

## Clinical Study Protocol

### Protocol Pelle-926-202

#### Double-Blind, Dose Escalating, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle Applied Once or Twice Daily to Decrease the GLI1 Biomarker in Sporadic Nodular Basal Cell Carcinomas

Development Phase of Study:	2A
Study design:	Multicenter, Double-Blind, Dose Escalating, Vehicle-Controlled Clinical Study
IND #:	125461
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Amendment 1— Protocol Version 2.0	22 September 2016
Amendment 2--- Protocol Version 3.0	16 August 2017
Amendment 3--- Protocol Version 4.0	24 August 2017
Sponsor Representative:	Ervin Epstein, M.D. Chief Medical Officer Phone: PPD Email: PPD
Sponsor:	PellePharm, Inc. 275 Middlefield Rd., Suite 100 Menlo Park, CA 94025

#### CONFIDENTIAL

**Nothing herein is to be disclosed without prior approval of the sponsor.**

**This protocol will be conducted in compliance with procedures outlined in this document, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. This study will not be initiated without the approval of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Any changes to the protocol will be approved in writing by the IRB/IEC before implementation except where necessary to eliminate an immediate harm to the patient.**

## **Protocol Review and Approvals**

### **Double-Blind, Dose Escalating, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle Applied Once or Twice Daily to Decrease the GLI1 Biomarker in Sporadic Nodular Basal Cell Carcinomas**

**Reviewed and approved:**

Ervin Epstein M.D.  
Chief Medical Officer  
PellePharm, Inc.

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## Principal Investigator Protocol Agreement Page

I have carefully read the protocol entitled: *“Double-Blind, Dose Escalating, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle Applied Once or Twice Daily to Decrease the GLII Biomarker in Sporadic Nodular Basal Cell Carcinomas”* and, I declare that as a Principal Investigator the clinical protocol was subject to critical review and is approved by the Sponsor.

I agree to conduct this study in compliance with procedures outlined in this document according to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and applicable regulatory requirements. This study will not be initiated without the approval of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the competent authority, if applicable.

I understand that any substantial changes to the protocol must be approved in writing by the IRB/IEC and the competent authority, if applicable, before it can be implemented except where necessary to eliminate immediate harm to the subject. I will provide copies of the protocol and access to all information furnished by PellePharm to study personnel under my supervision and will discuss this material with them to ensure they are fully informed about the study. I understand that the study may be terminated or enrollment suspended at any time by PellePharm with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

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Investigator Signature

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Printed Name

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Date

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Institution Name

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Address

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City, State Zip Code

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Phone Number

## 1. SYNOPSIS

<b>Name of Sponsor:</b> PellePharm, Inc.
<b>Name of Investigational Product:</b> patidegib gel
<b>Name of Active Ingredients:</b> patidegib HCl
<b>Title of Study:</b> Double-Blind, Dose Escalating, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle Applied Once or Twice Daily to Decrease GLI1 Biomarker in Sporadic Nodular Basal Cell Carcinomas
<b>Number of Clinical Centers:</b> One investigational center (metasite) in the United States will participate in this study.
<b>Objective:</b> The primary objectives of the study are to evaluate the following: <ol style="list-style-type: none"><li>1. The safety and tolerability of treatment with patidegib gel 2%, 4%, or vehicle applied once or twice daily for 12 weeks.</li><li>2. The molecular efficacy of treatment as defined by reduction in the hedgehog (HH) signaling pathway (GLI1 biomarker) after treatment with patidegib gel 2%, 4%, or vehicle applied once or twice daily for 12 weeks to treatment-targeted BCCs.</li></ol> The secondary objective of the study is to evaluate the following: <ol style="list-style-type: none"><li>1. The clinical efficacy of patidegib as defined by the percent decrease in greatest diameter of baseline treatment-targeted basal cell carcinomas after 12 weeks of treatment. Treatment-targeted Basal Cell Carcinomas (BCCs) will be biopsied prior to treatment to confirm the clinical diagnosis of nodular BCC. Eligible tumors will have the clinical features of nodular BCC and prior to biopsy will be no less than 5 mm or greater than 15 mm in greatest diameter on the face (excluding the nose and periorbital skin) and no less than 9 mm or greater than 20 mm in greatest diameter at sites other than the face.</li></ol> Exploratory objective: <ol style="list-style-type: none"><li>1. To evaluate the utility of an investigator static global tumor assessment (ISGTA) in assessing the proportion of baseline treatment targeted basal cell carcinomas that are evaluated as being clear or almost clear.</li><li>2. To evaluate the utility of blinded assessment of change in BCC size using photographs</li></ol>



**Methodology:**

This is a double-blind, dose escalating, randomized, vehicle-controlled study designed to compare the efficacy and safety of patidegib gel 2% and 4% applied once or twice daily in comparison with that of vehicle.

Approximately 36 subjects who meet the study entry criteria will be enrolled into one of four sequential cohorts. As soon as one cohort has been completely enrolled, the next cohort will be enrolled. Each subject will treat no more than two previously untreated biopsy confirmed treatment-targeted nodular BCCs. If the subject has additional non-treatment targeted BCCs they can be treated surgically or with topical agents prior to or during the trial. Within each cohort subjects will be randomized in a 2:1 ratio to receive active or vehicle gel. The sequential cohorts will be:

- Cohort 1: patidegib gel 2% or vehicle, once daily
- Cohort 2: patidegib gel 4% or vehicle, once daily
- Cohort 3: patidegib gel 2% or vehicle, twice daily
- Cohort 4: patidegib gel 4% or vehicle, twice daily

The study drug will be applied topically to the treatment-targeted BCCs and a rim or adjacent skin for 12 weeks.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination (PE) will be performed at Baseline and Week 12.

The treatment-targeted BCCs will be identified by the Investigator at the Baseline visit and will be circled in ink at Baseline, Weeks 6 and 12, and photographed, and measured at all study visits (Baseline, Weeks 2, 6, 8, 10, and 12).

Blood samples for complete blood count and serum chemistry and urine for urinalysis will be collected from subjects at Screening, Week 6, and Week 12.

Subjects who terminate study participation early will be asked to complete all Week 12 assessments, as appropriate, prior to commencement of any alternative therapy for BCCs (if possible). Subjects who discontinue from the study during the treatment period will not be replaced.

If signs or symptoms develop in the treatment areas during the treatment period that restrict daily activities or make continued application of the study drug difficult due to discomfort, the Investigator may instruct the subject to interrupt use of the study drug temporarily and to resume application of the study drug once the signs and symptoms have resolved adequately to the point that the Investigator believes that treatment can safely be resumed. The

Investigator should try to minimize study drug interruptions; and if needed, make best efforts to limit a “drug holiday” to 7 days. If the study drug interruption exceeds 4 consecutive days, the Investigator should consult with the Medical Monitor to determine a course of action. If the study drug is interrupted, discontinued, or a concomitant medication is used to treat a sign or symptom, an AE shall be recorded.

Subjects who discontinue from the study due to clinically significant laboratory abnormalities, AEs or any other reason will be asked to complete all Week 12 evaluations. Any subject who has an AE during the treatment period will be monitored by the Investigator until resolution (return to normal or to the baseline state) or stabilization, as determined by the Investigator.

In addition, application of study drug may be delayed or halted at any time if ongoing safety data evaluations raise concern for subject safety. If the subject participation is suspended, all of the subject’s safety data will be reviewed by the Medical Monitor in conjunction with the Investigator to determine the course of action.

**Number of Subjects Planned:**

Approximately 36 subjects who meet the study entry criteria will be enrolled into one of four sequential cohorts.

**Inclusion Criteria:**

1. The subject is from 18 to 85 years of age, inclusive.
2. The subject must provide electronic informed consent prior to any study procedures.
3. If the subject is a woman of childbearing potential<sup>1</sup>, she is willing to use two effective methods of birth control during the duration of the trial and for one month after the last application of the gel. The two forms of birth control authorized are defined as the use of a barrier method of contraception (condom with spermicide) in association with one of the following methods of birth control: bilateral tubal ligation; combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to Baseline; hormonal intra-uterine device (IUD) inserted at least 1 month prior to Baseline. This proscription is based on the key role of the HH pathway in embryogenesis, the known preclinical teratogenic effects of systemic cycloamine, a naturally

<sup>1</sup> For the purpose of this trial, a female not of childbearing potential is defined as a sexually mature woman who: 1) has undergone a hysterectomy or bilateral oophorectomy; or 2) has been naturally postmenopausal for at least 12 consecutive months (i.e., has not had menses at any time in the preceding 12 consecutive months); or 3) is 41 years of age or older with physiologic symptoms of menopause and a Follicle Stimulating Hormone (FSH) level of  $\geq 30$  IU/L or 4) whose male sexual partner has had a vasectomy.

occurring inhibitor of SMO, and the unknown level of systemic exposure following topical application of patidegib in humans.

4. If the subject is a male with a female sexual partner who is of childbearing potential, the couple is willing to use two effective methods of birth control during the duration of the trial and for one month after the last application of the gel. Authorized birth control methods are outlined in Inclusion Criterion #3. Any woman of childbearing potential applying the gel to themselves, or assisting a subject, must comply with the same birth control measures.
5. One or two previously untreated BCCs with the clinical features of a nodular BCC confirmed by a biopsy done at or prior to screening confirming nodular BCC. These tumors must be suitable for surgical excision. The BCCs prior to biopsy must be no less than 5 mm or greater than 15 mm in greatest diameter on the face and no less than 9 mm or more than 20 mm in greatest diameter at sites other than the face. Tumors on the nose, periorbital skin, or on or below the knee are excluded.
6. The subject is willing to abstain from application of non-study topical prescription and over the counter medications within 5 cm of a treatment-targeted BCC for the duration of the study except as prescribed by the Investigator. Moisturizers and emollients are allowable. Subjects will be encouraged to use sunscreen with a sunscreen protection factor (SPF 15 or higher) at least once daily on all exposed skin sites.
7. Female subjects must have negative serum pregnancy test at Screening.
8. The subject is willing to contact the study center after each primary skin care physician (PSCP) visit to provide the study center details of the visit and any treatment of skin tumors.
9. The subject is willing to forego alternative treatment of the treatment-targeted baseline BCC for the duration of the trial.



**Exclusion Criteria:**

1. Subjects with basal cell nevus syndrome (BCNS, Gorlin syndrome, nevoid basal cell carcinoma syndrome; OMIM #109400).
2. The subject has used topical products within 5 cm of a treatment- targeted BCC or systemic therapies that might interfere with the evaluation of the study medication during the study. Specifically, these include the use of:
  - a. Topical glucocorticoids 30 days prior to screening
  - b. Retinoids (e.g., etretinate, isotretinoin, tazarotene, tretinoin, adapalene) systemically or topically, or > 5% of an alphahydroxy acid (e.g., glycolic acid, lactic acid), photodynamic therapy (PDT), or 5-fluorouracil or imiquimod (except as topical treatment to discrete BCCs) systemically or topically to the skin during the six months prior to entry.
  - c. Systemic chemotherapy within one year prior to screening. (Note: field therapy with topically applied treatments can be done as long as they are not applied within 5 cm of a treatment-targeted tumor).
  - d. Known inhibitors of the HH signaling pathway (e.g., vismodegib, patidegib, sonidegib, and itraconazole) topically or systemically within 6 months of entry into the study.
3. The subject has a history of hypersensitivity to any of the ingredients in the study medication formulation.
4. The subject is unable or unwilling to make a good faith effort to be present for all follow-up visits and tests.
5. The subject is a woman who is currently nursing.
6. The subject has any systemic disease that in the Investigator's opinion would interfere with the subject's ability to participate.
7. The subject has a clinically significant history of liver disease, including viral hepatitis, current alcohol abuse, or cirrhosis that in the investigator's opinion would interfere with the subject's ability to participate.
8. The subject has any condition or situation, which in the Investigator's opinion may put the subject at significant risk, could confound the study results, or could interfere significantly with the subject's participation in the study. This includes history of other

skin conditions or diseases, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of this investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications.

