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 Basal Cell Carcinoma (BCC)

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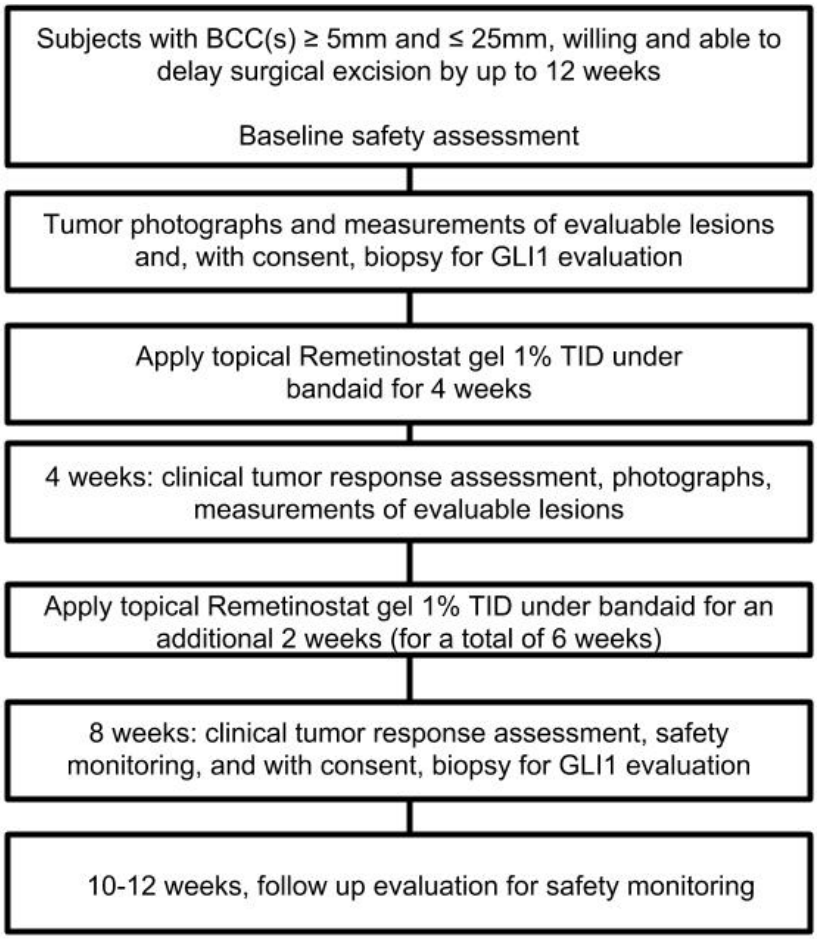
PROTOCOL SYNOPSIS

TITLE	A Phase 2 Open-label, Single-arm Trial of the Efficacy of and Safety of Topical Remetinostat Gel as Neoadjuvant Therapy in Patients with Basal Cell Carcinoma undergoing surgical resection
STUDY PHASE	Phase 2
INDICATION	Treatment of basal cell carcinoma
INVESTIGATIONAL PRODUCT	Topical remetinostat gel 1%
PRIMARY OBJECTIVE	• To determine if topical remetinostat gel will decrease BCC size by at least 30% following 6 weeks' TID treatment • To determine the overall response rate (ORR) of BCC tumors after 6 weeks of treatment TID
SECONDARY OBJECTIVE	1. To determine if topical remetinostat gel 1% will decrease HH biomarker GLI1 from baseline levels following 6 weeks' TID treatment: 2. To assess the safety of remetinostat gel 1% when applied topically TID under occlusion for 6 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
EXPLORATORY STUDIES	To assess local pharmacodynamics (PD) effects of remetinostat by immunohistochemistry (IHC) on histone acetylation in BCC biopsy sections
TREATMENT SUMMARY	Apply topical remetinostat gel 1% 3 times daily (TID) under bandage occlusion for 6 weeks
SAMPLE SIZE	30 BCC tumors treated per-protocol
STATISTICAL CONSIDERATIONS	Overall response rate of BCC tumors (Primary Objective and Primary Outcome) in subjects will be defined as at least a 30% decrease in the diameter of BCC lesion. With a planned analysis on 30 per-protocol BCCs, 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 (HH biomarker GLI1), at least 10 pre- and post-treatment (6 weeks) BCC tumor pairs will be analyzed. With a sample size of 10 paired BCCs, this study

	will have greater than 98% power to detect a 43% (SD: 30%) decrease in GLI1 mRNA levels at 2-sided alpha level 0.05. For Secondary Objective 2, toxicities will be graded according to the National Cancer Institute CTCAE v5.0. For the Exploratory Studies, PD endpoints will include, but are not limited to, an assessment of histone acetylation. The analysis will be performed on BCC biopsy sections using IHC.

