A Phase 2 Open-label, Single-arm Trial to Investigate the Efficacy and Safety of Topical Remetinostat Gel as Neoadjuvant Therapy in Patients Undergoing Surgical Resection of Squamous Cell Carcinoma (SCC)

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IRB-49542 **SKIN0050** **NCT03875859** **IND 134521**

Version Date: 19 July 2019

Version: 1
SRC approval date: pending

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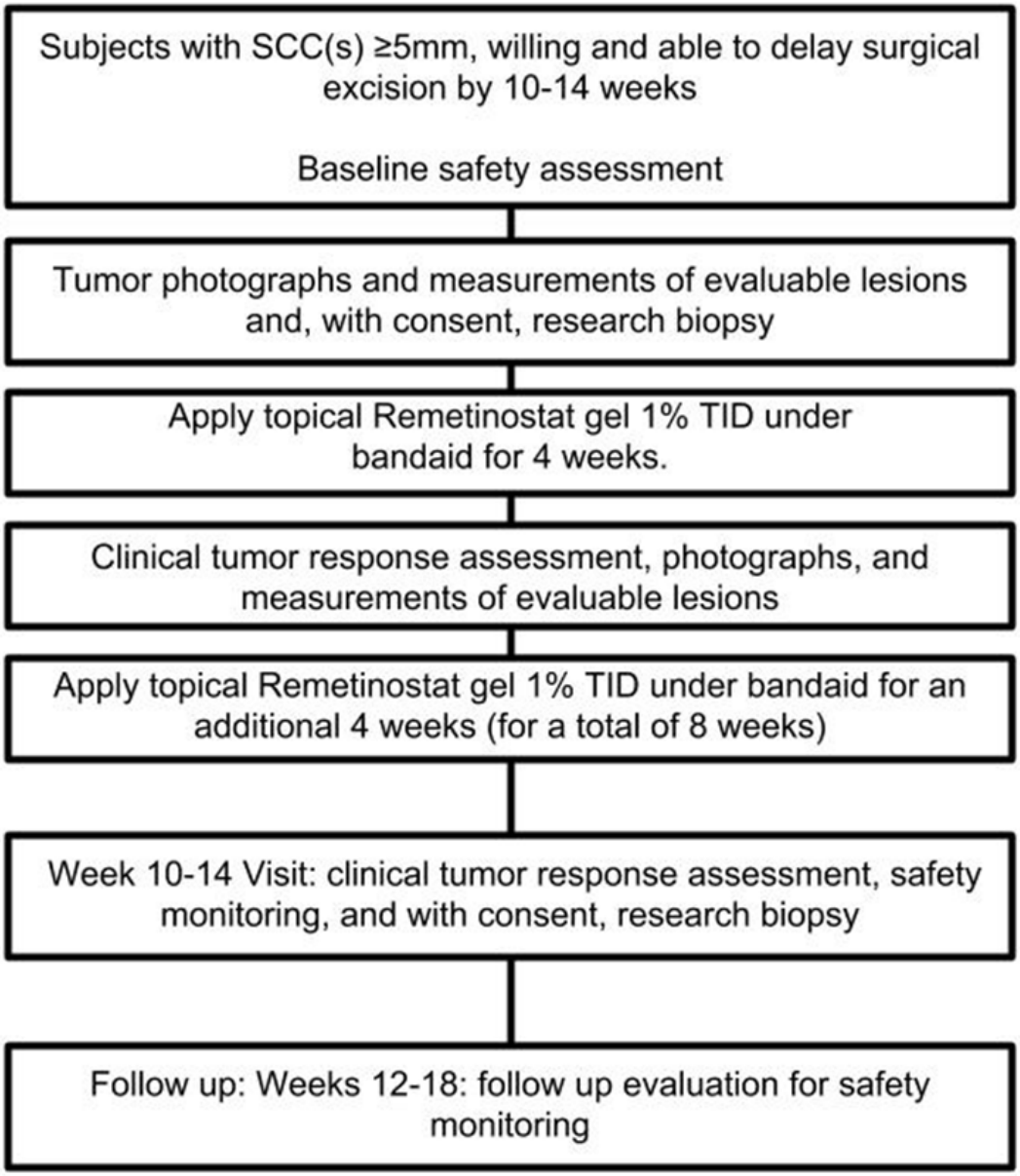
PROTOCOL SYNOPSIS

TITLE	A Phase 2 Open-label, Single-arm Trial of the Efficacy and Safety of Topical Remetinostat Gel as Neoadjuvant Therapy in Patients with Squamous Cell Carcinoma Undergoing Surgical Resection
STUDY PHASE	Phase 2
INDICATION	Treatment of squamous cell carcinoma (SCC) and squamous cell carcinoma *in situ* (SCC-IS)
INVESTIGATIONAL PRODUCT	Topical remetinostat gel 1%
PRIMARY OBJECTIVE	• To determine if topical remetinostat gel treatment 3-times-daily (TID) for 8 weeks will decrease SCC tumor area (in mm^2) by at least 30% • To determine the overall response rate (ORR) of SCC tumors to 8 weeks of TID treatment with topical remetinostat gel
SECONDARY OBJECTIVE	To assess the safety and tolerability of remetinostat gel 1% when applied topically TID under occlusion for 8 weeks as follows: • Incidence, type, and severity of adverse events (AEs) • Incidence and nature of serious adverse events (SAEs) • Incidence of AEs leading to remetinostat discontinuation or interruption • Adherence to the treatment, measured by number of patients discontinuing the treatment (for any reason) and treatment interruptions
TREATMENT SUMMARY	Apply topical remetinostat gel 1% 3 times daily (TID) under bandage occlusion for 8 weeks
STUDY POPULATION	Adults of either gender with squamous cell carcinoma (SCC) lesions ≥ 5 mm. See Section 3.1 for detailed eligibility.
SAMPLE SIZE	30 SCC per-protocol evaluable tumors. The maximum number of subjects contributing evaluable tumors will be 40, but can be less to obtain the 30 SCC per-protocol evaluable tumors. Participating subjects that do not contribute evaluable tumors will not be counted towards this total. It is anticipated that no more than 40 subjects will participate overall.

STATISTICAL CONSIDERATIONS	Overall response rate of SCC tumors (Primary Objective and Primary Outcome) in subjects will be defined as at least a 30% decrease in the area of each SCC lesion(s). With a planned analysis on 30 per-protocol evaluable SCCs, this study would provide 91% power to reject an ORR of 15% if the true ORR is 40% or better, at one-sided alpha level of 0.05 with at least 9 responders. For the Secondary Objective 1, toxicities will be graded according to the National Cancer Institute CTCAE v5.0.

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
CBC	Complete blood count
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
DLT	Dose-limiting toxicity
DSMC	Data Safety Monitoring Committee
EKG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HDAC	Histone deacetylase
HH	Hedgehog
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
OS	Overall survival
PLT	Platelet
PD	Progressive disease
PR	Partial response
PTCH1	Protein patched homolog 1
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SCC	Squamous cell cancer / carcinoma
SCC-IS	Squamous cell cancer/carcinoma *in situ*
SD	Stable disease
Shh pathway	Sonic hedgehog pathway
SMO	Smoothened
TID	Three times daily
ULN	Upper limit of normal

1. OBJECTIVES

1.1. Primary Objective

Overall response rate of SCC in subjects defined by at least a 30% decrease in SCC tumor area (in mm^2) at end of study measurement as compared with baseline measurements. The threshold for positive response will be at least 30% decrease in tumor area (Note: RECIST v1.1 criteria have limited utility for SCCs under 10 mm, and will not be used for that reason).