9. The subject has a history of invasive cancer within the past five years excluding non-melanoma skin cancer, Stage I cervical cancer, ductal carcinoma in situ of breast, or chronic lymphocytic lymphoma (CLL) (Stage 0).
10. The subject is currently participating in an experimental drug study, (within 4 weeks of Baseline visit), or plans to participate in an experimental drug study while enrolled in this study.
11. The subject is on a concomitant medication that is a strong CYP3A4 inhibitor. These include, but are not limited to: larithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

**Investigational Product, Reference Therapy, Dosage and Mode of Administration:**

- patidegib gel 2%, applied topically, once daily for 12 weeks
- patidegib gel 4%, applied topically, once daily for 12 weeks
- patidegib gel 2%, applied topically, twice daily for 12 weeks
- patidegib gel 4%, applied topically, twice daily for 12 weeks
- vehicle gel, applied topically, once daily for 12 weeks
- vehicle gel, applied topically, twice daily for 12 weeks

**Application Instructions:**

The Investigator or their designee will instruct the subject on how to apply the study drug to the previously biopsied treatment-targeted BCCs identified at the Baseline visit by the Investigator. The staff member will instruct the subject on the proper application procedure during the Baseline visit. The quantity of gel to be applied will be defined using laminated dosing cards. Approximately 20 mg of gel will be applied to each tumor at each treatment. The subject is to treat no more than two treatment-targeted BCCs. If the subject has additional BCCs they may be treated surgically or topically during the trial. In addition to the verbal instructions given during the visit, the subjects will be provided with written instructions for proper application technique.

Because sunlight can increase the development of skin cancers subjects will be advised to avoid or minimize exposure to direct sunlight while in the study. Subjects will also be advised to wash their hands before and after application of the study drug.

The amount of study drug used by the subjects will be guided by instructing the subjects to use dosing cards that will provided to them, and monitored by weighing each newly dispensed study drug tube, and re-weighing each returned study drug tube.

**Duration of Treatment:**

All subjects will be treated for 12 weeks.

**Criteria for Evaluation:**

The study will be conducted as outlined in the Schedule of Assessments ([Table 1](#)). For all efficacy measurements, the Investigators will be provided with study specific training to ensure consistent evaluations. The assessments for a particular subject should be performed by the same investigator at all study visits whenever possible.

**Safety Measurements:**

Dermal Safety and Tolerability: Safety and tolerability will be evaluated through assessment of selected local signs and symptoms (pain / burning, pruritus, erythema, edema, and scabbing / crusting). Each of the identified BCCs will be evaluated separately for these signs and symptoms of application site reactions. Any local skin reaction that requires use of a concomitant therapy or causes study drug interruption or discontinuation should be reported as an AE. The scales to be used for assessing local skin reactions at treatment sites follow:

<b>Score</b>	<b>Grade</b>	<b>Description</b>
<i>Pain/Burning: as reported by the subject as being the greatest intensity they have experienced at the application site within the last 24 hours at Baseline or since the last visit at subsequent visits.</i>		
0	None	No pain/burning
1	Mild	Slight burning/stinging sensation; not really bothersome
2	Moderate	Definite warm, burning/stinging that is somewhat bothersome
3	Severe	Hot burning/stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep
<i>Pruritus: as reported by the subject as being the greatest intensity they have experienced at the application site within the last 24 hours at Baseline or since the last visit at subsequent visits.</i>		
0	None	No pruritus
1	Mild	Slight pruritus, not really bothersome
2	Moderate	Definite pruritus that is somewhat bothersome
3	Severe	Intense pruritus that may interrupt daily activities and/or sleep
<i>Erythema: as assessed by the Investigator at each site</i>		
0	None	No erythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color
<b>Score</b>	<b>Grade</b>	<b>Description</b>
<i>Edema: as assessed by the Investigator at each site</i>		
0	None	No edema

1	Mild	Slight, but definite edema
2	Moderate	Definite edema
3	Severe	Marked edema
<i>Scabbing/Crusting: as assessed by the Investigator at each site</i>		
0	None	No scabbing/crusting
1	Mild	Slight, but definite scabbing/crusting
2	Moderate	Definite scabbing/crusting
3	Severe	Marked scabbing/crusting

Symptoms of Hedgehog Inhibitor Toxicity: At each visit subjects will be asked if they have experienced any symptoms that have been associated with systemic use of this class of drugs, in particular hair loss, taste loss, muscle cramps, bowel changes, fatigue.

Adverse Events: During the study, subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, and seriousness, action taken regarding the study drug, corrective treatment, outcome, and the Investigator’s assessment of causality. AEs present at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

Safety Laboratory Tests: Routine safety laboratory tests (complete blood count/differential urinalysis and serum chemistry) will be performed at Screening, Week 6, and Week 12. Any out-of-range laboratory result that is considered clinically significant by the Investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the Investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

Physical Examinations: An abbreviated physical examination including measurements of height, weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) will be performed at Baseline and Week 12.

Pregnancy Tests: All female subjects will have a pregnancy test performed at the Screening visit. Females of childbearing potential will take a home pregnancy urine test at Weeks 2, 8, and 10 and will have a serum pregnancy test at Weeks 6 and 12.

**Efficacy Measurements:**

Primary:

**Biomarker:** At screening the treatment-targeted BCC will be biopsied to confirm the clinical diagnosis of nodular BCC. In addition, at or within 14 days of the Week 12 visit the

treatment site will be excised. Both of these tissue samples will be tested for GLI1 mRNA levels.

Secondary:

The clinical efficacy of patidegib as defined by the percent decrease from Baseline of the longest diameter of treatment-targeted BCC after 12 weeks of treatment.

Exploratory:

- To evaluate the utility of an investigator static global tumor assessment (ISGTA) in assessing the proportion of baseline treatment-targeted BCCs that are evaluated as being clear or almost clear.
- Histologic Cure: The proportion of the excisional samples obtained at or shortly after the Week 12 visit that demonstrate no residual BCC.

**Statistical Methods:**

All subjects who are randomized and dispensed study drug will be included in the intent-to-treat (ITT) analysis set. All subjects who are randomized, receive at least one confirmed dose of study drug, and have at least one post-baseline safety assessment will be included in the safety population.

No imputation will be made for the primary endpoint. For the secondary endpoint, last observation carried forward (LOCF) will be used to impute efficacy data that are missing post-baseline through Week 12. No imputations will be made for missing safety data.

Per protocol analysis will be performed – we will exclude samples with insufficient BCC, subjects with poor treatment compliance, or tumors where the diameter was incorrectly measured based on review of photographs. We will also analyze BCC size change based on photographs.

***Efficacy Summaries:***

The efficacy endpoints are intended to compare once and twice daily application of 2% patidegib gel, 4% patidegib gel, and vehicle gel. Efficacy assessments will be summarized descriptively by treatment group and visit.

Primary Efficacy Endpoints:

- Change in GLI1 mRNA levels in drug-treated vs. vehicle-treated tumors after 12 weeks of treatment.

Secondary Efficacy Endpoint:

- Decrease in tumor size defined as percent decrease in the greatest diameter of baseline treatment-targeted BCCs at the Week 12.

Exploratory Efficacy Endpoint:

- The proportion of baseline treated tumors are smaller based on photographic review
- The proportion of baseline treatment targeted BCCs that are evaluated as being clear or almost clear at Baseline, Weeks 2, 6, 8, 10, and 12 based on the ISGTA.

Efficacy Analyses:

The primary endpoint and the secondary endpoints of change in tumor size, and reduction in the HH signaling pathway will be evaluated with an analysis of covariance (ANCOVA) with treatment group as factor and baseline value as a covariate. Pairwise comparisons will be performed using contrasts within the ANCOVA. Additionally, t-tests for pairwise comparisons of the primary endpoint will be done, or alternatively a non-parametric approach may be used.

The exploratory analysis of ISGTA will be analyzed with a Cochran-Mantel-Haenszel test

***Safety:***

Safety Endpoints:

- Adverse Events
- Dermal Safety and Tolerability including pain/burning, pruritus, erythema, edema, and scabbing/crusting
- Clinical laboratory assessments

Safety Analyses:

Subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, action taken regarding the study drug, corrective treatment, outcome, and Investigator's assessment of causality. All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious adverse events

(SAEs) will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the Investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

The frequency of dermal safety and tolerability assessments including pain/burning, pruritus, erythema, edema, and scabbing/crusting will be summarized by treatment group and visit.

Changes from baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Screening and Weeks 6 and 12. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each Investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

**Sample Size Calculations:**

This is a dose ranging study.



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### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation or Specialist Term</b>	<b>Definition or Explanation</b>
AE	Adverse Event
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
ANCOVA	Analysis of Covariance
BCC	Basal Cell Carcinoma
BCNS	Basal Cell Nevus Syndrome
BUN	Blood Urea Nitrogen
CBC/Diff	Complete Blood Count with Differential
CLL	Chronic Lymphocytic Lymphoma
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GLI 1	Glioma-associated oncogene homolog 1
GMP	Good Manufacturing Practices
GRAS	Generally Recognized as Safe
HCl	Hydrogen Chloride
HH	Hedgehog
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISGTA	Investigator Static Global Tumor Assessment
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Affairs
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mRNA	Messenger Ribonucleic Acid
PDT	Photodynamic Therapy
PTCH1	Patched Protein 1
PSCP	Primary Skin Care Physician
RBC	Red Blood Cell
SAE	Serious Adverse Event

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<b>Abbreviation or Specialist Term</b>	<b>Definition or Explanation</b>
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SEB	Surgically Eligible Basal Cell Carcinoma
SMO	Smoothened
SPF	Sunscreen Protection Factor
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
US	United States
UV	Ultraviolet
WBC	White Blood Cell Count

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#### 4. INTRODUCTION

PellePharm, Inc. is developing patidegib gel for the management of the burden of disease in patients with basal cell nevus syndrome (BCNS), a rare genetic disease characterized by the development of numerous basal cell carcinomas over a lifetime. This trial will evaluate the ability of patidegib gel to shrink BCC tumors in patients with sporadic BCCs as a proof-of-concept for the mechanism of patidegib on BCCs. It is hoped that results from this study will inform the dose and dosing regimen prior for future trials, thereby maximizing the therapeutic potential.

**Basal cell carcinomas:** These tumors are the most common of human cancers, occurring in an estimated 2-3 million Americans each year. The overwhelming majority of these tumors occur sporadically with a strong predilection for sun exposed skin sites in persons of Northern Europe descent who have had excessive sun exposure. Sporadic BCCs are most commonly seen starting in the 4<sup>th</sup> decade of life. Current treatment depends in large part on physical destruction of the tumors, most commonly with surgery and less commonly with ionizing radiation.

