Clinical Study Protocol

Protocol Pelle-926-201

Double-Blind, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients

Development Phase of Study:	2A
Study design:	Multicenter, Double-Blind, Randomized, Parallel-Group, Controlled Clinical Study
EUDRACT #:	2015-004274-15
Date of Original Protocol:	14 December 2015
Amendment 1 – Protocol Version 2.0:	27 January 2016
Amendment 2 – Protocol Version 3.0	02 March 2016
Amendment 3 – Protocol Version 4.0 (not approved and not implemented)	24 May 2016
Amendment 4-Protocol Version 5.0	18 August 2016
Sponsor Representative:	PPD PPD 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 study will be performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This protocol follows guidelines outlined by the International Conference on Harmonization (ICH). All data furnished to the Investigator and his/her staff, and all data obtained through this study, will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the Medicines and Healthcare Products Regulatory Agency (MHRA) or other local authority, without written consent from the sponsor.

Protocol Review and Approvals

Double-Blind, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients

Reviewed and approved:

PPD

PellePharm, Inc.

PPD

30 August 2016
Date

PPD

CMS International, Inc.

PPD

1gnature

30 August 2016
Date

PPD

PellePharm, Inc.

PPD

:signature

Date

Personnel Responsible for Conducting the Study

Double-Blind, Randomized, Vehicle-ControlledProof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients

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Principal Investigator Protocol Agreement Page

I have carefully read the protocol entitled: *"Double-Blind, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients"* and,

I declare that this 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 patient. 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 patients.

_____
Investigator Signature

_____ _____
Printed Name Date

_____
Institution Name

_____
Address

_____ _____
City, State Zip Code Phone Number

1. SYNOPSIS

Name of Sponsor: PellePharm, Inc.

Name of Investigational Product: patidegib gel

Name of Active Ingredients: patidegib HCl

Title of Study: Double-Blind, Randomized, Vehicle-Controlled Proof of Concept Clinical Trial of Patidegib Gel 2%, 4%, and Vehicle to Decrease the Number of Surgically Eligible Basal Cell Carcinomas in Gorlin Syndrome Patients

Number of Clinical Centers: Approximately 3 investigational centers in Europe will participate in this study.

Objective:

The primary 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 Surgically Eligible basal cell carcinomas (SEBs) after 26 weeks of treatment (SEBs are defined as clinically diagnosed basal cell carcinoma (BCC) 5 mm or greater in diameter on the face excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face).
2. The molecular efficacy of treatment as defined by reduction in the hedgehog (HH) signaling pathway target gene GLI1 after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 6 weeks to treatment-targeted SEBs.
3. The safety and tolerability of treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 26 weeks.

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

1. The clinical efficacy of treatment as defined by percent decrease in greatest diameter of baseline central facial SEBs (BCCs 3 mm or greater in diameter at Baseline located on the nose or periorbital area).
2. The frequency of new SEBs on the face. (A new SEB is defined as a SEB first noted at a visit after Week 2 and that developed at a site where there was no visible BCC of any size at the Baseline or the Week 2 visit.)
3. The proportion of non-central facial BCCs that at Baseline and/or Week 2 visit were less than 5 mm in greatest diameter but by the Week 6, 10, 14, 18, 22, or 26 visit have become greater than 5 mm in greatest diameter.
4. The proportion of baseline treatment targeted SEBs that at the end of 26 weeks of treatment are no longer large enough to be classified as SEBs (i.e., that is the proportion of baseline treatment targeted SEBs on the face that become less than 5 mm in greatest diameter and non-facial baseline treatment targeted SEBs that become less than 9 mm in greatest diameter).

Exploratory objective:

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

Methodology:

This is a multicenter, double-blind, randomized, vehicle-controlled study designed to compare the efficacy and safety of patidegib gel, 2% and 4% in comparison with that of vehicle. To be eligible for the study, subjects must be at least 18 years of age and must meet the diagnostic criteria for basal cell nevus syndrome (BCNS).