1.2. Secondary Objectives

- Safety assessment of remetinostat after 8 weeks of topical treatment will be evaluated as follows:
  - Incidence, type, and severity of adverse events (AEs)
  - Incidence and nature of serious adverse events (SAEs)
  - Incidence of AEs leading to treatment discontinuation or interruption
  - Adherence to the treatment, measured by number of patients discontinuing the treatment (for any reason) and treatment interruptions

2. BACKGROUND

2.1 Study Disease

Cutaneous squamous cell carcinoma (SCC) is one of the most common human cancers and is the second most common skin cancer, comprising at least 20% of all non-melanoma skin cancers, affecting approximately 700,000 Americans each year (as non-melanoma skin cancers are not reported to cancer registries, the exact incidence of SCC is not known)[1]. Similar to other skin cancers, risk factors for development of SCC include age, lighter skin tones, and importantly, chronic exposure to ultraviolet light[2]. Exposure to ionizing radiation, arsenic, chronic inflammatory processes (such as in chronic wounds), and HPV infection also predispose patients to developing cutaneous SCC[2]. SCC is also more common in patients who have been exposed to arsenic[3,4], or have taken photo-sensitizing drugs such as thiazide diuretics[5]. Up to 50% of transplant patients on immunosuppressive therapy develop cutaneous SCC after long-term therapy; these SCCs also tend to behave more aggressively[2].

Given their frequencies, treatment of non-melanoma skin cancers (NMSC) represents a significant annual cost to the United States health care system. Amongst all cancers treated in the Medicare population, NMSC represented the 5th-most-costly cancer to Medicare overall and represented 4.5% of all Medicare cancer costs[6]. This high expenditure is largely influenced by the high frequency of NMSC rather than a high per-patient cost. The incidence of NMSC has increased since the mid-1960s at a rate of approximately 2% to 8% per year[6,7], so overall healthcare spending to treat SCC, with its continually-increasing incidence, is very likely to continue to rise.

While the exact mechanism of pathogenesis in SCC is unknown[8], multiple genetic mutations have been associated with and are thought to contribute to the development of SCC. Mutations in *p53*, *CDK2NA*, *RAS*, *MYC*, and *KNSTRN, NOTCH1,* and *NOTCH2* have all been associated with SCC[2,9-11] and MC1R polymorphisms can influence individuals' risk for developing SCC[12]. *EGFR* and *IKK* expression have been found to be predictive of metastatic capability in SCC[7]. A study of conjunctival epithelial tumors suggested that Sonic hedgehog signaling (Shh) pathway

alterations could lead to transformation of intraepithelial neoplasia into invasive squamous cell carcinoma[8].

2.2 Study Agent

Histone deacetylase (HDAC) inhibitors are anticancer agents. Two HDAC inhibitors, vorinostat and romidepsin, were approved by the US FDA for the treatment of cutaneous T-cell lymphoma (CTCL)[13]. HDAC inhibitors antagonize tumors by altering the expression of oncogenes or tumor suppressors by modulating the level of acetylation/deacetylation of histones and/or non-histone proteins such as transcription factors. Preclinical studies suggest that HDAC inhibitors may potentially be effective anti-SCC agents, as murine studies have shown HDAC inhibitors can inhibit the growth of SCC cells and SCC tumors both *in vitro* and *in vivo*[14].

Remetinostat is also known as suberohydroxamic acid phenyl ester (SHAPE); SHAPE Gel; SHP 141; and 4 [[8 (hydroxyamino) 1,8 dioxooctyl]oxy] benzoic acid methyl ester. Remetinostat is a histone deacetylase inhibitor (HDACi) that was designed with a metabolically labile ester bond so that topical application would produce effective local histone deacetylase (HDAC) inhibition in cutaneous lesions while resulting in only negligible systemic HDAC inhibition.

Preclinical studies have demonstrated a role for histone deacetylase 1 and 2 (HDAC1/2) in modulating Gli1 transcription and basal cell carcinoma (BCC) growth in cell lines and mouse models. We conducted an open-label clinical trial of the pan-HDAC inhibitor, remetinostat, as a neoadjuvant treatment for basal cell carcinoma (BCC). Participants applied topical remetinostat 1% gel three times per day under bandage occlusion to BCC(s) for six weeks prior to undergoing surgical excision. The primary outcome was overall response rate (ORR) as measured by at least a thirty percent decrease in BCC greatest diameter. In addition, tumor area was assessed as well as percent of tumors with complete response. Secondary objectives include suppression of Gli1 expression in post-treatment tumors and remetinostat tolerability. This trial has enrolled 17 BCCs tumors, ranging in baseline size from 6-25 mm greatest diameter, with enrollment goal of 30 tumors. Among the 14 BCCs that have completed the trial, the ORR is 64%. The longest tumor diameter of BCCs shrank by an average of 62%, and tumor area was reduced by an average of 70%. 43% (6) of tumors reached clinical resolution. Side effects associated with treatment included grade 1-2 eczematous reaction in 71% (10), and application site pain in 36% (5). Remetinostat gel for BCC offer a potentially effective, non-surgical intervention for treatment of localized BCCs.

HDAC inhibitors can suppress growth of SCC tumor xenografts

In one study[14], vorinostat was found to suppress the proliferation of epidermoid carcinoma cells *in vitro*. Highly-immunosuppressed female athymic mice were injected with epidermoid carcinoma A431 cells; once tumors were palpable, vorinostat or placebo vehicle was injected intraperitoneally. After three weeks, the mice were sacrificed and their tumors analyzed. Treated tumors demonstrated increased acetylation of histone H3 and p53 and apoptosis of tumor cells. Consistent with this finding, histologic evaluation of treated tumors demonstrated large necrotic areas. Further evaluation demonstrated that vorinostat inhibits cell cycle regulatory proteins (with notable reduction in the production of cyclins A ($p = 0.002$) and E ($p = 0.015$). Expression of total and phosphorylated ERK, activation of which is known to regulate cell proliferation[15], was also assessed. Treatment with vorinostat resulted in significant reduction of ERK1/2 phosphorylation. Additional anti-tumor effect is thought to be due to

reduction in phosphorylation of Akt, resulting in reduction of mTOR and its downstream targets (S6 ribosomal protein, p70S6 kinase, and 4E-BP1)[14].

HDAC inhibitors are well-tolerated and have resulted in promising clinical responses in patients with advanced stage head and neck squamous cell carcinoma

A phase 1 study of 26 patients with advanced stage head and neck SCCs of mixed etiology demonstrated similar to more-favorable safety and tolerability profiles when compared to pre-existing chemoradiation regimens that did not include a HCAC inhibitor. While clinical response to therapy was not the primary endpoint of this phase 1 study, encouraging tumor responses were observed despite the subjects' advanced-stage tumors[16].

Altogether, the preliminary data suggests HDAC inhibitors are a promising new candidate therapy for SCC.

Remetinostat is a novel histone deacetylase inhibitor (HDACi) that was designed with a metabolically-labile ester bond so that topical application would produce effective local histone deacetylase (HDAC) inhibition in cutaneous lesions while resulting in only negligible systemic HDAC inhibition. Remetinostat is rapidly degraded into primary metabolites SHP-100 and methylparaben. Three studies (an *in vitro* Franz Diffusion Cell assay; a 28-day study in minipigs; and a 90-day study in minipigs) showed that uptake of remetinostat through skin into the systemic circulation was minimal. In both dermal and intravenous (IV) studies in animals, remetinostat was metabolized in the blood rapidly to the primary metabolites. These findings suggest that dermal application of remetinostat largely obviates systemic exposure to the HDAC inhibitor remetinostat and, consequently, sequelae from systemic inhibition of HDAC. This observation was supported by the fact that in a Phase 1 study in patients with cutaneous T-cell lymphoma (CTCL), plasma concentrations of remetinostat were minimal and at or below the lower limit of quantitation of the assay indicating minimal systemic exposure. The lack of measurable levels of remetinostat in blood is consistent with the rapid conversion of remetinostat to its metabolites.