**Basal cell nevus syndrome:** BCCs are one of the most prominent phenotypic features of patients with the BCNS (Gorlin) syndrome (OMIM #109400)<sup>1</sup>. This syndrome is inherited as an autosomal dominant condition, and patients are susceptible to many abnormalities, including, most frequently, palmar and plantar pits and jaw cysts, and medulloblastomas. Reports of its prevalence vary; the highest estimate is 1:31,000. In one study of patients with heritable cancer syndromes studies, those with BCNS had the longest expected lifespan of 73 years<sup>2</sup>, which is not unexpected for a cancer that grows locally and metastasizes only very rarely. Diagnosis of BCNS commonly is made when patients are in their teens<sup>3</sup>. The burden of BCCs varies among BCNS patients. For example, in a Children's Hospital Oakland and Stanford combined registry of 100 BCNS patients living throughout the United States, 1/3 had a total of 5 or fewer BCCs in the previous two years, 1/3 had 6-20 BCCs treated, and 1/3 had more than 20 BCC in the past 2 years<sup>3</sup>.

**Aberrant Hedgehog signaling in BCCs:** In 1996, two groups identified the PTCH1 gene as the locus of the mutations that cause BCNS<sup>4-6</sup>. Patients with BCNS have one defective heritable copy of this gene, and sporadic loss of the second allele is crucial to the development of all of their BCCs. Despite this identification, diagnosis of BCNS still relies primarily on clinical findings<sup>7</sup> because a significant percentage of patients with clinically typical BCNS have PTCH1 mutations that are not detectable with current sequencing approaches. The function of the PTCH1 gene is well known from studies conducted over three decades - it encodes the primary inhibitor of the hedgehog (HH) signaling pathway and its function is to inhibit signaling by the next "downstream" member of the HH pathway - SMOOTHENED (SMO). Approximately 90% of sporadic BCCs have lost function of PTCH1, and approximately 10% of sporadic BCCs have an activating mutation in SMO that renders the protein resistant to inhibition by PTCH1 protein<sup>8</sup>. By comparison, all BCNS BCCs have loss of PTCH1 without activating mutations of SMO<sup>9</sup>. Indeed

all BCCs, whether arising in BCNS patients or sporadically, have up-regulated output of the HH pathway as their fundamental molecular defect. This signaling pathway is crucial to development of many organs during embryogenesis but in adult life functions in only a limited number of sites, among which is the hair follicle. This is consistent with the finding that in some mouse models BCCs arise from the hair follicles. The importance of aberrant HH signaling as the driver of BCCs was proved indisputably by the strong anti-tumor effect of small molecules that down-regulate this pathway [vide infra].

Growth of BCCs: As expected, given the common underlying molecular underpinning of all BCCs, the biology of sporadic BCCs and BCCs in BCNS patients is very similar and is characterized by slow growth and very low frequency of metastasis. Thus Kirkup and De Berker found a median increase of 0.5 mm in the longest diameter of sporadic BCCs untreated for a mean of 70 days<sup>10</sup>. Similarly, Tan et al found an increase in longest diameter of 0.75 mm per month in periocular BCCs<sup>11</sup>. Growth specifically of BCCs in BCNS patients also is slow, with minimal enlargement in subjects randomized to the placebo arm of a double-blinded study of the efficacy of vismodegib<sup>12</sup>.

BCNS is a chronic disease: In one recent report of a cohort of BCNS patients, the average time since diagnosis was 28 years<sup>13</sup> and in a combined registry of 100 patients at Children's Hospital Oakland and Stanford, the median age of diagnosis was 15 years<sup>3</sup>, the median survival in BCNS patients being reported as 73 years<sup>2</sup>. Fewer than 10% of BCNS patients report having locally advanced BCCs – the majority had tumors that were surgically operable.

In general, BCNS patients have their BCCs treated as they become problematic, i.e. at risk of invasion of vital structures such as eyes, nose, or ears or large enough off the face such that they are uncomfortable, bleed, etc. Thus BCNS patients typically never are free of BCCs - in a trial of the effects of vismodegib vs. BCCs in BCNS patients (vide infra), BCNS subjects had an average of 27 BCCs present at baseline, and although oral vismodegib can produce complete clinical clearing, once the drug is stopped the BCCs recur<sup>12</sup>.

Pharmacologic treatment of BCCs: Several topically-applied drugs are used in the treatment of BCCs, such as imiquimod and 5-fluoruracil. Both of these can cure approximately 80% of the superficial subtype of BCCs most of which generally occur off the face, but generally are not useful vs. nodular BCCs, which are the more prevalent subtype, especially on the face. Prevention of sporadic BCCs so far has been limited to admonitions to avoid sunlight, advice which is followed infrequently. With identification of uncontrolled HH signaling as the driving molecular abnormality in all BCCs, several anti-HH drugs have been developed for oral treatment of BCCs, and two of these - vismodegib (Genentech/Roche) and sonidegib (Novartis) - have been approved for systemic treatment of advanced BCCs. The latter are defined as BCCs whose surgical excision likely would produce unsatisfactory results (i.e. "locally advanced") or those which have become metastatic<sup>14</sup>. Approximately 50% of such BCCs fail to respond initially, frequently due to

mutations in the SMOOTHENED gene, which encodes the protein to which these drugs bind. Of those that do respond, a significant proportion develop secondary resistance, often due to mutations in the drug binding pocket of the SMO protein<sup>15</sup>. Vismodegib also has been studied for efficacy vs. BCCs in patients with BCNS<sup>12</sup>. Unlike results in advanced BCCs, all Gorlin non-advanced tumors respond by shrinking, eventually most disappearing completely both clinically and histologically. This is consistent with the finding that all non-advanced BCCs in BCNS patients lack SMO mutations. In addition, the BCCs in BCNS patients fail to develop resistance and, so long as BCNS patients continue to take the drug, no new surgically-eligible BCCs (SEB) developed. The combined result of shrinkage of existing BCCs and blockage of the development of new BCCs is that these patients have no need for surgery so long as they continue to ingest vismodegib. But because of annoying class-specific side effects most patients discontinue vismodegib, and all the clinically and histologically cleared BCCs recur to the same size as before treatment<sup>12</sup>. Of note, the rate of development of new SEBs was lower after vismodegib was discontinued (0.7 new SEBs/month) than it had been during initial placebo treatment (2.4 new SEBs/month), suggesting that vismodegib may have a more robust, long-lasting effect on smaller BCCs than on SEBs and hence may be more effective at inhibiting progression by blocking the growth of new SEBs than by shrinking existing SEBs<sup>12</sup>. Small as well as large but operable sporadic BCCs respond to vismodegib unless they are among the approximately 10% of sporadic BCCs that are driven by SMO mutations rather than by loss of PTCH1 mutations<sup>16</sup>.

Patidegib is a semi-synthetic small molecule, and the topical drug product is manufactured with generally accepted, safe excipients. Oral patidegib has a good therapeutic efficacy versus locally advanced and metastatic BCCs but produces the same types of adverse effects as do other systemic HH inhibitors. Topical patidegib has been shown to be stable in the developed gel formulation and can be applied to mini-pig skin without irritation. Topical application of patidegib significantly reduces murine BCC tumor size in vivo and reduces GLII1 biomarker expression in vitro in human BCC tumor explants.

If proven to be safe and effective in future clinical trials patidegib gel may offer BCNS patients a safe and effective therapy to manage their burden of disease by decreasing the number of surgeries they will require over their lifetime. This trial will evaluate the safety, the tolerability, and the ability of four different dosing regimens applied for 3 months to shrink nodular BCC tumors in patients with sporadic BCCs.

The goal of the present trial is to evaluate topical patidegib's safety, tolerability, and effects on the size of preexisting sporadic previously untreated nodular BCCs and thereby to establish a dose and dosing regimen for future trials in the BCNS orphan population. It is anticipated that subsequent trials will focus on reducing the number of facial surgeries required by patients with BCNS and not on the "treatment" of individual sporadic BCCs. If the efficacy with topical patidegib can approach the level of efficacy of oral HH inhibitors seen in BCNS patients while avoiding their systemic side effects, it would represent a major advance for BCNS patients.



**Rationale for using telemedicine-based and photographic assessments of BCC in clinical trials:** For medical science to progress, technology must advance to bridge the gap between research and the real-world patient application of medical discovery. For example, researchers are beginning to have a better understanding of the complexity of the genetic and environmental factors that contribute to the development of skin cancer. But to decipher the complexity of this relationship across growing and diverse populations, new technology and methodology is needed to connect with patients. Keeping pace with the advent of electronic medical records, social networking, and smartphones, new applications of technology will allow patients to interact with physicians and researchers more regularly and directly from home in a way that will lead to better treatment and understanding of the diseases that afflict us. These technologies will also unlock access to a more diverse population of patients and also to allow for more real time evaluation of adverse events in these patients.

The concept of using mobile smartphone technology in medicine and research is not new. Even with regard to skin cancer, research instruments such as telemedicine, mobile electronic devices, and the internet have been used. Specifically, this technology has been used to assist with compliance, medical education, physician-patient interactions, medical access, and evaluation of treatment efficacy in many areas including dermatology. Many FDA guidelines for registered trials in skin disease strongly suggest that a digital photographic record of all patient visits be made available as the gold standard for FDA audit of clinical outcomes.

Access issues continue to limit biomedical research and healthcare. Access limits connections between patients and physicians and between researchers and needed subjects. As modern medical practice shifts toward patient-centered care, a push toward greater patient engagement must also evolve. A better partnership between patients and doctors to improve understanding and management of disease will lead to better healthcare. As an example, patients will be able to enter their own data into secure electronic health records (EHR). Today, some patients enjoy access to their EHR through providers such as Kaiser Permanente and are allowed to procure certain samples for lab analysis (e.g. fecal occult blood test) in their home. This very same principle of patient empowered medical evaluation can be applied to research and made easy for patients to access. Note that physician guidance is still the foundation of medical and investigational practice. However, application of patient involvement can be as simple as using a mobile device to securely update reliable patient reported outcomes (PROs) within clinical trials. Additionally, less than 5% of clinical research participants nationally are minorities. The decentralized clinical trial model will unlock access to minorities and underserved populations that are not normally cared for at traditional clinical research sites and thus better reflect the national diversity of race and ethnicity in the United States.

New technology exists to bridge access between clinical research and the need for patient-centered care. One such application of technology is NORA (Network Oriented Research Assistant). NORA is currently being used successfully in other FDA-registered decentralized

clinical trials to assess rare skin and mucosal disease in the home. NORA is a combination technology that includes the functionality of a telemedicine platform, an EMR, an EDC, an eConsent and a mobile data collection tool. NORA was recently used to compare digital photography as a correlate of face-to-face acne and blister scoring but has been used in other therapeutic areas as well. This approach will hopefully improve patient outcomes and advance the field of medicine by using more real world data and a better diversity of patients.

## 5. STUDY OBJECTIVES

The primary objectives of the study are to evaluate the following:

1. The safety and tolerability of treatment with patidegib gel 2% or 4% or vehicle applied once or twice daily for 12 weeks.
2. The molecular efficacy of treatment as defined by reduction in the hedgehog (HH) signaling pathway after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 12 weeks to treatment-targeted BCCs.

The secondary objectives of the study are to evaluate the following:

1. The clinical efficacy of patidegib as defined by the percent decrease in greatest diameter of baseline treatment targeted basal cell carcinomas after 12 weeks of treatment. Treatment targeted BCCs will be biopsied prior to treatment to confirm the clinical diagnosis of nodular BCC. Eligible tumors will have the clinical features of nodular BCC and prior to biopsy will be no less than 5 mm or greater than 20 mm in longest diameter on the face (excluding the nose and periorbital skin) and no less than 9 mm or greater than 20 mm in longest diameter at sites other than the face.