Approximately 18 subjects who meet the study entry criteria will be randomized in a 1:1:1 ratio to receive patidegib gel 2%, patidegib gel 4%, vehicle gel. One or two tubes of the assigned study drug will be dispensed to the subject at the Baseline visit. Additional tubes will be dispensed at subsequent visits through Week 22. The study drug will be applied topically to the entire face as well as to treatment-targeted SEBs at other anatomical sites twice daily for 26 weeks of treatment.

Information on reported and observed adverse events (AEs) will be obtained at each visit. An abbreviated physical examination (PE) will be performed at Baseline, Week 14, and Week 26.

At Baseline and Weeks 2, 6, 10, 14, 18, 22, and 26, all visible BCCs (excluding areas below the knees) will be identified by the Investigator, circled in ink, photographed, measured, and recorded on a body diagram. Treatment targeted SEBs are defined as the five SEBs on the face and/or other anatomical areas identified at Baseline as SEBs will be treated during the 26 week treatment phase. If a subject has 5 eligible previously untreated facial SEBs (excluding tumors on nose and eyelids) these tumors will be the subject's 5 baseline treatment targeted SEBs and non-facial baseline SEBs will not be treated with study medication.

Biomarkers: A single treatment targeted baseline SEB, preferably with the clinical features of a nodular BCC, will be biopsied with a 2 mm punch biopsy both at Baseline and at the Week 6 visit for determination of GLI1 mRNA levels. In addition, whenever possible, available non-treatment targeted tumors that are biopsied or any tumor treated by surgical removal during the trial will be evaluated for 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, Week 14, and Week 26. Additionally, blood samples will be collected at Screening and Weeks 6, 14, and 26 to determine plasma concentrations of patidegib.

Subjects who terminate study participation early will be asked to complete all Week 26 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 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 26 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 18 adult subjects (approximately 6 subjects per investigational center) will be enrolled and randomized in the study. With a 1:1:1 randomization ratio, it is anticipated that:

- 6 subjects will be randomized to receive patidegib gel 4%
- 6 subjects will be randomized to receive patidegib gel 2%
- 6 subjects will be randomized to receive vehicle gel

Inclusion Criteria:

1. The subject is from 18 to 85 years of age, inclusive.
2. The subject must provide written informed consent prior to any study procedures.
3. The subject must meet diagnostic criteria for basal cell nevus syndrome (BCNS) including major criterion #3a plus one additional major criterion or major criterion #3a plus two of the minor criteria outlined below:

   Major Criteria:

   a. More than 2 histologically confirmed BCCs or one under the age of 20 years
   b. Odontogenic keratocysts of the jaw proven by histology
   c. Three or more palmar and/or plantar pits
   d. Bilamellar calcification of the falx cerebri (if less than 20 years old)
   e. Fused, bifid, or markedly splayed ribs.
   f. First degree relative with basal cell nevus syndrome (BCNS)
   g. PTCH1 gene mutation in normal tissue

   Minor Criteria

   a. Macrocephaly
   b. Congenital malformations: cleft lip or palate, frontal bossing, "coarse face",

moderate or severe hypertelorism
   c. Skeletal abnormalities: sprengel deformity, marked pectus deformity, or marked syndactyly of the digits
   d. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame shaped lucencies of the hands or feet
   e. Ovarian fibroma
   f. Medulloblastoma

(modification of criteria outlined by Kimonis et al, Am J Med Genetics 69:299- 308, 1997)

4. The subject must have a history of at least 10 BCC in toto present at Baseline and/or treated within 24 months prior to screening.
5. The subject has at Baseline a total of at least 5 previously untreated SEBs (greatest diameter 5 mm or greater on the face excluding the nose and periorbital skin, 9 mm or greater on non-facial areas excluding the skin below the knees), as documented clinically by the Investigator at Baseline. Untreated is defined as no previous surgical or topical or intralesional drug treatment. Previous treatment with systemically administered drugs more than 6 months prior to baseline is not considered previous treatment as long as there was no clinical evidence of resistance to oral HH (e.g., vismodegib, patidegib, and sonidegib inhibitors. Baseline treatment targeted SEBs must not exceed a diameter of >2cm. At least one of these tumors must be appropriate for a 2 mm punch biopsy for biomarker analysis and Baseline and Week 6 visits. If a subject has 5 or more facial, excluding periorbital and nasal skin, SEBs at Baseline, non-facial SEBs will not be treatment targeted SEBs.
6. The subject is willing to have SEBs biopsied for biomarkers and plasma to be collected to measure drug levels as required in the protocol.
7. The subject is willing to abstain from application of non-study topical prescription and over the counter medications to facial skin and within 5 cm of treatment targeted SEBs at other anatomical areas 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.
8. Female subjects must have a negative serum pregnancy test at Screening.

