant local skin reactions or evidence of systemic toxicity. Systemic paclitaxel absorption was negligible. There was preliminary evidence of decreased lesion progression and reduction in total lesion area in most CM subjects. There was a reduction in lesion area at the 2.0% dose and lesion size appeared stabilize from Day 29 to end of study, as compared to either of the 0.15% or 1.0% doses. This preliminary efficacy signal showed a dose/duration response suggesting further investigation of the 2.0% dose with extended treatment duration. There were also preliminary signs of partial to complete pain relief for approximately half of each Group A and Group B subjects. Additional investigations of SOR007 2% are in planning to further evaluate the potential of this investigational drug to offer palliative clinical benefit to patients suffering from cutaneous metastases of breast and other cancers who currently have limited options for lesion-directed therapy.

Study Contacts:

Sponsor
Study Director: Rose Marie Cavanna-Mast
Rosemarie.cavanna@usbiotest.com
Medical Director: Gere diZerega
Gere.dizerega@usbiotest.com

Active Sites
USC Norris Comprehensive Cancer Center
Julie.lang@med.usc.edu
Memorial Sloan-Kettering Cancer Center
LacoutuM@mskcc.org
Sarcoma Oncology Research Center
SantChawla@sarcomaoncology.com

References

1. Alcaraz I, Cerroni L, Rütten A, Kutzner H, Requena L Cutaneous metastases from internal malignancies: a clinicopathologic and immunohistochemical review. Am J Dermatopathol. 2012 Jun;34(4):347-93.
2. Spratt DE, Gordon Spratt EA, Wu S, DeRosa A, Lee NY, Lacouture ME, Barker CA. Efficacy of skin-directed therapy for cutaneous metastases from advanced cancer: a meta-analysis. J Clin Oncol. 2014 Oct 1;32(28):3144-55.
3. Verco S, Maulhardt H, Baltezor M, Williams E, Iacobucci M, Wendt A, Verco J, Marin A, Campbell S, Dorman P, diZerega GS. Local Administration of Submicron Particle Paclitaxel to Solid Carcinomas Induces Direct Cytotoxicity and Immune-Mediated Tumoricidal Effects without Local or Systemic Toxicity: Preclinical and Clinical Studies. Drug Deliv Transl Res. (in press)
4. Mullany S, Miller DS, Robison K, Levinson K, Lee YC, Yamada SD, Walker J, Markman M, Marin A, Mast P, diZerega GS. Phase II Study of Intraperitoneal Submicron Particle Paclitaxel (SPP) Plus IV Carboplatin and Paclitaxel in Patients with Epithelial Ovarian Cancer Undergoing Cytoreductive Surgery. Gynecol Oncol Rep., 2020
5. Sharma N, Othman M, Mendoza-Ladd A, Verco S, Verco J, diZerega G, Lo S (2020) Sa2006 EUS-Guided Injection of Intratumoral Submicron Particle Paclitaxel (SPP) for the Treatment of Locally Advanced Pancreatic Adenocarcinoma (LAPC):Phase 2 Study. Gastrointestinal Endoscopy, 91, 6S.
6. Othman M, Patel K, Krishna S, Mendoza-Ladd A, Verco S, Verco J, Wendt A, diZerega G (2020) Sa1399 Intracystic Injection of Submicron Particle Paclitaxel (SPP) for the Treatment of Mucinous Pancreatic Cystic Lesions Resulted in Reduction in Cyst Volume, an Interim Report. Gastrointestinal Endoscopy, 91, 6S.