The exploratory objectives of the study are to evaluate the following

1. To evaluate the utility of an investigator static global tumor assessment (ISGTA) in assessing the proportion of baseline treatment-targeted BCCs that are evaluated as being clear or almost clear.
2. To evaluate the utility of blinded assessment of change in BCC size using photographs

### 5.1 Overall Study Design and Plan

This is a double-blind, dose escalating, randomized, vehicle-controlled study designed to assess the efficacy and safety of patidegib gel 2% and 4% in comparison with vehicle applied once or twice daily. The population of subjects will be enrolled from the PPD .

Approximately 36 subjects who meet the study entry criteria will be randomized to one of four sequential cohorts. Each cohort will have 6 subjects randomized to active drug and 3 randomized to vehicle. The four sequential cohorts will be patidegib gel 2% or vehicle applied once daily, patidegib gel 4% or vehicle applied once daily, patidegib gel 2% or vehicle applied twice daily, and patidegib gel 4% or vehicle applied twice daily. As soon as one cohort has been enrolled the next cohort will be recruited. The study drug will be applied topically to the treatment-targeted

nodular BCCs once or twice daily for 12 weeks of treatment. Subjects will apply their treatments at home as explained by the Investigator or their designee. The subject will apply the initial application under the supervision of the study staff. If a subject has a treatment targeted BCC on an anatomical location that the subject cannot reach such as the back, a friend or family member may apply the treatment. In this case the friend or family member applying the gel, a woman of childbearing potential should follow the birth control requirements outlined in the Inclusion Criteria, and the person should apply the gel using a latex or vinyl glove. As skin cancer patients are routinely advised, all subjects will be instructed to avoid exposure to direct sunlight and to continue their use of sunscreens to minimize their exposure to ultraviolet (UV) radiation.

It should be noted that 3 months of treatment with oral vismodegib caused a 50% reduction in the sum of the greatest diameters of BCCs in 50% of BCNS patients. Therefore, even if topical patidegib were as effective as oral vismodegib in shrinking BCCs there likely will be enough residual BCC at Week 12 to allow for meaningful evaluation of biomarkers.

Subjects will return their tubes of study drug, which will be evaluated for drug usage compliance. While individual usage rates of topical products will vary, the use of a dosing card should help limit the variation in dosing inherent with topical products. Approximately 20 mg of the gel represents a single applied dose. Thus a subject treating a single tumor once daily for 12 weeks will apply a total dose of 1.6 gm of gel and those treating two tumors twice daily for 12 weeks will apply a total dose of 6.4 gm of gel. In terms of actual drug, 20 mg of patidegib gel 2% and 4% contains 0.4 mg and 0.8 mg of patidegib, respectively. Thus the total dose of drug in the 2% once daily group treating a single tumor will be approximately 34 mg while subjects treating two tumors twice daily for 12 weeks with patidegib gel 4% will receive a total of 134 mg of patidegib. To put this in perspective in previous trials with an oral formulation of patidegib subjects were treated with a daily oral dose of 130 – 160 mg, many for longer than 6 months.

Upon completion of the 12-week treatment period, all subjects will be asked to return to the investigational center for final evaluation. At the Week 12 visit the treatment site(s) will be excised. The area excised should at a minimum include the original diameter of the tumor. This means that if the tumor has shrunk in size the entire original area of the BCC will be excised, not just the visually apparent residual tumor. During the study, subjects will be allowed to use moisturizers and emollients and sunscreen. The Investigator will assess the areas affected at each visit.

The treatment-targeted BCC(s) will be identified by the Investigator at the Baseline visit and will be circled in ink at Baseline, Weeks 6 and 12, and photographed, and measured at all study visits (Baseline, Weeks 2, 6, 8, 10, and 12).

**Biomarkers:** On each subject one or two baseline previously untreated nodular BCCs designated as a treatment-targeted tumor will be biopsied and at the end of 12 weeks of treatment the treatment

site(s) will be excised. Both samples will be evaluated histologically and for determination of GLI1 mRNA levels.

Blood samples for complete blood count and serum chemistry and urine for urinalysis will be collected from subjects at Screening, Week 6, and Week 12.

Subjects who terminate study participation early will be asked to complete all Week 12 assessments, as appropriate, prior to commencement of any alternative therapy for BCC (if possible). Subjects who discontinue from the study during the treatment period will not be replaced.

If signs or symptoms develop in the treatment areas during the treatment period that restrict daily activities or make continued application of the study drug difficult due to discomfort, the Investigator may instruct the subject to interrupt use of the study drug temporarily and to resume application of the study drug once the signs/symptoms have subsided. The Investigator should try to minimize study drug interruptions; and if needed, make best efforts to limit a “drug holiday” to no more than 7 days. If the study drug interruption does exceed 4 consecutive days, the Investigator should consult with the Medical Monitor to determine a course of action. If the study drug is interrupted, discontinued, or a concomitant medication is used to treat a sign or symptom, an AE shall be recorded.

Subjects who discontinue participation in the study due to clinically significant laboratory abnormalities or AEs will be asked to complete all Week 12 evaluations. Any subject who has an AE during the treatment period will be monitored by the Investigator until resolution (return to normal or to the baseline state) or stabilization, as determined by the Investigator.

In addition, application of study drug may be delayed or halted at any time if ongoing safety data evaluations raise concern for subject safety. If the subject participation is suspended, all of the subject’s safety data will be reviewed by the Medical Monitor in conjunction with the Investigator to determine course of action.

**Table 1: Schedule of Assessments**

Assessments	Screening	Baseline (Within 6 weeks of Screening)	Week 2	Week 6	Week 8	Week 10	Week 12 / ET <sup>a</sup>	Week 14
Day	-42 to 0	1	15	43	57	71	85	99
Window (days)			± 2	± 3	± 3	± 3	± 3	± 7
Informed Consent	X							
Eligibility Confirmation	X	X						
Demographics	X							
Medical History	X	X <sup>c</sup>						
Height, Weight	X	X <sup>d</sup>					X	
Physical Examination (vital signs)		X					X	
Laboratory Testing (blood and urine) <sup>e</sup>	X			X			X	
Serum Pregnancy Test	X			X <sup>f</sup>			X <sup>f</sup>	
Home Pregnancy Urine Test <sup>g</sup>			X		X	X		
Randomization		X						
Tasks to be Done by Physician								
Identification of the BCC to be Biopsied	X							
Application Site Evaluation		X	X	X	X	X	X	
ISGTA		X	X	X	X	X	X	
Measure and Map BCCs	X	X	X	X	X	X	X	
Determine Clinical Tumor Type	X							
2mm Punch or Shave Biopsy	X							
End of Treatment Excision							X <sup>h</sup>	
BCC Imaging <sup>i</sup>	X	X	X	X	X	X	X	

Systemic Symptoms		X	X	X	X	X	X	
Patidegib /Vehicle Applications <sup>J</sup>		X	X	X	X	X		
Study drug review/Instructions Dispensation <sup>J</sup>		X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	
Review Test Article Compliance/Accountability		X	X	X	X	X	X	
Clinical Evaluation of Surgical Site(s)								X

BCC= basal cell carcinoma; ET = early termination; ISGTA = investigator static global tumor assessment;

<sup>a</sup> for subjects who discontinue early during the treatment period, all procedures outlined for the ET visit should be completed at the time of discontinuation.

<sup>b</sup> Must be signed prior to any study procedures.

<sup>c</sup> Medical history will be updated at Baseline visit.

<sup>d</sup> Height will be measured at Baseline only.

<sup>e</sup> Blood samples for laboratory tests will be collected at Screening. Clinically significant laboratory findings at Week 6 or Week 12 will be repeated at the discretion of the Investigator, and the subject will be followed until resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

<sup>f</sup> Week 6 and 12 serums to be done only for women of child bearing potential

<sup>g</sup> Only to be done for women of child bearing potential

<sup>h</sup> Must be within 48 hours of the Week 12 visit.

<sup>1</sup> Imaging requirements are provided in the imaging manual.

<sup>J</sup> Subjects will be trained on how to administer the study drug at the Baseline visit and retrained at subsequent visits, if necessary. The study drug may be applied at the study visit. Subjects will record any missed doses and provide to the study site for review

## 6. SELECTION AND WITHDRAWAL OF SUBJECTS

### 6.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. The subject is from 18 to 85 years of age, inclusive.
2. The subject must provide electronic informed consent prior to any study procedures.
3. If the subject is a woman of childbearing potential<sup>2</sup>, she is willing to use two effective methods of birth control during the duration of the trial and for one month after the last application of the gel. The two forms of birth control authorized are defined as the use of a barrier method of contraception (condom with spermicide) in association with one of the following methods of birth control: bilateral tubal ligation; combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to Baseline; hormonal intra-uterine device (IUD) inserted at least 1 month prior to Baseline. This proscription is based on the key role of the HH pathway in embryogenesis, the known preclinical teratogenic effects of systemic cyclopamine, a naturally occurring inhibitor of SMO, and the unknown level of systemic exposure following topical application of patidegib in humans.
4. If the subject is a male with a female sexual partner who is of childbearing potential, the couple is willing to use two effective methods of birth control during the duration of the trial and for one month after the last application of the gel. Authorized birth control methods are outlined in Inclusion Criterion #3. Any woman of childbearing potential applying the gel to themselves, or assisting a subject, must comply with the same birth control measures.
5. One or two previously untreated BCCs with the clinical features of a nodular BCC confirmed by a biopsy done at or prior to screening confirming nodular BCC. These tumors must be suitable for surgical excision. The BCCs prior to biopsy must be no less than 5 mm or greater than 15 mm in greatest diameter on the face and no

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<sup>2</sup> For the purpose of this trial, a female not of childbearing potential is defined as a sexually mature woman who: 1) has undergone a hysterectomy or bilateral oophorectomy; or 2) has been naturally postmenopausal for at least 12 consecutive months (i.e., has not had menses at any time in the preceding 12 consecutive months); or 3) is 41 years of age or older with physiologic symptoms of menopause and a Follicle Stimulating Hormone (FSH) level of  $\geq 30$  IU/L or 4) whose male sexual partner has had a vasectomy.



less than 9 mm or more than 20 mm in greatest diameter at sites other than the face. Tumors on the nose, periorbital skin, or on or below the knee are excluded.

6. The subject is willing to abstain from application of non-study topical prescription and over the counter medications within 5 cm of a treatment-targeted BCC for the duration of the study except as prescribed by the Investigator. Moisturizers and emollients are allowable. Subjects will be encouraged to use sunscreen with a sunscreen protection factor (SPF 15 or higher) at least once daily on all exposed skin sites.
7. Female subjects must have negative serum pregnancy test at Screening.
8. The subject is willing to contact the study center after each primary skin care physician (PSCP) visit to provide the study center details of the visit and any treatment of skin tumors.
9. The subject is willing to forego alternative treatment of the treatment-targeted baseline BCC for the duration of the trial.

## **6.2 Subject Exclusion Criteria**

Subjects meeting any of the following criteria will be excluded from the study:

1. Subjects with basal cell nevus syndrome (BCNS, Gorlin syndrome, nevoid basal cell carcinoma syndrome; OMIM #109400).
2. The subject has used topical products within 5 cm of a treatment- targeted BCC or systemic therapies that might interfere with the evaluation of the study medication during the study. Specifically, these include the use of:
  - a. Topical glucocorticoids 30 days prior to screening
  - b. Retinoids (e.g., tretinoin, isotretinoin, tazarotene, tretinoin, adapalene) systemically or topically, or > 5% of an alpha-hydroxy acid (e.g., glycolic acid, lactic acid), photodynamic therapy (PDT), or 5-fluorouracil or imiquimod (except as topical treatment to discrete BCCs) systemically or topically to the skin during the six months prior to entry.
  - c. Systemic chemotherapy within one year prior to screening. (Note: field therapy with topically applied treatments can be done as long as they are not applied within 5 cm of a treatment-targeted tumor).