SCHEMA



LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BCC	Basal cell cancer / carcinoma
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
GLI1	Glioma-associated oncogene 1
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
PFS	Progression-free survival
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
SD	Stable disease
SMO	Smoothened
TID	Three times daily
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

Overall response rate of BCC in subjects defined by at least a 30% decrease in BCC tumor diameter at end of study measurement as compared with baseline measurements. RECIST v1,1 criteria can no longer be used as BCC patients with BCCs under 10 mm will be enrolled. Therefore, the threshold for positive response will be at least 30% decrease in tumor size.

1.2. Secondary Objectives

- Suppression of GLI1 expression in treated BCC as compared with baseline.
- Safety assessment of remetinostat after 6 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 remetinostat 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

Basal cell carcinomas (BCCs) are the most common human cancer, affecting approximately 750,000 Americans per year (Epstein, 2008). Based on rapidly rising tumor incidence rates, it is estimated that almost 1 in 3 Caucasians born in the United States after 1994 will develop a BCC during their lifetime (Miller and Weinstock, 1994). Like that of other skin cancers, BCC risk is correlated inversely with the degree of skin pigmentation and positively with exposure to ultraviolet (UV) or ionizing radiation (IR). Patients affected by the basal cell nevus syndrome (BCNS, Gorlin syndrome, nevoid basal cell carcinoma syndrome; OMIM #109400), a rare autosomal dominant inherited disorder, have a dramatically increased risk of developing BCCs (developing tens to hundreds to thousands of BCCs) and as well as an increased risk of developing certain extra cutaneous tumors (eg, medulloblastomas and rhabdomyosarcomas) (Gorlin, 1987). Patients with BCNS inherit a defective copy of the tumor suppressor gene, *PTCH1*, which acts as a primary inhibitor of the hedgehog (HH) signaling pathway (Hahn, *et al*, 1996; Johnson, *et al*, 1996). *PTCH1* gene mutations and loss of the remaining wild-type allele also have been identified in sporadic basal cell carcinomas and medulloblastomas, suggesting a common genetic basis for the sporadic and syndrome-associated cancers (Hahn, *et al*, 1996; Johnson, *et al*, 1996; Xie, *et al*, 1997; Raffel, *et al*, 1997; Ling, *et al*, 2001). Mutations in SMO, the downstream molecule that is the target of PTCH1 inhibition, occur in approximately 10% of sporadic BCCs with resultant resistance of SMO protein to inhibition by normal PTCH1 protein (Xie, *et al*, 1998; Reiffenberger, *et al*, 1998). Essentially all BCCs, whether or not associated with identifiable mutations of PTCH1 or of SMO, have enhanced HH signaling. BCCs generally are treated by local excision, which in many cases is scarring and disfiguring. Currently there is no reliable medical (non-surgical) therapy for treatment of either BCNS-related or sporadic BCCs. Oral retinoid treatment of BCNS patients can reduce the rate of development of BCCs but does so only at a dose that usually produces intolerable side effects (Peck, *et al*, 1988; Tangrea, *et al*, 1992). The clinical use of SMO antagonists which suppress HH signaling have efficacy and are FDA approved for the treatment of BCC providing strong scientific evidence

that HH inhibition can be a highly effective approach to chemotherapy and chemoprevention of BCC (Tang, *et al*, 2016).

2.2 Study Agent

Histone deacetylase (HDAC) inhibitors, including vorinostat and romidepsin were approved by the US FDA for the treatment of cutaneous T-cell lymphoma (CTCL) (Mann BS, *et al*, 2007). HDAC inhibitors antagonize tumors by altering the expression of oncogenes or tumor suppressor, through modulating the level of acetylation/deacetylation of histones and/or non-histone proteins such as transcription factors.

Unpublished data has shown HDAC inhibitors can inhibit the growth of BCC cells and BCC tumors *in vitro* and *in vivo*.

HDAC inhibitors can suppress growth of BCC cell lines

To study the efficacy of HDAC1 inhibition in BCCs *in vitro,* a murine BCC cell line (ASZ) resistant to SMO inhibitors but dependent on GLI1 was treated with increasing doses of vorinostat, a pan-HDAC inhibitor, and parthenolide, a HDAC1-depleting compound. Vorinostat treatment resulted in a dose-dependent reduction in HH signaling as assayed by qPCR of GLI1 mRNA, a canonical target gene of the HH pathway and BCC proliferation (Figure 1). Similarly, results were seen with parthenolide, a specific inhibitor of HDAC1 expression implicating HDAC1 as the critical target of HDAC inhibitors for BCC.