Remetinostat has been tested in a battery of safety pharmacology studies. Remetinostat did not affect the functional observational battery (FOB) parameters in rats given IV doses of up 100 mg/kg/day, which is equivalent to a dose of approximately 970 mg in a 60-kg human subject. Remetinostat also did not inhibit human ether à-go-go-related gene (hERG) current *in vitro* at concentrations up to approximately 32,000 ng/mL and did not affect cardiovascular function in minipigs given IV doses of up to 100 mg/kg, which is equivalent to a dose of approximately 5,700 mg in a 60-kg human subject. Based on the lack of effect observed in these studies, it was anticipated that remetinostat would be unlikely to adversely affect nervous system or cardiovascular system function when administered topically to humans. This observation has been supported by the clinical data, to date.

A program of Good Laboratory Practice (GLP) - compliant toxicity studies evaluated the safety of multiple doses of remetinostat administered IV to rats and administered topically to minipigs. In addition, the genotoxicity of remetinostat and the local tolerance and sensitizing potential of remetinostat and placebo gel solutions were assessed. Remetinostat and placebo gel were tolerated, with only excipient-related local irritation when applied topically, and renal histopathologic changes not relevant in humans when administered IV. The 28-day No-Observed-Adverse-Effect-Level (NOAEL) for remetinostat administered IV to rats was

30 mg/kg/day. When remetinostat gel 1.5% was applied topically in minipigs, the 28-day and 90-day NOAEL of 150 μg/cm^2 of skin yielded a total dose of approximately 6 mg/kg.

Based on these findings, a phase 1 (SHP-141-001) study was conducted (NCT01433731) in 18 patients with stage IA-IIA MF-CTCL. This randomized, double-blind, placebo-controlled dose-escalating study was designed to evaluate the safety, pharmacokinetics and pharmacodynamics of remetinostat gel administered topically twice-daily up to 28 days in patients. Escalating doses of remetinostat gel, 0.1%, 0.5% and 1%, were administered BID for a maximum of 28 days to 3 cohorts of patients (n = 6 patients per cohort, active:placebo ratio 5:1).

A phase 2, multicenter, open-label, randomized study (SHP-141-003, NCT02213861) to evaluate the efficacy and safety of remetinostat applied topically in 60 patients with stage IA to IIA MF-CTCL was completed in September 2016. Three doses of remetinostat were evaluated in three treatment arms (n = 20 per treatment arm, 1:1:1 randomization). The three dosing regimens of remetinostat (1% QD, 0.5% BID and 1% BID) were tested in this study for between 6 to 12 months.

All doses and schedules of remetinostat were well tolerated. There were three CTCAE Grade ≥3 remetinostat treatment related AEs, with 2/20 patients discontinuing treatment due to remetinostat related AEs, for the highest dose group of 1% gel BID (2/20 and 6/20 for the 1% gel QD and 0.5% gel BID dose groups respectively). There were no remetinostat treatment related systemic adverse events reported in either clinical study, which is consistent with the minimal systemic exposure and very short half-life of remetinostat in human blood.

A phase 1 study in patients with psoriasis resulted in limited efficacy but the safety profile was similar to the MF-CTCL studies; no serious adverse events were seen on this study.

Remetinostat is not currently approved by FDA for any use, and an Investigational New Drug application (IND) is required. This protocol is submitted to IND 134521.

2.3 Rationale

The severity of SCC burden differs widely among patients from those who develop early SCCs, have advanced SCC, or suffer from numerous SCC lesions. In the more severely-affected, such as those who have undergone organ transplantation or are otherwise immunosuppressed, or those with extensive chronic sun exposure, their quality of life is severely affected by the need for frequent, repetitive surgical procedures. Procedures can be time-consuming and expensive, and they inevitably produce scarring. Other patients may have fewer tumor lesions, but they occur in cosmetically-disfiguring areas or near functional areas, where surgery is not ideal.

SCCs are usually treated with surgical excision, with resultant scars that can be disfiguring. Several non-surgical treatments are sometimes utilized to treat SCC and SCC-IS. Cryotherapy can be used for low-risk invasive cutaneous SCCs and SCC-IS, but is less effective than surgery and can be complicated by post-procedure hypopigmentation, hypertrophic scaring, or hair loss of the treated area[17]. Photodynamic therapy (PDT) is an option for patients with non-invasive SCC, but is not a suitable option for invasive SCC given high recurrence rates[17]. Similarly, topical fluorouracil and imiquimod are both used to treat SCC-IS, especially amongst patients who refuse surgical treatment. However, both of these uses are off-label and have significant inflammatory reactions that can cause patients to discontinue their use[18,19]. For patients with SCCs in areas not suitable for surgical resection, for those who are not surgical

candidates, or for tumors with significant perineural or large nerve involvement, radiation therapy can be considered[20,21]. However, limitations exist with each of these non-surgical modalities. Additionally, patients who develop multiple SCCs and/or tumors in sensitive areas would likely greatly benefit from additional non-surgical treatment options.

Given the limitations of current treatment modalities and the pre-clinical murine and phase 1 studies that demonstrate HDAC inhibitors impact the proliferation and survival of SCC cells, the topical HDAC inhibitor remetinostat is promising potential therapy for cutaneous SCCs.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance (see Section 10 for additional information)

- The primary purpose of this study is:
    - To determine if 8 weeks of topical remetinostat gel applied TID under occlusion will suppress SCC growth
    - To determine the overall response rate (ORR) of SCCs after 8 weeks of treatment with topical remetinostat gel 1%, as measured by at least 30% decrease in greatest area (in mm^2).
- Subjects with at least 1 biopsy-proven cutaneous SCC will be recruited for this study.
- Subjects will apply remetinostat gel 1% to at least 1 SCC.
- Non-invasive cutaneous SCC lesions, including Bowen's disease, are also eligible for this study
- There is 1 treatment option: Topical remetinostat gel 1% applied 3 times daily.
- The study is a single-arm, open-label design
- For purposes of ClinicalTrials.gov, there is no secondary outcome.

2.5 Correlative Studies Background

There are no planned correlative studies.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Participant Eligibility Checklist

Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the subject's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	A Phase 2 Open-label, Single-arm Trial to Investigate the Efficacy and Safety of Topical Remetinostat Gel as Neoadjuvant Therapy in Patients Undergoing Surgical Resection of Squamous Cell Carcinoma (SCC)
Protocol Number:	**IRB-49542 / OnCore TBD**
Principal Investigator:	**Kavita Sarin, MD, PhD**

II. Subject Information:

Subject Name / ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC-approved ☐ IRB-approved ☐ Contract signed ☐

	Inclusion Criteria (From IRB-approved protocol)	Yes	No	N/A	Supporting Documentation*
1	Must have at least one cutaneous SCC or SCC *in situ* lesion greater than or equal to 5 mm. Non-invasive SCC lesion(s), including (SCC-IS), are eligible, but must be amenable to surgical resection.	☐	☐	☐	
2	18 years of age or older	☐	☐	☐	
3	Must be willing to apply the topical remetinostat 3 times daily for 8 weeks and cover with an occlusive bandage.	☐	☐	☐	
4	Negative serum pregnancy test within 14 days prior to the first dose of study therapy [for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally postmenopausal for at least 24 consecutive months (e.g., who has had menses any time in that period)]	☐	☐	☐	
5	Sexually-active women of child bearing potential and male patients with a female partner of child-bearing potential must agree to use acceptable methods of contraception to avoid pregnancy (e.g., oral; injectable; or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized male) before the 1st dose of study therapy and for 3 months after the last dose of study therapy	☐	☐	☐	