- d. Known inhibitors of the HH signaling pathway (e.g., vismodegib, patidegib, sonidegib, and itraconazole) topically or systemically within 6 months of entry into the study.
3. The subject has a history of hypersensitivity to any of the ingredients in the study medication formulation.
4. The subject is unable or unwilling to make a good faith effort to be present for all follow-up visits and tests.
5. The subject is a woman who is currently nursing.
6. The subject has any systemic disease that in the Investigator's opinion would interfere with the subject's ability to participate.
7. The subject has a clinically significant history of liver disease, including viral hepatitis, current alcohol abuse, or cirrhosis that in the investigator's opinion would interfere with the subject's ability to participate.
8. The subject has any condition or situation, which in the Investigator's opinion may put the subject at significant risk, could confound the study results, or could interfere significantly with the subject's participation in the study. This includes history of other skin conditions or diseases, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of this investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications.
9. The subject has a history of invasive cancer within the past five years excluding non-melanoma skin cancer, Stage I cervical cancer, ductal carcinoma in situ of breast, or chronic lymphocytic lymphoma (CLL) (Stage 0).
10. The subject is currently participating in an experimental drug study, (within 4 weeks of Baseline visit), or plans to participate in an experimental drug study while enrolled in this study.
11. The subject is on a concomitant medication that is a strong CYP3A4 inhibitor. These include, but are not limited to: larithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

### 6.3 Subject Withdrawal Criteria

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason and is under no obligation to disclose the reason. If a subject withdraws, the Investigator is to be informed immediately.

The Investigator has the right to terminate participation of a subject at any time for any of the following:

- Intake or use of non-permitted concomitant medication
- Lack of subject compliance
- Protocol violation - Contact PellePharm or designee before making decision.
- Disease progression – The Investigator and/or PSCP believe that delaying the treatment of the treatment targeted tumor until the end of the trial would cause harm to the subject.
- Worsening of any condition - Subject requires alternate treatment before the end of the study and the Investigator determines it is not due to lack of efficacy.
- A perceived safety risk
- Adverse Event – Complete AE form
- Lost to Follow-Up – Document with at least 2 phone calls and a certified letter
- Subject Request – Consent withdrawal, subject moved, schedule conflicts
- Pregnancy – If subject or subject’s sexual partner become pregnant the subject will discontinue study drug immediately, but the pregnancy will be followed until delivery. Complete pregnancy form
- Lack of Efficacy – Subject requires alternate treatment after at least 2 weeks of study drug treatment and the Investigator determines that the risk of continuing the subject in the study outweighs the benefit. However, if a subject has two treatment-targeted BCCs and one of the BCCs requires treatment because of an increase in size, the tumor can be treated and the subject can remain in the trial.
- Other – Specify in comments section of electronic case report form (eCRF)

If a study subject experiences disease progression or begins another treatment for his/her disease, follow-up per protocol will no longer be required.

Subjects who terminate treatment early will be asked to complete all Week 12 assessments prior to commencement of any alternative therapy (if possible). Subjects who discontinue from the study during the treatment period will not be replaced.

All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management, and subjects, when appropriate, will be placed on other conventional therapy upon request or whenever clinically necessary as determined by their physician.

All premature discontinuations and their reasons must be carefully documented by the Investigator on the final eCRF, and, if need be, on the AE form.

If, for any reason, a subject is discontinued during the treatment period prior to Week 12, all end of treatment study (i.e., Week 12) evaluations should be performed at the time of early termination and the reason for termination will be recorded in the end of study source documentation. All data gathered on the subject prior to termination will be made available to PellePharm. Subjects who discontinue during the post-treatment follow-up period should have the assessments performed and reported on the eCRFs for that corresponding visit.

#### **6.4 Study Drug Discontinuation**

The Investigator may discontinue study drug administration for any subject at any time. The study drug administration must be discontinued for any of the following:

- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator.
- Occurrence of AEs, if discontinuation of study drug is desired or considered necessary by the Investigator or subject.
- Pregnancy
- Disease progression -The Investigator and/or PSCP believe that delaying the treatment of the treatment targeted tumor until the end of the trial would cause harm to the subject.

#### **6.5 Discontinuation of the Study**

Study discontinuation is at the discretion of PellePharm or the Investigator in any of, but not limited to, the following events:

- Occurrence of unusual AEs in terms of their nature, severity, duration, or unexpected incidence.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of the subjects.

## **6.6 Stopping Criteria**

Sponsor will monitor frequency of systemic signs and symptoms associated with this class of drug as well as any lab abnormalities. If clinically significant signs or symptoms of hedgehog inhibitors are detected, in particular hair loss, taste loss, muscle cramps, bowel changes, fatigue, as well as abnormal liver function tests, dosing will be stopped.

## **7. TREATMENT PLAN**

### **7.1 Methods of Assigning Subjects to Treatment Groups**

This is a double-blinded study, in which the identity of the study drug will be unknown to Investigator and subjects, as well as to all individuals closely associated with the study.

Subjects will be enrolled into 1 of the 4 sequential study drug groups of 9 subjects with 6 being randomized to active and 3 to vehicle within each group. The sequential groups will be patidegib or vehicle gel 2% applied once daily, patidegib or vehicle gel 4% applied once daily, patidegib or vehicle gel 2% applied twice daily, patidegib or vehicle gel 4% applied twice daily). Each screened subject will be assigned a unique 5-digit study subject number assigned by the investigational center, which will consist of the 2 digit investigational center number and the 3 digit chronological screening order number, starting with 001 (e.g., 01001, 01002). The study drug kit will be assigned to subjects based on a randomization code, and kits will be dispensed to the subjects at Baseline in the order that they are enrolled by taking the lowest numbered kit available in inventory at the investigational site. A study drug accountability log will document the inventory and dispensing of study drug at the investigational center.

### **7.2 Randomization and Blinding**

The study drugs will be packaged and labeled identically, and the study drug kits will be numbered sequentially and dispensed randomly to the subjects on the study. Study drug supplies will be distributed to the investigational center to maintain the randomization ratio.

As a double-blinded study, the Investigators, the site staff, PellePharm, and the Clinical Monitor(s) will not be aware of the treatment assigned to the individual study subjects. Delegated staff members at the investigational center will dispense the study drugs and will collect and weigh all used and unused study drug tubes as scheduled.

### **7.3 Unblinding**

The treatment assignments for all enrolled subjects will be unblinded on a cohort by cohort bases. The sponsor and CRO, but not site staff, will be unblinded in order to examine limited safety and efficacy results.

In the case of a medical emergency, the Investigator can break the blind for the subject involved only after making an effort to contact the Medical Monitor. After the code is broken the Investigator will contact the PellePharm representative for unblinding information. The Investigator will record the code break in the subject's source documents.

#### **7.4 Prior and Prohibited Concomitant Medication or Therapy**

Subjects must not have used topical products within 5 cm of a treatment targeted SEB or systemic therapies that could interfere with the evaluation of the study medication during the study. Specifically, these include use of the following:

- Topical glucocorticoids 30 days prior to Screening
- Retinoids (e.g., etretinate, isotretinoin, tazarotene, tretinoin, adapalene) systemically or topically, or > 5% of an Alphahydroxy acid (e.g., glycolic acid, lactic acid), photodynamic therapy (PDT), or 5-fluorouracil, or imiquimod (except as topical treatment to discrete BCCs) systemically or topically to the skin during the six months prior to entry.
- Treatment with systemic chemotherapy within one year prior to screening.
- Known inhibitors of the HH signaling pathway (e.g., vismodegib, patidegib, itraconazole, and sonidegib) topically or systemically within 6 months of entry into the study.
- Strong CYP3A4 inhibitors, including but not limited to: larithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir.

Subjects will not be allowed to use topical or systemic therapies that may affect treatment targeted BCCs. Tumors that the Investigator or PSCP determines require treatment during the trial can be removed by the modality selected by their PSCP.

During the study, subjects will be allowed to use moisturizers and emollients and will be encouraged to use sunscreen of SPF at least 15 at least once daily on all exposed skin sites.

Subjects using concomitant therapies during the course of the study that could interfere with the interpretation of the study results (including but not limited to those listed above) should not be withdrawn, but the use of the concomitant product should be discontinued. No other topical treatment (except as noted above) other than the study drug will be permitted.

Information on concomitant therapies will be recorded in the source document. Any therapy used by the subject will be considered concomitant therapy (e.g., aspirin,

paracetamol/acetaminophen, vitamins, moisturizers, sunscreens). Every attempt should be made to keep concomitant therapy dosing constant during the study. Any change to concomitant therapy should be noted on the source document and eCRF.

## **7.5 Treatment Compliance**

Each subject will be instructed on the importance of returning the study drug. Each tube will be weighed by the Investigator or designee prior to dispensation and after collection. The subject will be asked to keep a record of missed doses. A subject who deviates significantly from the prescribed application amount will be counseled. Any missed applications of study drug will be noted in the appropriate source document. Missed applications will be documented in the eCRF.

The Investigator will record the time and dose of all administrations in the eCRF. Any reasons for non-compliance will also be documented including:

- Missed visits
- Interruptions in the schedule of administration
- Non-permitted medications

## **7.6 Protocol Deviations and Violations**

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion with the Medical Monitor and the Investigator, with appropriate documentation of the Medical Monitor's approval prior to effecting the changes agreed upon.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by PellePharm and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and agreed to by the Investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve eligibility or primary endpoint criteria.

A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the subject, when the subject or Investigator has failed to adhere to significant protocol requirements (eligibility criteria) and the subject was enrolled without prior PellePharm approval, or when there is non-adherence to Food and Drug Administration (FDA) or local authority regulations and/or ICH GCP guideline.

The Investigator or designee must document and explain in the subjects' source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior

IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to PellePharm for agreement, and to the regulatory authorities, if required.



## 8. STUDY DRUG MATERIALS AND MANAGEMENT

Patidegib is generated from a plant source by the extraction of crude cyclopamine. Cyclopamine is carried through a series of synthetic steps to yield the well-characterized starting material for Good Manufacturing Practice (GMP) conversion to patidegib.

Patidegib HCl active ingredient is found as a white free-flowing crystalline solid. Patidegib topical gel is a smooth clear viscous hydro-alcoholic gel for topical administration. The gel is non-irritating and easy to spread on the lesions as directed.

The following excipients are used in the formulation of patidegib topical gel: All components of patidegib gel meet standard US or international compendial standards and are generally recognized as safe (GRAS).

**Table 2: Excipients of Patidegib Topical Gel**

Component	Monograph
Patidegib	N/A
Transcutol P	USP, NF, Ph. Eur.
Ethanol	USP, NF, JP, Ph. Eur.
Propylene Glycol	USP, NF, Ph. Eur.
Purified Water *	USP, Ph. Eur.
Boric Acid *	Ph. Eur.
Sodium Hydroxide *	NF, BP, JP, Ph. Eur.
Phenoxyethanol	Ph. Eur.
Hydroxypropylcellulose HF	Ph. Eur.

\*Components for pH 7.5 borate buffer

**Table 3: Specific Compositions of the Vehicle, 2% and 4% Patidegib Gels**

Component	4%*	2%*	Placebo
Patidegib	4.97	2.49	0.00
Transcutol P	18.80	18.80	18.80
Ethanol	23.50	23.50	23.50
Propylene Glycol	18.80	18.80	18.80
pH 7.5 Borate buffer	30.93	33.41	35.90
Phenoxyethanol	1.00	1.00	1.00
HPC-HF**	1.00	1.00	1.00
<b>TOTAL</b>	<b>100.00</b>	<b>100.00</b>	<b>100.00</b>

\*The label strength of patidegib topical gels is on a free base adjusted for HCl, trace solvents, moisture etc.; while compounding is on the as-is bases corrected by the potency of the particular API lot.