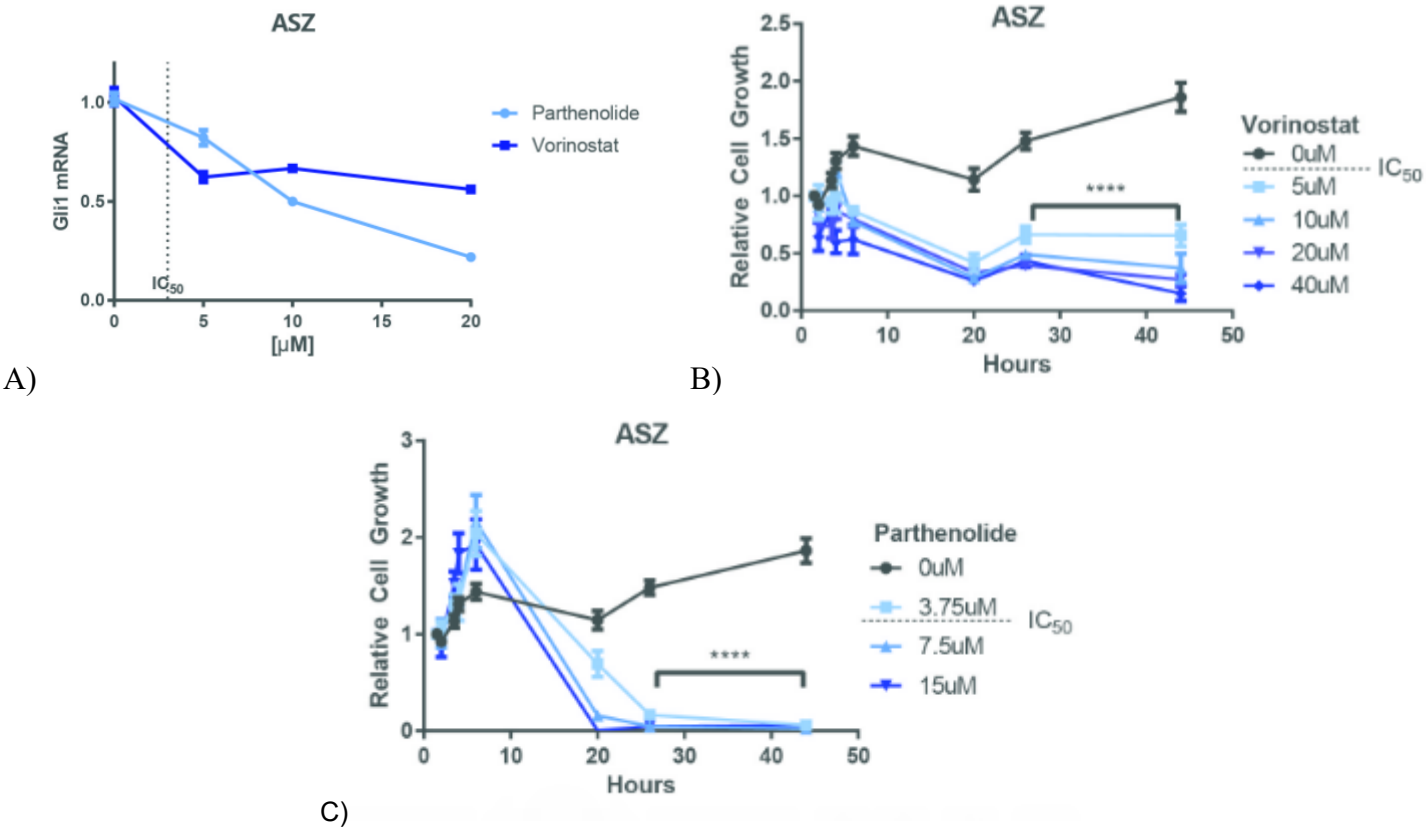


Figure 1. A) HH target genes transcripts dose response to vorinostat and parthenolide in ASZ cells with drug IC_{50} represented by dotted line (n = 9). *GLI1* transcript measured by quantitative PCR and normalized against HPRT. B,C) Relative ASZ cell growth measured by Real Time Glo Reagent following vorinostat (B) and parthenolide (C) treatment (n = 3).

HDAC inhibitors can suppress growth of BCC tumor allografts

BCCs allografts, generated from *Ptch1$^{+/-}$ K14-Cre-ER2 p53 $^{fl/fl}$* mice were injected subcutaneously into NOD/SCID mice as previously described and allowed to engraft for 3 weeks until a consistent 5 mm palpable tumor was visible. 100 mg/kg of vorinostat administered intraperitoneally twice daily *in vivo* on the BCC allografts resulted in inhibition of GLI1 and completely suppressed tumor growth at 14 days compared to a 350% growth in tumor volume in the placebo. Skin and organ toxicity was not observed in mice at these dosages. (Figure 2). Altogether, the preliminary data implicates HDAC inhibitors as a promising new candidate therapy for BCC.