	Inclusion Criteria (From IRB-approved protocol)	Yes	No	N/A	Supporting Documentation*
6	Has signed and dated the current IRB-approved informed consent document	☐	☐	☐	

	Exclusion Criteria (From IRB-approved protocol)	Yes	No	N/A	Supporting Documentation*
1	Any large (> 20 mm) SCC lesion. Patients with large SCC lesion(s) will be referred for evaluation for surgical resection.	☐	☐	☐	
2	Inoperable locally-advanced and/or non-cutaneous metastatic SCC	☐	☐	☐	
3	SCC lesion(s) in cosmetically-sensitive areas (e.g., tip of nose, eyelid). If a prospective subject has SCC lesion(s) in other areas, those tumor(s) may be considered for enrollment.	☐	☐	☐	
4	Taking any medication known to affect SCC growth	☐	☐	☐	
5	Within the past 6 months, has used topical or systemic therapies that might interfere with the evaluation of the study medication during the study. Specifically, these include the topical use at the site of the study tumors: o Glucocorticoids o Retinoids either systemically or topically at the tumor site (e.g., etretinate, isotretinoin, tazarotene, tretinoin, adapalene) o Alpha-hydroxy acids (e.g., glycolic acid, lactic acid) to the tumor site o 5-fluorouracil or imiquimod: --	☐	☐	☐	
6	Has received treatment with systemic chemotherapy within 60 days prior to starting study medication	☐	☐	☐	
7	Currently receiving systemic medications that could affect SCC tumors (e.g., oral retinoids) or might interact with remetinostat	☐	☐	☐	
8	Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, recurrent seizure history or psychiatric illness/social situations that would limit compliance with study requirements	☐	☐	☐	
9	Moderate to significant immunosuppression (e.g., active cancer, significant autoimmune disease) and/or receiving immunosuppressive drugs that result in moderate to significant immunosuppression (e.g., low dose oral glucocorticoids do **not** necessarily exclude a patient)	☐	☐	☐	
10	Known or previous hypersensitivity to HDACi	☐	☐	☐	
11	History of congestive heart failure, cardiac arrhythmias, or other findings of ventricular dysfunction	☐	☐	☐	
12	Pregnancy or breast-feeding	☐	☐	☐	

IV. Statement of Eligibility

By signing this form of this trial, I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Investigator Signature:	Date:
Printed Name:	
Secondary Reviewer Signature:	Date:
Printed Name:	
Tertiary Reviewer Signature:	Date:
Printed Name:	

3.2 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent prior to participation in any study-specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the subject's research file.

3.3 Randomization Procedures

This study does not have randomization. All subjects must at least have one cutaneous SCC lesion and will apply topical remetinostat to SCC(s). If the subject has more than one SCC, a body map will remind subjects where to apply gel.

3.4 Study Timeline

Primary Completion:

The study will reach primary completion 18 months from the time the study opens to accrual. Individual subjects will reach primary completion 8 weeks after starting topical remetinostat treatment.

Study Completion:

The study will reach study completion 24 months from the time the study opens to accrual, e.g., allowing 6 months from Primary Completion for data analysis. Individual subjects will complete the study about 14 to 18 weeks after starting topical remetinostat treatment (e.g., Screening; 8 weeks treatment; post-treatment visit and surgical excision at Week 10 to 14, 4 weeks follow-up).

4. TREATMENT PLAN

Adult subjects in the clinic who have one or more biopsy-proven cutaneous SCC or SCC-in situ (hereafter referred to as "SCC") lesions greater than or equal to 5 mm in diameter, at least one of which is being biopsied as a normal course of care, will be invited to participate in this trial. Eligibility of prospective participants will be confirmed, and subjects will enroll according to stated inclusion and exclusion criteria.

Screening visits may be combined with or without day 1 visit.

Prospective participants must be willing to sign a consent form. Subjects will also give consent to donate their SCC tissue for biomarker measurement and apply medication 3-times daily under bandage occlusion for 8 weeks. The anticipated bandage will be an adhesive bandage (e.g., "Band-Aid") with a non-adherent dressing, or paper tape with a non-adherent dressing.

Drug treatment: Subjects will be instructed to apply topical remetinostat to individual SCCs 3-times daily (TID) for 8 weeks. Patients will be asked to discontinue application of the medication at 8 weeks, approximately 2 weeks prior to their surgical excision(s), as dermal irritation from study drug may interfere with lesion identification at excision.

At least 1 target SCC will be identified requiring surgical excision per standard of care. In addition to being measured and photographed, this lesion(s) may be biopsied. Week 8 biopsy may be collected at the time of surgical excision of lesion(s). Histopathological evaluation of the specimen may be performed.

After an initial treatment application demonstration by the study team, treatment applications will be self-administered by the subject or a caregiver. Patients will receive oral and written administration instructions at the outset of the trial as follows:

> "Study medication is to be applied to dry skin. Apply the study medication to the SCC lesion(s) designated by your physician, 3 times daily for 8 weeks, using clean washed finger(s)/ hand as applicable. Cover the treated SCC lesions(s) with a sticky strip bandage, such as a Band-Aid. If you start to treat new lesions or stop treating any lesion, please inform your physician so a record can be kept of which lesions are being treated with study medication. There is no need to leave large amounts of residue on your skin. If someone else helps apply the study medication, they should follow the same instructions. Immediately following application, wipe the finger(s) and hands you have used to apply the study drug with a disposable tissue and wash your hands using soap and water. If the study medication gets on the skin of other people, they should wash with soap and water. Alternatively, you or a caregiver can wear disposable gloves to apply the study medication, which will be supplied to subject on request."

Diary: after an initial explanation by the study team at the first visit, patients will be requested to fill out a medication diary to document application of the study drug (see Appendix A.) Patients will be requested to fill this out daily and requested to bring their diary with them to each study visit for review by the study team.

Tumors to be treated will be clearly identified. Patients will be instructed to store research medication in a refrigerator (see Appendix B). Patients will be offered a small portable medication cooler to utilize to keep their study drug cold.

All tumors will be measured and photographed at baseline, 4 weeks and after applying remetinostat for 8 weeks (at the Week 10 visit).

Paper case report forms will be used to capture source data for this study. A physician note will also be entered into Stanford's electronic medical record system for each of the study visits.

Patients may be contacted periodically to check on compliance and to follow up on AEs. Additional clinic visit(s) may be scheduled to assess AEs.

Given the absence of any remetinostat treatment related systemic AEs, together with the lack of effect on laboratory parameters or EKG, the minimal levels of remetinostat detected systemically reported in clinical studies to date, and the small BSA (< 0.5%) that will be treated with remetinostat gel, no lab assessments will be performed with the exception of a serum pregnancy test for women of child-bearing potential at baseline to assess eligibility for enrollment.

It is anticipated that the entire target tumor(s) will be surgically removed after the 8th week of treatment, in accordance with regular medical care; it is estimated that the surgical excision will occur between Weeks 10 to 14, depending on surgeon availability. A dose of remetinostat will be applied to the SCC by study personnel in clinic 30 mins before surgical excision. If surgical excision is delayed, i.e., does not occur at Week 10, remetinostat application may be continued for up to 4 additional weeks until surgical excision.