\*\*Hydroxypropylcellulose –HF

### **8.1 Identity of the Study Drug**

The study drug is identified as patidegib with appropriate labeling, marked “New Drug – Limited by Federal (or United States) law to investigational use only”.

### **8.2 Packaging and Dispensation of Study Drug**

The study drug will be dispensed by a trained qualified member of the study staff assigned by the Investigator to this task. The study drug will be packaged in 15 gm tubes and provided in kits. Subjects will be dispensed the study medication at Baseline and resupplied as needed, through Week 12. The tubes will be weighed prior to dispensing. The subject will return the tube(s) to the study center, where they will be collected and weighed; partially used tubes can be re-dispensed along with new tubes. If the subject loses a tube (lost or damaged tube), another tube will be dispensed. The goal is to ensure that the subject has an adequate supply of gel to able to administer all scheduled treatments.

Refer to the Pharmacy Manual for additional details about administration requirements, study drug supply and accountability procedures.

### **8.3 Storage, Handling, and Disposal of Study Drug**

The tubes should be stored under controlled room temperature at 20° – 25° C (68° – 77° F). Normal variations in temperatures are expected and acceptable around these target temperatures for subject’s storage of dispensed tubes.

### **8.4 Application**

The Investigator or their designee will instruct the subject to apply the study drug to the affected treatment areas identified at the Baseline visit by the Investigator. The Investigator or their designee will instruct the subject on the proper use of laminated dosing cards during the Baseline visit. In addition to the verbal instructions given during the visit, the subjects will be provided with written instructions.

Subjects will be instructed to apply a thin layer of study drug to each treatment-targeted BCC as indicated on the body diagram once or twice daily up to the Week 12 visit. Subjects will be advised to avoid or minimize exposure to direct sunlight while in the study and to wash their hands before and after application of the study drug.

Subjects will be instructed to store their test article in a secure location away from children. Women of childbearing potential should not come in contact with the gel.

The amount of study drug used by the subjects will be monitored by weighing each newly dispensed study drug tube and re-weighing each returned study drug tube at all applicable study visits.

## **8.5 Study Drug Accountability**

Upon receipt of the study drug, the Investigator is responsible for ensuring that the designated study drug staff conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. The Investigators must agree to keep all study materials in a secure location with restricted access. The Investigator will keep a record of the inventory and dispensing of all study drugs. This record will be made available to the Clinical Monitor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigators will be accounted for and, in no case, used in any unauthorized situation. Each tube will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate eCRF. All supplies will be returned to the sponsor for destruction at the conclusion of the study.

## **9. STUDY PROCEDURES AND EVALUATIONS**

The study will be conducted as outlined in the Schedule of Assessments ([Table 1](#)). The Screening, Week 6, Week 12 and Week 14 study visits will take place in person. The Weeks 2, 8, and 10 visits may take place using telemedicine and/or an in-person visit. Telemedicine will be conducted using a 21 CFR Part 11 and HITRUST/HIPAA compliant platform on a mobile device. Telemedicine video and phone conferences are not recorded.

All subject information and data obtained during the study visits will be recorded in the electronic source documents, applicable study logs, and eCRFs.

Investigators must have appropriate, documented experience and training, or obtain approval from PellePharm based on experience (or through additional training organized by PellePharm).

At each study visit, every attempt should be made to ensure that the same Investigator assesses the same subject. The sponsor realizes that the conduct of a clinical trial involves a team of study staff who perform a variety of functions under the supervision of the Principal Investigator. Tasks and responsibilities are delegated by the Principal Investigator as dictated by local laws and institutional regulations. There are specific tasks that PellePharm requires be done by a licensed healthcare professional with appropriate experience. As outlined below and in the Schedule of Assessments ([Table 1](#)), these tasks include biopsy for biomarkers, measuring and mapping of treatment-targeted tumor(s), determination of clinical tumor type, recording application site reactions, and the determination of the ISGTA.

PellePharm also realizes that scheduling visits can be challenging and has allowed for study windows. It should be noted that the indicated visit day is in reference to the Baseline visit. For example the Week 6 (Day 43) visit is intended to be Day 43 after the Baseline visit.

### **9.1 Schedule of Evaluations and Procedures**

#### **9.1.1 Screening Visit (Day -42 to Day 0)**

Following virtual electronic informed consent from each subject, the Investigator will determine whether subjects are eligible to participate in the study by performing screening tests and evaluations.

At the Screening visit, continuous monitoring of current and concomitant medications and therapies (including prophylactic treatments and medical interventions) and AEs throughout the study period will begin.

Screen failure information will be maintained at the site to document specified information, including but not limited to, reason for failure.

The following procedures will be conducted at this visit:

1. Obtain informed consent from the subject prior to performing any study related procedures. The subject will receive a copy of their signed consent form.
2. Review and explain the nature of the study and what will be expected at each visit to ensure subject can meet the requirements and has adequate transportation.
3. Assign the subject a 5-digit subject number, which will consist of the 2-digit site number and the 3-digit chronological screening order number, starting with 001 (e.g., 01 001, 01 002).
4. Record the subject's demographic information.
5. Record the subject's medical history.
6. Record all medications for BCC used during the prior year in the eCRF. Include all medications used in the past 30 days and any therapy that requires a washout prior to Baseline.
7. Record any prescription or over-the-counter therapies that are being used concomitantly in the eCRF.
8. The Investigator will identify 1 or 2 previously untreated non central facial BCCs
9. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 6.1 and 6.2.
10. Discuss the use of moisturizers and emollients with the subject.
11. Obtain a biopsy from the baseline treatment targeted BCC(s).
12. Collect blood samples for routine laboratory analysis [complete blood count/differential (CBC/Diff), urinalysis, serum chemistry and serum pregnancy test for females].
13. Record any AEs related to screening procedures on the AE eCRF.
14. Schedule subject's Baseline/Day 1 visit. If the subject requires a washout, schedule the Baseline/Day 1 visit to occur after the washout is complete.

### **9.1.2 Baseline Visit (Day 1)**

The following procedures will be conducted at this visit:

1. Record any changes in medical history since Screening.
2. Record changes in any previous BCC medications since the previous visit in eCRF. Check for prohibited concomitant therapies and confirm any therapy that requires a washout prior to Baseline as per Section 7.4.
3. Record changes in any concomitant medications since the previous visit in eCRF. Check for prior and concomitant therapies as per Section 7.4.

4. Verify that the subject continues to meet the applicable study eligibility criteria as outlined in Sections 6.1 and 6.2.
5. An abbreviated physical examination including measurements of weight.
6. The Investigator will perform the clinical evaluation to identify the treatment-targeted tumors which will be clinically classified as superficial, nodular, infiltrative, morpheeic, pigmented or micronodular/morpheaform to be circled in ink, photographed, measured, and recorded on a body diagram.
7. The Investigator or designee will assess the areas to be treated by observations and questioning the subjects as necessary for the signs and symptoms of irritation including pain/burning, pruritus, erythema, edema, and scabbing/crusting.
8. The Investigator will query the subject about the symptoms of any abnormalities in taste, frequency and severity of muscle cramps, recent changes in quality or quantity of hair in treated and untreated areas and any change in frequency of shaving of treated or untreated areas, any change in frequency of obtaining haircuts.
9. Randomize the subject to a treatment group and record the assigned kit number in the source document and in the eCRF.
10. The designated study drug staff will weigh each tube within the assigned kit and dispense them to the subject.
11. The Study Coordinator or designee will instruct the subject on the proper application procedure for the study drug. For the first application, the subject will apply the study drug at the investigational center under the direction of the Study Coordinator or designee. The study drug should be applied **after** all clinical assessments. The subjects will be asked to avoid exposure to direct sunlight on the initial application day and thereafter. The Study Coordinator or designee will instruct the subjects to apply the study drug once or twice daily at home and review patient instruction sheets and dosing card.
12. Record any AEs reported spontaneously by the subject.
13. If the subject is a woman of childbearing potential, the Study Coordinator or designee will provide the subject with three home pregnancy urine tests.
14. Schedule the next study visit at Week 2 (Day 15 ± 2 days).

### 9.1.3 Weeks 2, 6, 8, and 10

The following procedures will be conducted at this visit:

1. Record changes in any concomitant medications since the previous visit in the eCRF. Check for prior and concomitant therapies as per Section 7.4.
2. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
3. The treatment-targeted BCCs identified by the Investigator at the Baseline visit will be photographed and measured using the provided hand held device. *For the Week 6 visit*

*only*, the treatment-targeted tumors will be, circled in ink, photographed, measured, and recorded on a body diagram.

4. The Investigator or designee will assess the treated areas by observations and questioning the subjects as necessary for the signs and symptoms of irritation including pain/burning, pruritus, erythema, edema, and scabbing/crusting.
5. The Investigator will question the subject about any concurrent illness or systemic sign or symptom including but not limited to fatigue, loss or change in taste, nausea, vomiting, diarrhea, muscle spasms or cramps, changes in quality or quantity of hair in treated areas and any change in frequency of shaving or haircuts.
6. Collect blood samples for routine laboratory analysis (CBC/Diff and serum chemistry) (*Weeks 6 only*).
7. If the subject is a woman of childbearing potential, they will take a home pregnancy urine test and disclose the results to the Investigator or designee (*Weeks 2, 8, and 10 only*).
8. The Study Coordinator or designee will weigh the previously dispensed study drug tube. The study coordinator or designee will weigh and dispense a new study drug tube from the subject assigned kit if necessary. (*Baseline and Week 6 only*)
9. Any missed doses or deviations should be reported.
10. The Study Coordinator or designee will remind the subject of the proper technique for application of the study drug. If needed, the subject can apply the study drug at the investigational center during the day under the direction of the Study Coordinator or designee to confirm proper technique.
11. Schedule the next study visit.

#### **9.1.4 Week 12 (Day 85 ± 3 Days) / Early Termination**

The following procedures will be conducted at this visit:

1. Record changes in any concomitant medications since the previous visit in the eCRF. Check for prior and concomitant therapies as per [Section 7.4](#).
2. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs. Record subject weight.
3. Perform a brief physical exam including vital signs and weight.
4. Collect blood samples for routine laboratory analysis (CBC/Diff and serum chemistry).
5. The Investigator or designee will assess the treated areas by observations and questioning the subjects as necessary for the signs and symptoms of irritation including pain/burning, pruritus, erythema, edema, and scabbing/crusting.
6. The treatment site(s) will be excised.
7. The Investigator will question the subject about any concurrent illness or systemic sign or symptom including but not limited to fatigue, loss or change in taste, nausea,

vomiting, diarrhea, muscle spasms or cramps, changes in quality or quantity of hair in treated areas and any change in frequency of shaving.

8. The Study Coordinator or designee will collect and weigh the previously dispensed study drug tube.
9. Any missed doses or deviations should be reported.
10. Exit the subject from the study and complete the end of study eCRFs.

### **9.1.5 Week 14 (Day 99 ± 7 Days) / Post Operation Follow-up**

The following procedures will be conducted at this visit:

1. The Principal Investigator will do a clinical evaluation of the surgical site(s) to confirm adequate healing.

## **9.2 Evaluation of Efficacy**

### Clinical Descriptions of Basal Cell Carcinoma

#### *Nodular basal cell carcinoma*

A pearly, waxy, semi-translucent nodule sometimes forming a central depression that may or not be ulcerated or crusted. There can be overlying telangiectasias and characteristically there is a “rolled border”.