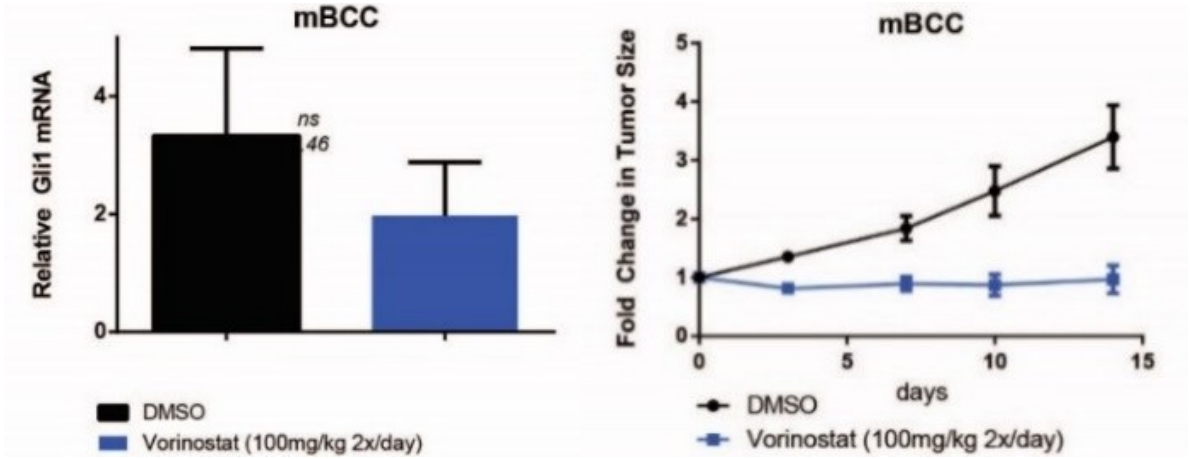


Figure 2. (left) Vorinostat suppresses growth of BCC allografts (blue) as compared to placebo / DMSO (black) (right) GLI1 mRNA levels are suppressed by vorinostat in murine tumor allografts.

HDAC1 has been previously shown to provide a pivotal step in the activation of GLI1 through deacetylation at K518 (Canettieri, *et al*, 2010), suggesting a potential mechanism of action by which HDAC1-inhibition can suppress HH signaling and suppress BCC.

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 3 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. The IND number is IND 134521.

2.3 Rationale

The severity of BCC burden differs widely among patients from those who develop early BCCs, have advanced BCC; or suffer from numerous BCCs lesions. In the more severely-affected, such as those with basal cell nevus syndrome or extensive chronic sun exposure, essentially all of their skin appears to be susceptible to the development of BCCs, and their quality of life is severely degraded by the need for frequent, repetitive surgical procedures (Bree AF, *et al*). Some patients need to have a dozen or more BCCs treated each year. These procedures are time-consuming and expensive, and they inevitably produce scarring. Exhortations to avoid sunlight have minimal effect on slowing the rate of development of BCCs in these patients. Hence the patients currently have an endless vista of surgical procedures in their future, with no light at the end of the tunnel. Other patients may have fewer tumor lesions but they occur in cosmetically-disfiguring areas or near functional areas where surgery is not ideal.

The pivotal molecular abnormality in basal cell carcinoma is constitutive activation of the hedgehog (HH) signaling pathway, commonly due to mutational inactivation of the gene encoding the tumor suppressor, Patched1 (Ptch1). Ptch1 is a transmembrane receptor for the hedgehog ligand and is the key natural inhibitor of HH signaling. It accomplishes this by preventing signaling by SMO and hence inhibits activation of the transcriptional factor, GLI. In addition to uniform constitutive activation of the HH pathway, human BCCs also frequently have mutations in p53.

All BCCs have up-regulation of HH signaling due to loss of PTCH1 or activation of SMO (Epstein, 2008). SMO inhibitors replace the function of mutant PTCH1 by inhibiting HH signaling and have efficacy in treatment of BCCs. However, after varying duration, patients may find the adverse effects of the drug to be intolerable and may stop taking treatment, leading to recurrence of BCC. Therefore, a downstream topical HH inhibitor is likely to be better-tolerated because of the expected lack of adverse effects, and inhibition of hedgehog signaling by a topical agent is likely to inhibit BCC carcinogenesis. Therefore, as HDAC inhibitors work further downstream to SMO inhibitors to inhibit the HH signaling pathway, it is hope that remetinostat may show efficacy without the adverse effects of SMO inhibitors.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

- The primary purpose of this study is;
    - To determine if 6 weeks of topical remetinostat gel applied TID under occlusion will suppress BCC growth
    - To determine the overall response rate (ORR) of BCCs after 6 weeks of treatment with topical remetinostat gel 1%, as measured by at least 30% decrease in greatest diameter.
- Subjects with at least 1 cutaneous BCC will be recruited for this study.
- Subjects will apply remetinostat gel 1% to at least 1 BCC.
- All BCC types, ie, superficial, nodular, micronodular, or morpheaform, are 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 Inclusion Criteria

1. Must have at least one cutaneous BCC lesion greater than or equal to 5 mm. BCC lesion(s) can be superficial, nodular, micronodular, or morpheaform BCC, 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 6 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, 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 (ie, who has had menses any time in the preceding 24 consecutive months)
5. Sexually active women of child bearing potential (WCBP) and male patients with a female partner of child-bearing potential must agree to use acceptable methods of contraception to avoid pregnancy (for example, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) before the first dose of study therapy and for 3 months after the last dose of study therapy
6. Has signed and dated the current IRB-approved informed consent document.