A follow-up visit will occur between Weeks 12 to 18 (approximately 2 to 4 weeks after Mohs/surgical excision), which may be in conjunction with surgery or a surgical follow-up visit,

or the visit may be conducted by phone. Patients may be contacted after completion of the study for additional follow up if deemed necessary by the Study Doctor.

SCC tissue biopsies will be collected from those who consent at baseline and Week 10 to evaluate the tumors treated with topical remetinostat gel 1%. The SCC biopsy will be collected in RNA later.

4.1 General Concomitant Medication and Supportive Care Guidelines

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a subject between 1 month preceding the screening evaluation and the end of study visit.

Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy will continue their use. All concomitant medications will be reported to the investigator and recorded on the appropriate CRF.

4.2 Criteria for Removal from Study

The trial will be terminated in the event of an SAE (Serious Adverse Event) related to the intervention. A Serious Adverse Event is any of the following:

- Fatal (i.e., the AE actually causes or leads to death).
- Life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death). It does not include an AE that, had it occurred in a more severe form, might have caused death (life-threatening does not include events such as blood values that do not by themselves represent an immediate risk of death).
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Any occurrence considered by the investigator to be a significant medical event (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the medical outcomes listed above). All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of the study drug:

- **Probably-related**: An adverse event has a strong temporal relationship to the study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.
- **Possibly-related**: An adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared the potential relationship to study drug.
- **Probably Not Related**: An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
- **Not Related**: An adverse even is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug.

Subjects may be removed from the study because of subject wishes, non-compliance, or development of any medical condition that puts the subject at increased risk, in the opinion of the investigator.

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Any subject who presents at screening or during treatment with a large (> 20 mm) SCC lesion: such a lesion will be discontinued from treatment (if applicable) and referred for evaluation for surgical resection. (If the patient has other, smaller lesions, these smaller lesions may be considered for enrollment in the study.)
- Subject withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Surgical or other treatment of target SCC before Week 8
- Pregnancy

4.3 Alternatives

Alternatives to participation in the study include participating in a different clinical study, receiving medical care outside of a research study (including immediate surgical treatment), or no treatment.

5. INVESTIGATIONAL DRUG INFORMATION

5.1 Investigational Drug

Remetinostat is also known as suberohydroxamic acid phenyl ester (SHAPE); SHAPE Gel; SHP-141; and 4-[[8-(hydroxyamino)-1,8-dioxooctyl]oxy]-benzoic acid methyl ester. Remetinostat is a histone deacetylase inhibitor (HDACi) that was designed with a metabolically-labile ester bond so that topical application would produce effective local histone deacetylase (HDAC) inhibition in cutaneous lesions while resulting in only negligible systemic HDAC inhibition.

In this single-arm study, remetinostat is formulated at a strength of 1.0% in a gel consisting of dehydrated alcohol; propylene glycol; hexylene glycol; glycerin; oleyl alcohol; diisopropyl adipate; hydroxypropylcellulose; butylated hydroxytoluene and citric acid (anhydrous). The overall concentration of ethanol in the gel is approximately 50% (w/w). The primary packaging for remetinostat gel is aluminum tubes with plastic screw-on caps. The 60-g tubes are packaged in paper cartons (both labeled with identical labels).

See the remetinostat Investigator Brochure for additional information including the mechanism of action; summaries of animal and clinical studies; non-clinical and clinical pharmacokinetic; major route of elimination; safety profile; and the non-clinical and clinical data supporting the dose and regimen chosen for this study.

5.2 Availability

Medivir AB is providing drug for this study.

5.3 Agent Ordering

Remetinostat will be ordered by the Principal Investigator and shipped directly to the Stanford Dermatology Clinic, where it will be stored per manufacturer's guidelines and Stanford SOPs. Investigational drug will not be shipped to or held by Stanford Investigational Drug Services. The contact for drug ordering is:

Medivir AB
Box 1086
141 22 Huddinge, Sweden
Tel: +46(0)8-5468 31 00
E-mail: Torbjorn.larsson@medivir.com

5.4 Storage Conditions

The Investigator is responsible for the control of the drug under investigation. The study agent will be kept in a locked refrigerator (2 to 8ºC) in a secure area. Only trained research staff will have access to the locked refrigerator.

5.5 Agent Accountability

Adequate records for the receipts (e.g., Drug Receipt Record) and disposition (eg, Drug Dispensing Log) of the study drug will be maintained. Accountability and subject compliance will be assessed by maintaining adequate "drug dispensing" and return records.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following information:

- Documentation of drug shipments received from the Sponsor (date received, quantity, and tube number)
- Disposition of unused study drug not dispensed to subject

A Drug Dispensing Log will be kept current and will contain the following information:

- The identification of the subject to whom the study medication was dispensed
- The date(s), quantity, and kit number of the study medication dispensed *to* the subject.
- The date(s), quantity and kit number of the study medication returned *by* the subject

Subjects will be asked to return all used and unused drug supply containers during and at the end of the treatment.

The investigational product will be returned to the Sponsor for disposal, or with the agreement of the drug manufacturer, destroyed in accordance with institutional SOPs.

6. DOSE MODIFICATIONS

Detectable systemic levels of remetinostat after topical application for 8 weeks are not anticipated. Treatment with topical remetinostat may be interrupted or dose modified as detailed below. Subjects who require discontinuation of treatment for any reason will go

off-study. The Study Doctor will assess and determine if an individual subject needs to be taken off the study due to side effects.

6.1. Dose Modifications due to Toxicity and Stopping Criteria

Patients experiencing any treatment-related Grade 3 or higher local dermal irritation will be required to have their treatment exposure suspended until the irritation reduces to at least Grade 2. Guidelines for dose reduction, interruption and discontinuation are provided below:

Table 1: Dose Modification

Grade of Local Dermal Irritation	Defining Clinical Signs	Proposed Treatment Modification
0 (No Reaction)	None	No action required; observation
1 (Mild)	Definite pink to red coloration	
2 (Moderate)	Increased redness, with or without edema	
3 (Moderately Severe)	Very red, with edema and vesiculation	Treatment must be suspended until irritation improves to Grade 2 or lower (this must occur within 2 weeks). After the irritation improves to Grade 2 or lower, treatment may be re-started, initially TID every second day, then increased to TID daily, if tolerated. If dermal irritation does not improve to Grade 2 or lower after 2 weeks, treatment should be discontinued, and the patient withdrawn. If event re-occurs, consider discontinuation of treatment.
4 (Severe)	Deep red, swelling and edema with bullae formation and necrosis	Treatment must be suspended until irritation improves to Grade 2 or lower (this must occur within 2 weeks). After the irritation improves to Grade 2 or lower, treatment may be re-started, initially TID every second day, then increased to TID daily, if tolerated. If dermal irritation does not improve to Grade 2 or lower after 2 weeks, treatment should be discontinued, and the patient withdrawn. If event re-occurs, consider discontinuation of treatment.

Treatment may be stopped approximately 2 weeks before surgical excision if the PI determines that local dermal irritation may interfere with lesion identification at excision.

Based on remetinostat safety data collected to date in earlier MF-CTCL studies, systemic adverse events are not anticipated.

In the unlikely event that a patient experiences any systemic AE which is consistent with the effects of systemic HDAC inhibition, such as diarrhea or thrombocytopenia **and** the AE is considered possibly related to treatment with remetinostat gel, their treatment will be modified, as follows:

Thrombocytopenia CTC Grade 2 (platelet count ≥ 50 to ≤ 75 x 10^9/L): Reduce treatment frequency of remetinostat gel to BID every second day. Recommence TID daily treatment once platelet count reaches ≥ 75 x 10^9/L. If platelet count does not recover after 2 weeks' every 2nd day dosing, suspend treatment until platelet count reaches ≥ 75 x 10^9/L (maximum period of treatment suspension is 4 weeks).