#### *Superficial basal cell carcinoma*

An erythematous scaly thin plaque or patch often with areas of hypopigmentation and superficial scarring, occasionally with a thin crust. Careful examination will often show a subtle raised border.

#### *Infiltrative basal cell carcinoma*

An erythematous, frequently ulcerated or crusted ill-defined plaque. Occasionally it can be quite indurated or elevated.

#### *Morpheic or sclerosing basal cell carcinoma*

An ill-defined hypopigmented sclerotic plaque, sometimes with subtle telangiectasias. Rarely ulcerated or crusted. They can present with an atrophic or depressed appearance centrally often mimicking an old scar.

#### *Micronodular basal cell carcinoma*

A dome-shaped sclerotic hypopigmented or flesh colored nodule or plaque with undermining borders where a mass-like effect is palpable below normal appearing skin.

#### *Pigmented basal cell carcinoma*



Each of the classic variants described above may be pigmented, particularly in Types III-V skin. These will have blue, black, brown pigmentation usually involving part or most of the tumor with more classic or characteristic features often noted elsewhere.

### 9.2.1 Assessment of BCCs

One or two treatment-targeted BCCs on each subject will be identified by the Investigator at the following visits: Screening, Baseline, Weeks 2, 6, 8, 10, and 12. The BCCs being followed will be circled in ink, photographed, measured the greatest diameter, and recorded on a body diagram. Circling with ink will only be performed at Baseline, Week 6 and Week 12.

### 9.2.2 Messenger RNA (mRNA)

Biopsies of treatment targeted tumors done at Baseline as well as excisional samples from the end of study excisions will be evaluated for GLI1 mRNA levels.

### 9.2.3 Investigator Static Global Tumor Assessment

The Investigator will assess and record the Investigator Static Global Tumor Assessment (ISGTA) of baseline treatment targeted BCC(s) at Baseline, Weeks 2, 6, 8, 10 and Week 12.

**Table 4: Investigator Static Global Tumor Assessment**

0	Clear - no evidence of residual tumor is seen or palpated, faint ill-defined macular erythema may be present; normal skin markings are seen
1	Almost clear - residual macular erythema is clearly seen but there is no palpable* obvious tumor, scale, erosions, or ulcerations; normal skin markings are seen
2	Minimal residual tumor - macular erythema is clearly seen and visible slight palpable tumor with or without scale, erosions, ulcerations may be present; normal skin markings are not clearly visible
3	Clearly visible tumor - is seen and felt on palpation with or without rolled borders erosion, ulceration, or scale; normal skin markings not seen

\*Only evaluated at visits conducted at the study center.

## 9.3 Evaluation of Safety

### 9.3.1 Dermal Safety and Tolerability

Safety and tolerability will be evaluated through assessments of selected local signs and symptoms (pain / burning, pruritus, erythema, edema, and scabbing / crusting). Each of the

identified BCCs will be evaluated separately for these signs and symptoms of application site reactions. Any local skin reaction that requires use of a concomitant therapy or is a cause for study drug interruption or discontinuation should be reported as an AE. The scales to be used for assessing local skin reactions follow:

**Table 5: Dermal Safety and Tolerability Scales**

Score	Grade	Description
<i>Pain/Burning: as reported by the subject as being the greatest intensity they have experienced at the application site within the last 24 hours at Baseline or since the last visit at subsequent visits.</i>		
0	None	No pain/burning
1	Mild	Slight burning/stinging sensation; not really bothersome
2	Moderate	Definite warm, burning/stinging that is somewhat bothersome
3	Severe	Hot burning/stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep
<i>Pruritus: as reported by the subject as being the greatest intensity they have experienced at the application site within the last 24 hours at Baseline or since the last visit at subsequent visits.</i>		
0	None	No pruritus
1	Mild	Slight pruritus, not really bothersome
2	Moderate	Definite pruritus that is somewhat bothersome
3	Severe	Intense pruritus that may interrupt daily activities and/or sleep
<i>Erythema: as assessed by the Investigator at each site</i>		
0	None	No erythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color
<i>Edema: as assessed by the Investigator at each site</i>		
0	None	No edema
1	Mild	Slight, but definite edema
2	Moderate	Definite edema
3	Severe	Marked edema
<i>Scabbing/Crusting: as assessed by the Investigator at each site</i>		

0	None	No scabbing/crusting
1	Mild	Slight, but definite scabbing/crusting
2	Moderate	Definite scabbing/crusting
3	Severe	Marked scabbing/crusting

### **9.3.2 Medical History and Abbreviated Physical Examination**

A medical history will be taken at Screening, and confirmed and revised if needed, at Baseline. Medical conditions that resolved 2 or more years before baseline need not be collected unless considered relevant by the Investigator.

An abbreviated physical examination including measurements of height, weight and vital signs (blood pressure, heart rate, respiration rate, and oral temperature) will be performed at Baseline and Week 12. Height will be collected at Baseline only.

### **9.3.3 Safety Laboratory Tests**

Routine safety laboratory tests as per Appendix 16.4 will be performed at Screening, Week 6, and Week 12. Any out-of-range laboratory result that is considered clinically significant by the Investigator will be recorded as an AE and should be accessed for reproducibility by repeat testing at the discretion of the Investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the Baseline state) or until clinically stable as determined by the Investigator.

### **9.3.4 Pregnancy Tests**

All female subjects will have a serum pregnancy test at Screening. Females of childbearing potential will take a home pregnancy urine test at Weeks 2, 8, and 10 and will have a serum pregnancy test at Weeks 6 and 12.

### **9.3.5 Adverse Events**

#### **9.3.5.1 Definition of Adverse Event**

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. AEs include any unfavorable and unintended illness, sign (e.g., including an abnormal laboratory finding), symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or

worsened during the course of the clinical trial, regardless of causal relationship to the study drug(s) under study.

### **9.3.5.2 Documenting Adverse Events**

It is the responsibility of the Investigator to document all AEs that occur during the course of the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit.

All AEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Dermal safety and tolerability that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate CRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug
- Corrective treatment, if given
- Outcome

In addition, the Investigator's assessment of causality will be recorded.

Vital sign abnormalities are to be recorded as AEs only if they are clinically significant (for example: are symptomatic, requiring corrective treatment, leading to discontinuation or fulfilling a seriousness criterion).

Subjects will be questioned about any concurrent illness or systemic sign or symptom including but not limited to fatigue, loss or change in taste, nausea, vomiting, alopecia, diarrhea, and muscle spasms. Any incidence of these systemic signs or symptoms will be reported on the AE eCRF.

### **9.3.5.3 Serious Adverse Events**

All AEs will be assessed as either serious or non-serious.

An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in subject hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE)
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent any of the above listed outcomes

Note: A spontaneous abortion will be considered an SAE, and must be reported per Reporting of SAEs under [Section 9.3.5.6](#).

### **9.3.5.4 Assessment of Severity**

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening

### 9.3.5.5 Assessment of Causality

The Investigator should assess the relationship of the AE, if any, to the study drug. The following should be taken into account when assessing SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re-introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or a lack of efficacy.

The following classifications should be used when evaluating the relationship of AEs and SAEs to the investigational drug.

1. **None:** No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
2. **Unlikely:** The current state of knowledge indicates that a relationship is unlikely.
3. **Possibly:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
4. **Probably:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
5. **Definitely:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug and can be confirmed with a positive re-challenge test or supporting laboratory data

### 9.3.5.6 Reporting of Serious Adverse Events

When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the subject was hospitalized, a copy of the discharge summary must be included as part of the subject's medical file. In all instances, the Investigator should follow up with subjects until the outcome of the SAE is known.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the AE eCRF. Any clinically relevant change in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE eCRF. All AEs are to be followed until the event resolves or the clinical course is stabilized.

For SAEs, a SAE form must be completed with as much information as possible and submitted in the time frame described below.

PellePharm must be notified of all SAEs (regardless of casual relationship to study drug) within 24 hours of first knowledge of the event by the Investigator or other study personnel by faxing a completed SAE form to the contact information below.

<b>Safety Reporting Contact</b>	
<b>Name:</b>	PPD [REDACTED]
<b>Telephone:</b>	PPD [REDACTED] PPD [REDACTED]
<b>Mobile:</b>	PPD [REDACTED]
<b>Facsimile:</b>	PPD [REDACTED]
<b>Email:</b>	PPD [REDACTED]

If there are serious, unexpected AEs associated with the use of the study drug, PellePharm will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. It is the responsibility of the Investigator to promptly notify the IRB/IEC of all unexpected SAEs involving risk to human subjects.

The Investigator should take all appropriate measures to ensure the safety of the subjects, notably and should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by PellePharm.

### **9.3.5.7 Emergency Contact**

In the event of a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), investigational site personnel must immediately contact the Medical Monitor.

<b>Medical Monitor Contact</b>	
<b>Name:</b>	PPD [REDACTED]
<b>Telephone:</b>	PPD [REDACTED]
<b>Email:</b>	PPD [REDACTED]

### **9.3.5.8 Expedited Serious Adverse Event Reports**

An AE, whether serious or non-serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure or if the event is of greater frequency, specificity or severity.

Expedited SAE reports are those that document AEs that are both unexpected based on the reference document (Investigator Brochure) and are related (i.e., the relationship cannot be ruled out) to the study drug. These expedited reports are subject to reporting timelines of 7 (SAEs) and/or 15 (non SAE) calendar days to the regulatory reporting agency(ies). PellePharm will notify regulatory authorities of these AEs and all participating investigational centers in writing for submission by the Investigator to the IRB/IEC. This notification will be in the form of a Safety Update to the Investigator Brochure (i.e., “15-day letter”).

Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the responsible IRB/IEC according to local regulations. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

### **9.3.5.9 Other Required Safety Assessments**

A clinically significant worsening from Baseline of any abnormal study assessment, such as laboratory test, physical examination, or vital signs, should be considered an AE and recorded accordingly. If possible, a diagnosis for the clinically significant study assessment should be provided by the Investigator (e.g., urinary tract infection or anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has one or more of the following related to the abnormal study assessment:

1. Concomitant clinical signs or symptoms
2. Further diagnostic testing or medical/surgical intervention
3. A change in the dose of study drug or is discontinued from the study



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Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria.

## **10. STATISTICS**

All statistical processing will be performed using SAS<sup>®</sup> unless otherwise stated. If determined appropriate by the Sponsor, limited safety and efficacy interim analysis on tumor shrinkage and biomarkers may be performed.

No inferential testing will be performed. Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, and standard deviation, median, minimum, and maximum.

No imputation will be made for the primary endpoint. For the secondary endpoint, the last observation carried forward method (LOCF) will be used to impute missing efficacy data (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). No imputations will be made for missing safety data.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

### **10.1 Analysis Populations**

Per protocol analysis will be performed –samples with insufficient BCC, subjects with poor treatment compliance, or tumors where the diameter was incorrectly measured based on review of photographs will be excluded. BCC size change based on photographs will also be analyzed. Safety analyses will be performed using the safety population. All subjects who are randomized, receive at least 1 confirmed dose of study drug and have at least one post-baseline safety assessment will be included in the safety analysis set.

### **10.2 Subject Disposition**

A tabulation of subject disposition will be provided. The tabulation will include the numbers of subjects who enter the study, complete the study, and discontinue the study. The reasons for discontinuation will be included.