3.2 Exclusion Criteria

1. Any large (> 25 mm) BCC lesion. Patients with large BCC lesion(s) will be referred for evaluation for surgical resection.
2. Inoperable locally-advanced and/or non-cutaneous metastatic BCC.
3. Taking any medication known to affect HH signaling pathway such as itraconazole.

4. 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 to the study tumors of:
    - Glucocorticoids
    - Retinoids either systemically or topically at the tumor site (eg, etretinate, isotretinoin, tazarotene, tretinoin, adapalene)
    - Alpha-hydroxy acids (eg, glycolic acid, lactic acid) to > 5% of the skin or to the tumor site
    - 5-fluorouracil or imiquimod and/or
    - Itraconazole
5. Has received treatment with systemic chemotherapy or agents known to be inhibitors of HH signaling, within 60 days prior to starting study medication.
6. Currently receiving systemic medications that could affect BCC tumors (eg, oral retinoids) or might interact with remetinostat
7. 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.
8. Moderate to significant immunosuppression (eg, active cancer, significant autoimmune disease) and/or receiving immunosuppressive drugs that result in moderate to significant immunosuppression (eg, low dose oral glucocorticoids do **not** necessarily exclude a patient)
9. Known or previous hypersensitivity to HDACi
10. History of congestive heart failure; cardiac arrhythmias; or other findings of ventricular dysfunction.
11. Pregnancy or breast-feeding.

3.3 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.

3.4 Randomization Procedures

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

3.5 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 6 weeks after starting topical remetinostat treatment.

Study Completion:

The study will reach study completion 24 months from the time the study opens to accrual, ie, allowing 6 months from Primary Completion for data analysis. Individual subjects will complete the study about 13 weeks after starting topical remetinostat treatment (ie, Screening; 6 weeks treatment; 4 to 6 weeks follow-up).

4. TREATMENT PLAN

Adult subjects in the clinic who have one or more cutaneous BCCs 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 BCC tissue for biomarker measurement and apply medication 3-times daily under bandage occlusion for 6 weeks. The anticipated bandage will be an adhesive bandage (eg, “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 BCCs 3 times daily for 6 weeks. Patients will discontinue application of the medication at 6 weeks, approximately 2 weeks prior to their surgical excision(s) scheduled for approximately Week 8.

At least 1 target BCC will be identified requiring surgical excision per standard of care. This lesion(s) will be measured and photographed and may be biopsied. Week 8 biopsy may be collected at surgical excision of lesion(s). Histopathological evaluation of the specimen may be performed to evaluate for tumor clearance.

After an initial treatment application demonstration by the study team, treatment applications will be self-administered by the subject or a caregiver. If requested, patient will receive a body map which will demonstrate where the lesion is on their body. This will help the patient know where to apply the treatment drug. 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 BCC lesion(s) designated by your physician, 3 times daily for 6 weeks, using clean, washed finger(s)/hand as applicable. Cover the treated BCC 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 each patient on request.

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

Medication Cooler: patients will be offered a small portable cooler to utilize to keep their study drug cold.

Tumors to be treated will be clearly identified. Patients will be instructed to store research medication in a refrigerator (see Appendix B).

All tumors will be measured and photographed at baseline, 4 weeks and 6 weeks.

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.

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. Eligibility criteria will be used as baseline.

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

It is anticipated that the entire target tumor(s) will be surgically removed at or after the 8th week or treatment, is accordance with regular medical care. Patients will apply their last dose of Remetinostat 30 mins before surgical excision. If surgical excision is delayed, ie, does not occur at Week 8, the drug may be continued for up to four weeks until surgical excision.

Between Week 12 and Week 20, up to three attempts will be made to reach the patient for follow up phone call; the patient may also be seen for an in-person visit at the discretion of the investigator. This visit may be in conjunction with surgery, 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 physician.

BCC tissues will be collected from those who consent at baseline and Week 6 to measure the biomarker gene for BCCs treated with topical remetinostat gel 1%. BCC biopsy will be collected in RNA later to measure biomarkers for BCC using real-time PCR.

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 (ie, the AE actually causes or leads to death).
- Life threatening (ie, 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.).
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (ie, 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 (eg, 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 (> 25 mm) BCC lesion will be discontinued from treatment (if applicable) and referred for evaluation for surgical resection.
- 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 BCC 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 AGENT INFORMATION

5.1 Investigational Agent

Remetinostat, also known as suberohydroxamic acid phenyl ester (SHAPE); SHAPE Gel; SHP-141; and 4-[[8-(hydroxyamino)-1,8-dioxooctyl]oxy]-benzoic acid methyl ester, 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).

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
[redacted]
[redacted]

5.4 Storage Conditions

The Investigator is responsible for the control of drugs 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 (eg, 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, as a measure of compliance.

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 6 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 Principal Investigator / Protocol Director will assess and determine if an individual subject needs to be 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 will 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.