Thrombocytopenia CTC Grade ≥ 3 (platelet count ≤ 50 x 10^9/L): Treatment must be discontinued for up to 4 weeks, by which time treatment must be permanently discontinued if the platelet count does not recover to ≥ 75 x 10^9/L. On recovery of platelet count to ≥ 75 x 10^9/L, treatment with remetinostat should initially be re-started BID every second day and then increased to BID daily application if tolerated. If event re-occurs, consider discontinuation of treatment.

Diarrhea CTC Grade 1, an increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline: Reduce treatment frequency of remetinostat gel to every second day. Recommence BID daily treatment once diarrhea has resolved/returned to baseline status. If diarrhea does not recover after 4 weeks' every second day BID dosing, suspend treatment until diarrhea has resolved/returned to baseline status (maximum period of treatment suspension is 4 weeks).

Diarrhea CTC Grade ≥ 2, an increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily life (ADL): Treatment must be discontinued for up to 4 weeks, by which time treatment must be permanently discontinued if diarrhea does not resolve/recover to baseline status. Once diarrhea has recovered/returned to baseline status, treatment with remetinostat should initially be re-started BID every second day and then increased to BID daily application if tolerated. If event re-occurs, consider discontinuation of treatment.

If a patient lesion grows by 30% at the 4 week observation point, the patient would be directed to surgery instead of continued therapy on trial.

If 50% of total lesions being treated per protocol have grown, we would stop the study early.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Slight irritation of the skin was observed in some animal studies and was likely related to the ethanol in the formulation.

Escalating doses of remetinostat gel were administered to different cohorts of patients to assess safety and tolerability in a Phase 1 study in patients with CTCL. A total of 18 patients with CTCL were sequentially enrolled into one of three study cohorts consisting of six patients each. Within each study cohort of six patients, 5 were randomly assigned to receive remetinostat gel and 1 was randomly assigned to receive placebo. Patients received treatment for a maximum of 28 days. Three dose levels of remetinostat gel were evaluated at 0.1%, 0.5% and 1%.

The study drug was well-tolerated. Eight patients, including one who received placebo, experienced 11 treatment-related adverse events. The adverse events consisted of a skin burning or warming sensation, paraesthesia, and contact dermatitis and were all related to topical application of study drug to the index lesion treatment sites. Ten of the treatment-related

adverse events were mild (Grade 1) and one event (contact dermatitis) was Grade 2. Only the Grade 2 event of contact dermatitis required treatment, for which topical steroid and moisturizer were applied after the patient completed the 28-day course of remetinostat gel treatment, which resolved. All treatment-related adverse events had resolved prior to the Day 42 End-of-Study visit.

There were no hematological findings among the 18 treated patients. Among the 5 clinical laboratory changes reported as adverse events and the 4 clinical laboratory values that reached ≥ Grade 2, none was related to study drug administration.

For the phase 2 study, 60 patients were randomised in a 1:1:1 ratio to three treatment regimens of remetinostat gel (1% QD, 0.5% BID and 1% BID). Patients received treatment for 6 months and could continue on treatment for a further 6 months (12 months in total) if they received clinical benefit during the first 6-month period.

Remetinostat gel at dosing regimens of 1% QD, 0.5% BID and 1% BID was generally well tolerated, with no reports of adverse events associated with systemic HDAC inhibitors. There were 2 SAEs (acute heart failure and fracture), observed during the study, considered unrelated to treatment with remetinostat.

The most common adverse events were pruritus and skin irritation.

Approximately half of the patients in each group reported AEs considered related to treatment; 4 of these met CTCAE Grade ≥ 3 for severity and all were skin-related: The rate of discontinuations due to treatment-related AEs was low, with no indication of a higher rate in the highest (1% BID) dose group. Overall, the patients who had dose reduction/interruptions due to remetinostat related skin AEs in the 1% BID dose group stayed on treatment for a long time. The CTC Grade 3 events resolved, patients wanted to stay on treatment despite these AEs (except for a single patient) and most of the patients (4 of 6) in this highest dose group who remained on drug for > 6 months received benefit, in terms of objective CAILS and/or pruritus responses.

In the current study, skin will be carefully evaluated during treatment. Patients who develop contact dermatitis caused by the strip bandage adhesive per PI determination may discontinue bandage use.

No systemic abnormalities were found at any dose level in the nonclinical studies and no treatment-related observations other than those above were noted in any clinical trial. Thus, no special precautions are anticipated.

The effect of remetinostat in pregnancy has not been studied. Similarly, excretion of remetinostat into breast milk has not been examined. Therefore, pregnant and lactating women are excluded from clinical trials at this time.

Remetinostat is considered unlikely to be a photo-irritant as remetinostat absorbs light at a maximum of 234 nm in the UV/visible spectrum and does not meaningfully absorb light above 290 nm. Photo-irritation has not been observed in clinical trials of remetinostat gel. There is no information to indicate that abuse or dependency would occur with exposure to remetinostat gel.

Detectable systemic levels of remetinostat after topical application are not anticipated.

See the Investigator Brochure for details on AEs captured to date from CTCL study.

7.2 Adverse Event Reporting

For guidance on reporting adverse events, refer to the Stanford Cancer Institute Clinical Trials Office Adverse Event SOP.

Adverse events will be graded according to CTCAE v5.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Investigator's Brochure and/or protocol and related to the a) study drug or b) the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution or until 30 days after the last dose of the study treatment.

All AE and SAEs will be reported to the Principal Investigator. The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be informed of all SAEs. An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, in this study topical remetinostat, regardless of attribution. This includes the following: AEs not previously observed in the subject that emerge during the protocol specified AE reporting period, complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies); and preexisting medical conditions judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study-specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the last application of study drug. The investigator will discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (eg, an event in the fetus; an event in the mother during or after the pregnancy; or a congenital anomaly/birth defect in the child) will be reported per Stanford SOPs.

Male patients will be instructed to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last application of study drug.

8. EXPLORATIVE / CORRELATIVE / SPECIAL STUDIES

None.

9. STUDY CALENDAR

	Pre-treatment Day -2 to -30	Pre-treatment Day -1	Treatment Day 1	Treatment Week 4 (+/- 1 week)	Week 10 Visit* (+ 4 weeks)	Follow-up Week 12-18**	Early termination
Remetinostat treatment			**X**	**X**	**X**		
Informed consent	**X**						
Medical history	**X**						
Concurrent meds	**X----------►**						
Physical exam	**X**	**X**		**X**	**X**		**X**
Vital signs	**X**	**X**		**X**	**X**		**X**
Height	**X**						
Weight	**X**	**X**		**X**	**X**		**X**
ECOG score	**X**			**X**	**X**		**X**
Serum pregnancy test	**X**						
Adverse event evaluation			**X----------►**				
Tumor measurements and photographs		**X**		**X**	**X**		**X**
Tumor Biopsy		**X**			**(X)**		
Patient Calls			**X----------►**				

*Week 10 visit may occur between weeks 10-14, depending on surgeon availability. Study drug will be applied for 8 weeks in total; if surgical excision is delayed, the study drug may be applied for up to 4 additional weeks (for a total of up to 12 weeks)

**Follow up visit or phone call will occur between weeks 12-18 (approximately 2-4 weeks after Mohs/surgical excision)

10. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

10.1 Primary Outcome

Title: Overall Response Rate (ORR)

Description: The primary objective of this study is to determine if topical remetinostat will reduce squamous cell carcinoma (SCC) tumor size (measured in mm^2). Tumors will be measured with calipers throughout the study. The associated outcome is reported as the number of tumors who achieve a partial response (PR) or complete response (CR), and overall response (OR). CR and PR are defined below, and OR is the sum of PR and CR.