### **10.3 Demographics and Baseline Characteristics**

Subject demographic data and baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT and Safety populations.

## **10.4 Protocol Deviations**

All protocol deviations will be reported to the PellePharm and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

## **10.5 Compliance**

No formal evaluations of compliance are planned.

## **10.6 Interim Analyses**

If determined appropriate by the Sponsor, limited safety and efficacy interim analysis on tumor shrinkage and biomarkers may be performed.

## **10.7 Assessment of Efficacy**

### **10.7.1 Efficacy Summaries**

The efficacy endpoints are intended to compare once and twice daily application of 2% patidegib gel, 4% patidegib gel, and vehicle gel. Efficacy assessments will be summarized descriptively by treatment group and visit.

#### **10.7.1.1 Primary Efficacy Endpoint:**

Change in GLI1 mRNA levels in drug-treated versus vehicle-treated tumors after 12 weeks of treatment.

#### **10.7.1.2 Secondary Efficacy Endpoints:**

The secondary efficacy endpoint is the decrease in tumor size defined as percent decrease in the greatest diameter of baseline treatment targeted BCCs at the Week 12.

#### **10.7.1.3 Exploratory Efficacy Endpoints:**

To evaluate the utility of an investigator static global tumor assessment (ISGTA) in assessing the proportion of baseline treatment-targeted BCCs that are evaluated as being clear or almost clear.

To evaluate if the proportion of baseline treated tumors are smaller based on photographic review

### **10.7.2 Efficacy Analyses.**

The primary endpoint and the secondary endpoints of change in tumor size, and reduction in the HH signaling pathway will be evaluated with an analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate. Pairwise comparisons will be performed using contrasts within the ANCOVA. Additionally, t-tests for pairwise comparisons of the primary endpoint will be done, or alternatively a non-parametric approach may be used.

The exploratory analysis of ISGTA will be analyzed with a Cochran-Mantel-Haenszel test

## **10.8 Assessment of Safety**

### **10.8.1 Dermal Safety and Tolerability**

The frequency of dermal safety and tolerability assessments including pain/burning, pruritus, erythema, edema, and scabbing/crusting will be summarized descriptively by treatment group and visit.

### **10.8.2 Adverse Events**

Subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, action taken regarding the study drug, corrective treatment, outcome, and Investigator's assessment of causality. All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported SAEs will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the Investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

### **10.8.3 Safety Laboratory Values and Vital Sign Measurements**

Changes from Baseline in safety laboratory values and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Screening and Weeks 6, and 12. Normal ranges established by the local laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each Investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

### **10.8.4 Pregnancy Tests**

Pregnancy test results will be presented in a data listing.

### **10.8.5 Handling of Missing Data**

The last observation carried forward (LOCF) method will be used to impute missing efficacy data (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). No imputations will be made for missing safety data.

### **10.8.6 Multicenter Issues**

The study will be conducted at one metasite in the United States with the intention of pooling the results for analysis.

### **10.8.7 Multiplicity Issues**

Not applicable. Inferential tests will not be performed.

## **10.9 Sample Size Determination**

This is a dose ranging study.

## **11. QUALITY CONTROL AND QUALITY ASSURANCE**

### **11.1 Study Monitoring**

An Investigator Meeting and/or an initiation visit will be conducted with the Principal Investigator, Sub-Investigator, and Study Coordinator by PellePharm and/or its designee. During this meeting, an extensive review and discussion of the protocol, the role of the study technician, all study procedures, source documents, and eCRFs will be conducted. Evaluation procedures will be reviewed extensively and documentation of training will be recorded for training of sponsor-approved evaluators.

The clinical monitors will be trained prior to study initiation. Following this training, an overview of the study disease and study material background will be understood. Specific monitoring guidelines and procedures to be followed during monitoring visits will also be utilized. During the course of the study, all data will be 100% source document verified by the monitors. All subject source records must be made available to the monitors.

The conduct of the study will be closely monitored by the sponsor following GCP guidelines. The reports of these verifications will also be archived with the study report. In addition, inspections or on site audits may be carried out by local authorities or by the sponsor's Quality Assurance Department. The Investigators will allow the sponsor's representatives and any regulatory agency to examine all study records, corresponding subject medical records, clinical dispensing records and storage area, and any other documents considered source documentation. The Investigators agree to assist the representative, if required.

### **11.2 Audits and Inspections**

The study will be conducted under the sponsorship of PellePharm in conformation with all appropriate legal regulations, as well as ICH guidelines. Interim and end of study audits of raw data, study files, and final report may be conducted by PellePharm's Quality Assurance Department or designee.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study related investigational centers, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

### **11.3 Data Quality Assurance**

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The Investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the Investigator, with appropriate written protocol amendments made prior to implementing the agreed changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

## **12. ETHICS AND ADMINISTRATIVE ISSUES**

### **12.1 Ethical Conduct of the Study**

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements. The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

### **12.2 Independent Review Board Review**

This protocol, proposed informed consent form and other information to subjects, and all appropriate amendments will be properly reviewed and approved by the IRB/IEC. A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and Investigator prior to study initiation. The name and occupation of the chairman and members of the IRB/IEC will be supplied to the sponsor. The Investigator will provide required progress reports and report all SAEs to the IRB/IEC as required by the IRB/IEC.

### **12.3 Informed Consent**

Electronic informed consent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The informed consent form (ICF), as specified by the investigational site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 CFR Part 50.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the subjects. It is the responsibility of the Investigator to obtain consent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the source documentation prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by PellePharm or designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and PellePharm.

### **12.4 Subject Data Protection**

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdate), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be



presented in tabulated (i.e., aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

### **12.5 Financial Disclosure**

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

### **12.6 Investigator Obligations**

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice (GCP).

### **12.7 Changes to the Protocol**

The Investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the Investigator, with appropriate documentation of sponsor approval prior to effecting the changes agreed upon. Any amendment to the protocol containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

### **12.8 Confidentiality/Publication of the Study**

All the data furnished to the Investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the FDA or other regulatory body, without written consent from the sponsor.

### **13. DATA HANDLING AND RECORD KEEPING**

#### **13.1 Inspection of Records**

Investigators must maintain detailed records on all study subjects who are enrolled in the study or undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

The Investigator must keep accurate separate records (source documentation) of all subject visits, being sure to include all pertinent study related information. At a minimum, this includes the following information:

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that virtual electronic informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, screening evaluations)
- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

Notes describing telephone conversations and all electronic mail with the subject or the sponsor (sponsor's designee) concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

### **13.2 Retention of Records**

The Investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the Investigator until notified by the sponsor in writing that the records may be destroyed.

The Investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA or other applicable local authorities to inspect all study records, CRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and accuracy of the data being entered onto the CRF, and compliance with FDA or other local authority regulations.

### **13.3 Electronic Case Report Form Completion**

eCRFs will be completed for each enrolled subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

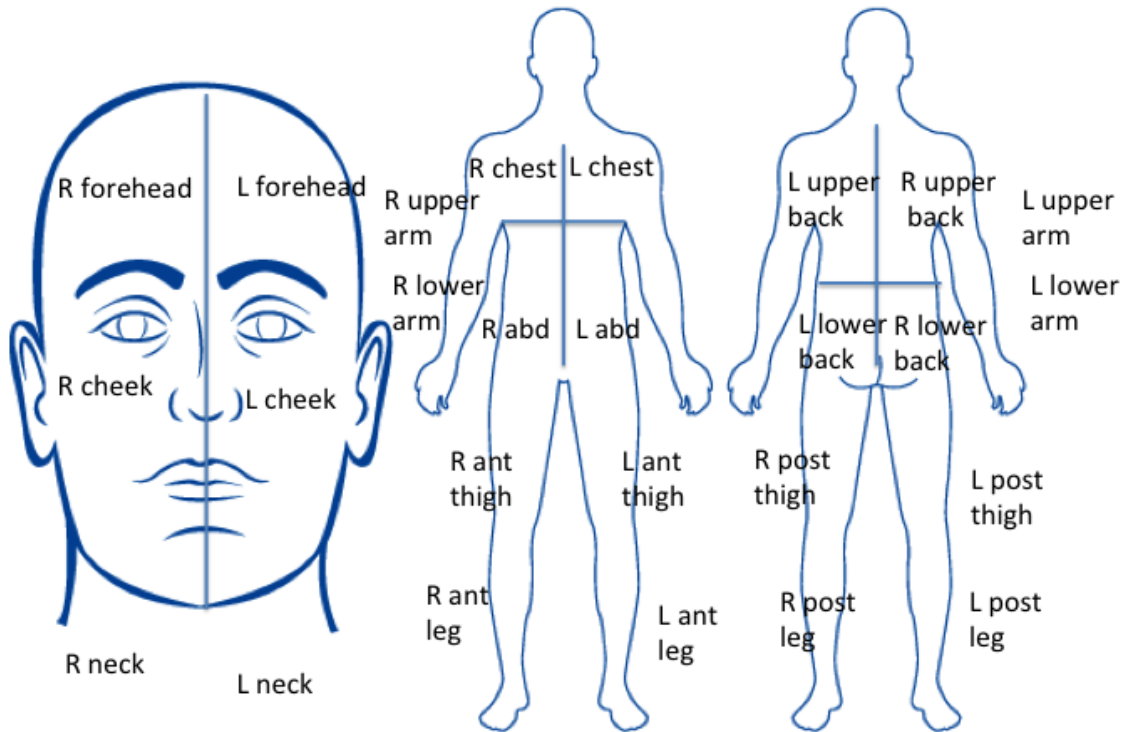
Investigators will maintain copies of the eCRFs at the investigational site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate eCRF.

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## 15. APPENDICES

### 15.1 Body Diagram



#### Appendix: Photographs of tumors and sequence of regional photos

1. At Baseline: Identify the 2 treatment targeted BCCs with labels
2. Measure greatest diameter of each tumor, perform ISGTA and determine clinical type.
3. Identify all other tumors measure and record their greatest diameter and the clinical type of each tumor.
4. Circle all tumors both treatment targeted tumors and other tumors:

#### 6 quadrants on face/neck:

- |               |               |
|---------------|---------------|
| 1. R forehead | 4. L forehead |
| 2. R cheek    | 5. L cheek    |
| 3. R neck     | 6. L neck     |

**20 quadrants on body:**

1. R chest
2. L chest
3. R abdomen
4. L abdomen
5. R upper arm
6. R lower arm
7. L upper arm
8. L lower arm
9. R anterior thigh
10. L anterior thigh
11. R anterior leg
12. L anterior leg
13. R upper back
14. L upper back
15. R lower back
16. L lower back
17. R posterior thigh
18. L posterior thigh
19. R posterior leg
20. L posterior leg

## 15.2 Safety Laboratory Tests

The following blood samples for laboratory tests will be collected:

- Alanine aminotransferase (ALT)
- Albumin, alkaline phosphatase
- Aspartate aminotransferase (AST)
- Total bilirubin
- Blood urea nitrogen (BUN)
- Calcium, carbon dioxide, chloride
- Creatinine
- Glucose
- Potassium
- Protein
- Sodium
- White blood cell (WBC)
- Red blood cell (RBC)
- Hemoglobin
- Hematocrit
- Mean Corpuscular Volume (MCV)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Red Cell Distribution Width
- Platelets, Mean Platelet Volumes
- Absolute/Percent Neutrophil Count
- Absolute/Percent Lymphocyte count
- Absolute/Percent Monocyte count
- Absolute/Percent Eosinophil Count
- Absolute/Percent Basophil Count

Urinalysis with reflex microscopic examination.