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 six 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 SHP-141 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 and 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, including signs or symptoms associated with basal cell nevus syndrome that were not present prior to the AE reporting period; complications that occur as a result of protocol-mandated interventions (eg, 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.

In addition to the above reporting procedures, all Serious Adverse Events (SAEs) and occurrences of pregnancy reports which occur in remetinostat investigator-initiated studies will be reported to Medivir AB. The responsibility of receipt and processing of the above-mentioned cases has been outsourced to a consultancy company, Diamond PV Services Ltd.

SAEs

Upon becoming aware of an SAE, the SAE form in Appendix D will be completed and sent to Diamond PV Services via fax or email. Events will be **reported within 24 hours** of becoming aware of the event.

All SAEs that occur from the time of signing informed consent until 30 days following cessation of treatment will be reported. In addition, any SAEs that occur after this period and are considered to be related to the study drug or the study procedure will be reported.

Pregnancies or lactation cases

All pregnancies or lactation cases that occur in the subject or partner of the subject's (regarding pregnancy cases only) enrolled in the study will be reported on the pregnancy report form (Appendix C) from the time of signing informed consent to within 3 months after the last application of the study drug.

Acknowledgement and queries

Diamond PV shall confirm receipt of the report within 1 business day. If an acknowledgement of receipt is not received within 1 business day, the report will be resent.

If Diamond PV has any follow up queries regarding the report they will send queries to the site via e-mail. The query letter will state the due date for receipt of the queries. All query letters will be responded to within the specified timelines. If the information requested is not available, the query letter responses will state this. All data provided will be in line with local data privacy regulations.

Updates to case reports

If additional information or changes to the information become available, an updated report form indicating the additional or amended information will be provided. If there is new information in the follow-up case report, this will be highlighted with an asterisk on the paper report form, with the reporter's initials and date of new information added. The updated form will be sent via fax or email.

Receipt of Suspected Unexpected Serious Adverse Reaction reports:

All reports of Suspected Unexpected Serious Adverse Reactions will be sent to sites by Diamond PV. Upon receipt of such a report, it will be reviewed, and a copy submitted to the IRB, and a copy filed in the Investigator file.

All SUSAR report letters shall have an acknowledgment of receipt attached which will be completed and returned to Diamond PV via fax to confirm that it has been received, reviewed and submitted as appropriate.

Pharmacovigilance contact person:

Tel: [redacted]
Local US no[redacted]
Fax:
Local US no [redacted]
Email: [redacted]

8. EXPLORATIVE / CORRELATIVE / SPECIAL STUDIES

For the Exploratory Studies, PD endpoints will include, but are not limited to,

- To assess local pharmacodynamics (PD) effects of remetinostat by immunohistochemistry on BCC biopsy sections, including histone acetylation.

8.1. Increased Acetylation of HDAC Substrates as a PD Marker

The Exploratory Objectives aim to determine by IHC on FFPE BCC tissues with indicated antibodies if topical remetinostat modulate the levels of acetylated-histone H3. Prior phase 2 clinical trial data have shown a clear reduction the levels of acetylated line in skin from CTCL-patients subjected to treatment with remetinostat.

8.2. Measurement Definition

This study will measure the levels of acetylation in BCC FFPE histology sections in situ.

8.3. Analysis Population

The analysis population for this objective is planned to include at least 5 subjects who have consented to undergo remetinostat treatment, and who also consent to have at baseline and post-treatment BCC biopsies (“paired BCC tumor samples”). In addition, subjects who had their tumor extracted at the end of the study without prior baseline biopsy can be included and assessed in comparison to untreated archival FFPE BCC tissues (“unpaired BCC tumor samples”).

8.4. Measurement Methods

Levels of histone acetylation in BCC will be measured by immunohistochemistry (IHC). Biopsies of BCC tumors will be processed as for standard histology and stored in FFPE-blocks. Biopsy FFPE blocks will be cut into 5-µm sections and oriented longitudinally on the slides to ensure sufficient representation of skin histology and lesion depth. Appropriate designated archival BCC FFPE-blocks based on tumor size and treatment history may be identified and retrieved from Stanford. FFPE-blocks or cut sections will be shipped to Medivir (funding sponsor) or to a by Medivir-designated CRO for IHC staining and analysis (see section 8.5 Analysis Plan).

8.5. Analysis Plan

Staining intensities of acetylated histones will be analyzed in paired BCC tumor samples relative to baseline and in unpaired BCC tumor samples relative to archival BCC tumors.