• CR = undetectable tumor lesion(s).

• PR = ≥ 30% decrease in total tumor area.

Timeframe: Up to 10 weeks

Safety Outcome?: No

10.1.1 Relevant Subset

All tumors with study drug application at 80% compliance and above will be included in analysis.

10.1.2 Measurement Definition

Tumor size will be measured by measuring the tumor with calipers at study visits week 0, 4, and 8.

10.1.3 Measurement Methods

Tumor size will be measured with calipers and will be recorded in millimeters.

10.1.4 Measurement Time Points

Tumor size will be measured at study visits week 0, 4, and 8.

10.1.5 Response Review

The primary outcome (tumor size) is measured in real time by a physician during the clinic visit; no radiologic images are obtained for later review in this study.

10.2 Secondary Outcomes

10.2.1 Overall Adverse Events (AEs)

Title: Overall Adverse Events (AEs)

Description: Participants will be monitored for adverse events (AEs) throughout the study period. The outcome will be reported as the number of participants who experience any AE, serious or non-serious, a number without dispersion.

Timeframe: Up to 10 weeks

Safety Outcome?: Yes

10.2.2 Serious Adverse Events (SAEs)

Title: Serious Adverse Events (SAEs)

Description: Participants will be monitored for serious adverse events (SAEs) throughout the study period. The outcome will be reported as the number of participants who experience any SAE, a number without dispersion.

Timeframe: Up to 10 weeks

Safety Outcome?: Yes

10.2.3 Adverse Event-related Treatment Discontinuation or Interruption

Title: Adverse Event-related Treatment Discontinuation or Interruption.

Description: Incidence of AEs leading to remetinostat discontinuation or interruption. Participants will be monitored for adverse events (SAEs) throughout the study period, and the relationship of remetinostat discontinuation or interruption to adverse events will be evaluated for all remetinostat discontinuation or interruption. The outcome will be reported as the number of participants who discontinued remetinostat or experienced treatment interruption due to an adverse event, a number without dispersion.

Timeframe: Up to 10 weeks

Safety Outcome?: Yes

10.2.4

Title: Treatment Schedule Compliance

Description: Participant adherence to the treatment schedule will be assessed as the number of patients who discontinue the treatment, or experience treatment interruption, for any reason. The outcome will be reported as a number without dispersion.

Timeframe: Up to 10 weeks

Safety Outcome?: Yes

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of

human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or a designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific case report forms (CRFs) will be developed to document treatment outcomes for data analysis. These CRFs will initially be developed on paper forms by the study coordinator but may transition to electronic forms (ie, in OnCore or RedCap). Subject charts will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

Shufeng Li, MS, is the statistician for this clinical trial.

12.1 Statistical Design

The Primary Objective and Primary Outcome of this study is to determine if topical remetinostat will reduce SCC tumor size, as defined by at least 30% decrease in SCC tumor area (in mm^2) at end of study as compared with baseline. Complete response (CR) will be defined as no clinically detectable tumor at EOS. ORR is defined as the proportion of tumors with either a complete response or a partial response (PR) among all eligible and treated lesions. Exact binomial 90% confidence intervals (CIs) will be computed for the ORR. With a planned analysis on 30 per-protocol SCCs, this study should provide 91% power to reject an ORR of 15% if the true ORR is 40% or better, at one-sided-alpha level of 0.05 with at least 9 responders.

12.1.1 Randomization

Not applicable, as this is a single-arm trial.

12.2 Interim analyses

None planned

12.3 Descriptive Statistics and Exploratory Data Analysis

The baseline characteristics of study subjects (age; gender; skin type; number of tumors; average size of tumors; tumor location; tumor histology; and prior treatments) will be summarized in tables. Wilcoxon signed rank tests for continuous variables and chi-square tests for dichotomous variables will be used. CONSORT guidelines will be followed to describe the number of subjects screened; enrolled; and completed the treatment. All AEs will be described in tabular format.

12.4 Primary Analysis

The primary endpoint is the overall response rate of SCC lesions as defined by at least 30% decrease in tumor area at EOS as compared to baseline. Note: RECIST v1.1 criteria have limited utility for SCCs under 10 mm, and will not be used for that reason.

12.4.1 Analysis Population

We will first analyze the data by intention to treat analysis and then per-protocol analysis by only including tumors ≥ 80% compliant with drug treatment. Tumors with 79% or less compliant with

drug treatment will be reported as a deviation; tumors at least 80% compliant with drug treatment will not be recorded as a deviation. Patients will be instructed to use a band-aid or other form of occlusion. If the patient has difficulty with band-aid usage, the patient may stop and this will be documented.

For subjects who drop out, we will use data from their last study visit if they contribute a biopsy. The analysis population will include participants who have consented to undergo remetinostat treatment and who have at least 1 SCC tumor.

Safety analyses will include all subjects who received at least one dose of study treatment. Graded AEs (number and percent) will be summarized and reported according to the NCI CTCAE v5.0.

12.4.2 Analysis Plan

We will analyze the overall response rate of SCC based on the change in tumor area. Objective response rate (ORR) will be defined as the proportion of tumors with either a complete response or a partial response (PR) among all eligible and treated tumors. Toxicities will be graded according to the National Cancer Institute CTCAE v5.0. Exact binomial 90% confidence intervals (CIs) will be computed for the ORR. With a planned analysis on 30 per-protocol SCCs, this study would provide 91% power to reject an ORR of 15% if the true ORR is 40% or better, at one-sided alpha level of 0.05 with at least 9 responders.

12.5 Secondary Analysis

12.5.1 Analysis Population

Data from all enrolled patients will be included in the below safety evaluations.

12.5.2 Analysis plan

For Secondary Objective 1, toxicities will be graded according to the National Cancer Institute CTCAE v5.0.

The safety of remetinostat when applied topically for 8 weeks will be assessed as follows:

- Incidence, type, and severity of adverse events (AEs)
- Incidence and nature of serious adverse events (SAEs)
- Incidence of AEs leading to treatment discontinuation or interruption
- Adherence to the treatment, measured by number of patients discontinuing the treatment (for any reason) and treatment interruptions

12.6 Sample Size

12.6.1 Overall Accrual estimates

Subjects will be enrolled from Stanford Dermatology (Adult) clinic which sees approximately 4,000 dermatology patients per month (or 48,000 visits per year). Approximately 20% of these patients have current or past skin cancer. Enrollment of SCC subjects for Stanford clinical trials has been rapid. 30 per-protocol SCC lesions are anticipated to be evaluated within the first 12 months. We will only advertise and enroll from Stanford Dermatology clinic. It is anticipated that at least 10 subjects will consent to baseline and post-treatment biopsies.

12.6.2 Sample size justification

For primary objective analysis, with a planned analysis on 30 per-protocol SCCs, this study would provide 91% power to reject an ORR of 15% if the true ORR is 40% or better, at one-sided alpha level of 0.05 with at least 9 responders.

12.6.3 Effect size justification

This is a single-arm (non-randomized) study of topical remetinostat. SCCs are not anticipated to self-regress in the absence of any treatment.

12.7 Criteria for future studies

If topical remetinostat reduces SCC size, it is anticipated that a larger, randomized, controlled trial will be proposed.