9. STUDY CALENDAR

Eligibility testing not shown	Screening Day -2 to -30	Screening Day -1	Treatment Day 1	Treatment Week 4* (+/- 1 week)	Week 6 Visit** (+/- 2 week)	Follow-up Week 12* (+/- 1 week)	Early termination
Remetinostat treatment			**X**	**X**	**X**		
Informed consent	**X**						
Medical history	**X**						
Concurrent meds	**X**----------►						
Physical exam	**X**	**X**		**X**	**X**	**X**	**X**
Vital signs	**X**	**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 4 visit and Follow up visit may occur +/- 1week to accommodate patient and physician schedules

** Week 6 visits may occur +/- 2 weeks to accommodate patient and physician/surgeon schedules

Screening visits may be combined with or without day 1 visit

10. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

10.1 Primary Outcome

Primary outcome measure: BCC response

The primary outcome of this study is to determine if topical remetinostat will reduce BCC tumors size. A partial response is defined as at least 30% decrease in total tumor diameter at end of study from baseline. A complete response is undetectable tumor lesions at end of study. Objective response rate (ORR) will defined as the proportion of subjects with either a complete response or a partial response (PR) among all eligible and treated subjects. 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.

10.1.1 No subset analysis

10.1.2 Measurement Definition

The diameter of BCC tumors treated with topical remetinostat gel will be measured with calipers throughout the study to determine if topical remetinostat could reduce BCC tumors size comparing to baseline.

10.1.3 Measurement Methods

BCC tumors will be photographed measured using a ruler and calipers and the tumors size (longest diameter) will be recorded in millimeters.

10.1.4 Measurement Time Points

BCCs will be measured at baseline, 4 weeks and 6 weeks.

10.1.5 Response Review

Overall response rate of BCC in subjects as defined by at least 30% decrease in tumor size at end of study as compared to baseline. All responses will be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the subjects' files and tumor photographs will be performed.

10.1.6 Measurement Time Points

BCC biopsies may be performed at baseline and end of trial. We are expecting to process all samples in six months after the last subject tumors collection is completed.

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

12.1 Statistical Design

The Primary Objective and Primary Outcome of this study is to determine if topical remetinostat will reduce BCC tumors size, as defined by at least 30% decrease in BCC tumor diameter 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 BCCs, 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.

12.2 Randomization

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

12.3 Interim analyses

None planned

12.4 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.

12.5 Primary Analysis

The primary endpoint is the overall response rate of BCC lesions as defined by at least 30% decrease in tumor size at EOS as compared to baseline.

12.5.1 Analysis Population

We will first analyze the data by intention to treat analysis and then per-protocol analysis by only including subjects that are > 70% compliant with drug treatment (patients who are 69% or less compliant will be reported as a deviation; patients who are 70% compliant will not be recorded as a deviation). 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 BCC 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.

12.5.2 Analysis Plan

We will analyze the overall response rate of BCC based on change of longest diameter of tumor. Objective response rate (ORR) will defined as the proportion of subjects with either a complete response or a partial response (PR) among all eligible and treated subjects. 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 BCCs, 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 Secondary Analysis

12.6.1 Secondary Objective Measure: Reduction in GLI1 expression

Secondary Objective 1 is to determine whether topical remetinostat reduces the BCC biomarker GLI1 as compared to baseline. Based on prior clinical trials, it is estimated that topical remetinostat would need to decrease the Hh pathway by at least 50% to have a clinically-significant anti-BCC effect in subjects. This will provide insight into whether remetinostat is an effective chemotherapeutic for BCC.

12.6.1.1 Measurement Definition

This study will measure GLI1 mRNA, representing Hedgehog target gene (GLI1) expression, in samples of BCC tumors using real-time QPCR.

12.6.1.2 Analysis Population

The analysis population for this objective is planned to include at least 10 subjects who have consented to undergo remetinostat treatment, and who also consent to have at baseline and post-treatment BCC biopsies (“paired BCC tumor samples”).

12.6.1.3 Measurement Methods

HH target gene (GLI1) expression in BCCs will be measured using real-time PCR. Biopsies of BCC tumors will be placed in RNAlater and stored at -80°C prior to analysis. Total RNA will be isolated from the collected BCCs using a RNeasy Fibrous Tissue Mini Kit (Qiagen, Valencia, CA) according to the manufacture's protocol. The RNA obtained will then be quantified using A260/A280 spectrophotometry. DNase treated RNA (2 µg) will reverse transcribed using the High Capacity RNA-to-cDNA kit (Like Technologies, Grand Island, New York). The obtained cDNA will be used in 20 µL PCR reactions containing 10 µL Maxima SYBR Green qPCR Master Mixes (Thermo Scientific, Pittsburg, Pennsylvania) 0.4 µL primers, 0.86 µL of cDNA template sample, and 8.74 µL of molecular grade water. Reactions will be performed in 284-well PCR plates and read on an ABI Prism 7900HT Sequence Detection System.

12.6.1.4 Analysis Plan

Post-treatment GLI1 mRNA levels in the paired BCC sample sets will be compared with baseline GLI1 levels for the respective subject to calculate percent change in GLI1 mRNA expression. Because GLI levels are not expected to be normally distributed, the comparison will be conducted using the using Wilcoxon signed rank test.

Data will be analyzed using the comparative CT method as a means of relative quantitation, normalized to an endogenous reference (HPRT cDNA) and relative to a calibrator (normalized Ct value obtained from controls) and expressed as the 2-ΔΔCt algorithm (also known as the delta-delta-Ct or ddCt algorithm) according to Applied Biosystems User Bulletin 2: Rev B, "Relative Quantitation of Gene Expression."

With a sample size of at least 10 paired-BCCs, the study will have greater than 98% power to detect a 43% (SD: 30%) decrease in GLI1 mRNA levels at 2-sided alpha level 0.05 assuming no change in GLI mRNA levels without remetinostat (effect size = 1.0, Wilcoxon signed rank test). This should provide sufficient power to determine whether topical remetinostat can block the hedgehog pathway in humans to the degree required to be an effective chemotherapeutic.

12.6.2 Secondary Objective Measure: Safety

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 6 weeks will be assess 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

12.7 Sample Size

12.7.1 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 BCC subjects for Stanford clinical trials has been rapid. We anticipate to be able to enroll 30 per-protocol BCC lesions 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.

12.7.2 Sample size justification

For primary objective analysis, with a planned analysis on 30 BCCs, 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 secondary outcome analysis, with a sample size of 10 paired BCC tumors, we will be able to detect a 43% decrease in GLI mRNA levels (SD: 30%) with 98% power at a two-sided alpha level of 0.05 assuming no change in GLI levels without remetinostat (effect size = 1.0, Wilcoxon signed rank test)

12.7.3 Effect size justification

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

12.8 Criteria for future studies

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

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APPENDIX A: 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 Basal Cell Carcinoma (BCC)
Protocol Number:	**IRB-40947**
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 BCC lesion greater than or equal to 5 mm. BCC lesion(s) can be superficial, nodular, micronodular, or morpheaform BCC, 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 6 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, 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 (ie, who has had menses any time in the preceding 24 consecutive months)	☐	☐	☐	
5	Sexually active women of child bearing potential (WCBP) and male patients with a female partner of child-bearing potential must agree to use acceptable methods of contraception to avoid pregnancy (for example, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) before the first dose of study therapy and for 3 months after the last dose of study therapy	☐	☐	☐	
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 (> 25 mm) BCC lesion. Patients with large BCC lesion(s) will be referred for evaluation for surgical resection.	☐	☐	☐	
2	Inoperable locally-advanced and/or non-cutaneous metastatic				

	BCC				
3	Taking any medication known to affect HH signaling pathway such as itraconazole	☐	☐	☐	
4	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 to the study tumors of: ○ Glucocorticoids applied **topically** at the tumor site (low dose oral glucocorticoids do **not** necessarily exclude a patient) ○ Retinoids either systemically or topically at the tumor site (eg, etretinate, isotretinoin, tazarotene, tretinoin, adapalene) ○ Alpha-hydroxy acids (eg, glycolic acid, lactic acid) to > 5% of the skin or to the tumor site ○ 5-fluorouracil or imiquimod and/or ○ Itraconazole	☐	☐	☐	
5	Has received treatment with systemic chemotherapy or agents known to be inhibitors of HH signaling, within 60 days prior to starting study medication	☐	☐	☐	
6	Currently receiving systemic medications that could affect BCC tumors (eg, oral retinoids) or might interact with remetinostat	☐	☐	☐	
7	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	☐	☐	☐	
8	Moderate to significant immunosuppression (eg, 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)	☐	☐	☐	
9	Known or previous hypersensitivity to HDACi	☐	☐	☐	
10	History of congestive heart failure; cardiac arrhythmias; or other findings of ventricular dysfunction	☐	☐	☐	
11	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:	

APPENDIX B: Study IRB-40947 Participant Information Sheet

Remetinostat 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 BCC lesion(s) identified by your physician. Apply to the BCC lesion(s) 3 times daily for 6 weeks as specified by your physician. Cover the treated BCC 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.

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APPENDIX C: Study IRB-40947 Participant Medication Application Diary

Study Participant Study Drug Application Diary

Participant Identifier: BCC-_____

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	1/1/18	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>				
Day 14	<prepopulated date>				

	Date	Gel Applied			Comments
		Dose 1	Dose 2	Dose 3	
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>				
Day 50	<prepopulated date>				

	Date	Gel Applied			Comments
		Dose 1	Dose 2	Dose 3	
Day 51	<prepopulated date>				
Day 52	<prepopulated date>				
Day 53	<prepopulated date>				
Day 54	<prepopulated date>				
Day 55	<prepopulated date>				
Day 56	<prepopulated date>				
Day 57	<prepopulated date>				
Day 58	<prepopulated date>				
Day 59	<prepopulated date>				
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Day 77	<prepopulated date>				
Day 78	<prepopulated date>				
Day 79	<prepopulated date>				
Day 80	<prepopulated date>				
Day 81	<prepopulated date>				
Day 82	<prepopulated date>				
Day 83	<prepopulated date>				
Day 84	<prepopulated date>				

APPENDIX D: Serious Adverse Event Report Form (Diamond Pharma services)