13. REFERENCES

1. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol.* May 1994;30(5 Pt 1):774-778.
2. Kraft S, Granter SR. Molecular pathology of skin neoplasms of the head and neck. *Arch Pathol Lab Med.* Jun 2014;138(6):759-787.
3. Guo HR, Yu HS, Hu H, Monson RR. Arsenic in drinking water and skin cancers: cell-type specificity (Taiwan, ROC). *Cancer Causes Control.* Dec 2001;12(10):909-916.
4. Karagas MR, Stukel TA, Morris JS, et al. Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. *Am J Epidemiol.* Mar 15 2001;153(6):559-565.
5. Pedersen SA, Gaist D, Schmidt SAJ, Holmich LR, Friis S, Pottegard A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. *J Am Acad Dermatol.* Apr 2018;78(4):673-681 e679.
6. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. *J Am Acad Dermatol.* Mar 2003;48(3):425-429.
7. Burton KA, Ashack KA, Khachemoune A. Cutaneous Squamous Cell Carcinoma: A Review of High-Risk and Metastatic Disease. *Am J Clin Dermatol.* Oct 2016;17(5):491-508.
8. Celebi AR, Kiratli H, Soylemezoglu F. Evaluation of the 'Hedgehog' signaling pathways in squamous and basal cell carcinomas of the eyelids and conjunctiva. *Oncol Lett.* Jul 2016;12(1):467-472.
9. Tsai KY, Tsao H. The genetics of skin cancer. *Am J Med Genet C Semin Med Genet.* Nov 15 2004;131C(1):82-92.
10. Lee CS, Bhaduri A, Mah A, et al. Recurrent point mutations in the kinetochore gene KNSTRN in cutaneous squamous cell carcinoma. *Nat Genet.* Oct 2014;46(10):1060-1062.
11. Wang NJ, Sanborn Z, Arnett KL, et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc Natl Acad Sci U S A.* Oct 25 2011;108(43):17761-17766.
12. Rees JL. The genetics of sun sensitivity in humans. *Am J Hum Genet.* Nov 2004;75(5):739-751.
13. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. *Oncologist.* Oct 2007;12(10):1247-1252.
14. Kurundkar D, Srivastava RK, Chaudhary SC, et al. Vorinostat, an HDAC inhibitor attenuates epidermoid squamous cell carcinoma growth by dampening mTOR signaling pathway in a human xenograft murine model. *Toxicol Appl Pharmacol.* Jan 15 2013;266(2):233-244.
15. Karam M, Legay C, Auclair C, Ricort JM. Protein kinase D1 stimulates proliferation and enhances tumorigenesis of MCF-7 human breast cancer cells through a MEK/ERK-dependent signaling pathway. *Exp Cell Res.* Mar 10 2012;318(5):558-569.
16. Teknos TN, Grecula J, Agrawal A, et al. A phase 1 trial of Vorinostat in combination with concurrent chemoradiation therapy in the treatment of advanced staged head and neck squamous cell carcinoma. *Invest New Drugs.* Dec 19 2018.

17. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ.* Nov 4 2013;347:f6153.
18. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol.* Mar 2001;44(3):462-470.
19. Morton C, Horn M, Leman J, et al. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or Fluorouracil for treatment of squamous cell carcinoma in situ: Results of a multicenter randomized trial. *Arch Dermatol.* Jun 2006;142(6):729-735.
20. Locke J, Karimpour S, Young G, Lockett MA, Perez CA. Radiotherapy for epithelial skin cancer. *Int J Radiat Oncol Biol Phys.* Nov 1 2001;51(3):748-755.
21. NCCN Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer. 2018; 2.2019:https://http://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed 16 January 2019.

APPENDIX A: Study IRB-49542 Participant Medication Application Diary

Study Participant Study Drug Application Diary

Participant Identifier: SCC-_____

STUDY DRUG INSTRUCTIONS:

Study Drug: Remetinostat 1% gel
How Much: Apply a thin layer over the tumor(s) identified by the study doctor.

How Often: Three times daily.
When: You should apply the gel in the morning, at mid-day, and in the evening.

SPECIAL INSTRUCTIONS:

This medication *must* remain refrigerated at all times.

Cover the area with a bandage after you apply the gel.

Wash your hands after you apply the gel.

APPLICATION LOG

Please indicate if you applied the gel for each dose listed below.

Please bring this diary to your next clinic visit.

	Date	Gel Applied			Comments
		Dose 1	Dose 2	Dose 3	
Example	4/1/19	x	x	x	Stinging after medication applied
Day 1	<prepopulated date>				
Day 2	<prepopulated date>				
Day 3	<prepopulated date>				
Day 4	<prepopulated date>				
Day 5	<prepopulated date>				
Day 6	<prepopulated date>				
Day 7	<prepopulated date>				
Day 8	<prepopulated date>				
Day 9	<prepopulated date>				
Day 10	<prepopulated date>				
Day 11	<prepopulated date>				
Day 12	<prepopulated date>				
Day 13	<prepopulated date>				

	Date	Gel Applied			Comments
		Dose 1	Dose 2	Dose 3	
Day 14	<prepopulated date>				
Day 15	<prepopulated date>				
Day 16	<prepopulated date>				
Day 17	<prepopulated date>				
Day 18	<prepopulated date>				
Day 19	<prepopulated date>				
Day 20	<prepopulated date>				
Day 21	<prepopulated date>				
Day 22	<prepopulated date>				
Day 23	<prepopulated date>				
Day 24	<prepopulated date>				
Day 25	<prepopulated date>				
Day 26	<prepopulated date>				
Day 27	<prepopulated date>				
Day 28	<prepopulated date>				
Day 29	<prepopulated date>				
Day 30	<prepopulated date>				
Day 31	<prepopulated date>				
Day 32	<prepopulated date>				
Day 33	<prepopulated date>				
Day 34	<prepopulated date>				
Day 35	<prepopulated date>				
Day 36	<prepopulated date>				
Day 37	<prepopulated date>				
Day 38	<prepopulated date>				
Day 39	<prepopulated date>				
Day 40	<prepopulated date>				
Day 41	<prepopulated date>				
Day 42	<prepopulated date>				
Day 43	<prepopulated date>				
Day 44	<prepopulated date>				
Day 45	<prepopulated date>				
Day 46	<prepopulated date>				
Day 47	<prepopulated date>				
Day 48	<prepopulated date>				
Day 49	<prepopulated date>				

APPENDIX B: Study IRB-49542 Participant Information Sheet

Remetinostat Participant Information Sheet

Remetinostat Application instructions:

Remetinostat gel 1% is to be applied to dry skin. Wash your hands and squeeze the amount of study medication that was demonstrated by the study team from the tube onto your index finger and apply to the SCC lesion(s) identified by your physician. Apply to the SCC lesion(s) 3 times daily for 8 weeks as specified by your physician. Cover the treated SCC lesions(s) with a sticky strip bandage, such as a Band-Aid.

There is no need to leave large amounts of residue on your skin. Immediately following application, wipe the finger(s) and hands you have used to apply the study drug with a disposable tissue and wash your hands using soap and water. If the study medication gets on the skin of other people, they should wash with soap and water.

If someone else helps apply the study medication, they should follow the same instructions.

If you start to treat new lesions or stop treating any lesion, please inform your physician so a record can be kept of which lesions are being treated with study medication.

Remetinostat Storage Instructions:

- Do not store the study medication in your car.
- Study medication should be stored in the refrigerator, away from heat or open flame.
- The study medication should be kept out of reach of children and unauthorized persons (not being patients participating in this study or their caregiver).

Risks from Remetinostat:

In prior studies, remetinostat caused some people to have some skin irritation such as a tingling or tickling feeling (“pins and needles”) on their skin, a warm or burning feeling on their skin or inflammation (redness and swelling). This may be due to the ingredients the drug is mixed in, or the drug itself. If you have any concerns, contact the study team.