9. 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. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months, must agree to use two effective methods of contraception for the duration of the study and at least 1 month after the last study drug application. 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.

10. 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.
11. The subject is willing to forego treatment of the treatment targeted baseline SEBs except when the Investigator and/or PSCP believes that delay in treatment potentially might compromise the health of the subject.

Exclusion Criteria:

1. The subject is a woman of childbearing potential. 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. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.
2. The subject has used topical products to the face or within 5 cm of a treatment targeted SEB 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) 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, and sonidegib) 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 return for all follow-up visits and tests.
5. The subject has uncontrolled systemic disease.
6. The subject has clinically important history of liver disease, including viral hepatitis, current alcohol abuse, or cirrhosis.
7. 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 an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk from treatment complications.

8. 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).
9. The subject has current, recent (within 4 weeks of Baseline visit), or planned participation in an experimental drug study while enrolled in this study.
10. Female sexual partner(s) of male subjects are unwilling or unable to comply with pregnancy prevention measures.

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

- patidegib gel 2%, applied topically, twice daily for 26 weeks.
- patidegib gel 4%, applied topically, twice daily for 26 weeks.
- vehicle gel, applied topically, twice daily for 26 weeks

Application Instructions:

The Study Coordinator or designee will instruct the subject on how to apply the study drug to the affected treatment areas identified at the Baseline visit by the Investigator. The staff member will instruct the subject on the proper application procedure during the Baseline visit. Subjects will be instructed to treat their entire face and if instructed to do so, to treat non-facial treatment targeted SEBs as well twice daily for 26 weeks. The quantity of gel to be applied will be defined using laminated dosing cards. It is approximately 330 mg of gel for the entire face and 20 mg of gel for each non-facial treatment targeted SEBs. 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 monitored by instructing them in the use of dosing cards and weighing each newly dispensed study drug tube and re-weighing each returned study drug tube at all applicable study visits.

Duration of Treatment:

All subjects will be treated for 26 weeks

Criteria for Evaluation:

The study will be conducted as outlined in the Schedule of Assessments (Table 2). For all efficacy measurements, the Investigators will be provided with training to ensure consistent evaluations across investigational centers. The assessments for a particular subject should be performed by the same investigator at all study visits whenever possible.

Safety Measurements:

De1mal Safety and Tolerability: Safety and tolerability will be evaluated through assessment of selected local signs and symptoms (pain / burning, prnritus, e1ythema, edema, and scabbing/crnsting). Each of the 5 baseline treatment-targeted tumor sites, as well as the face in general, 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 causing study drng inte1n1ption or discontinuation should be reported as an AE. The scales to be used for assessing local skin reactions follow:

Score	Grade	Description
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.		
0	None	No pain/burning
1	Mild	Slight burning/stinging sensation; not really bothersome
2	Moderate	Definite waim , burning/stinging that is somewhat bothersome
3	Severe	Hot burning/stinging sensation that causes definite discomfort and may inte1n1pt daily activities and/or sleep
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.		
0	None	No prnritus
1	Mild	Slight prnritus, not really bothersome
2	Moderate	Definite prnritus that is somewhat bothersome
3	Severe	Intense prnritus that may inte1n1pt daily activities and/or sleep
E1ythema: as assessed by the Investigator at each site		
0	None	No e1ythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Mai·ked e1ythema, bright red to dusky dai·k red in color
Score	**Grade**	**Description**
Edema: as assessed by the Investigator at each site		
0	None	No edema

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

Symptoms of Hedgehog Inhibitor Toxicity

At each visit subjects will be asked if they have experienced any symptoms that have been associated with this class ofdiugs.

Adverse Events: Dming the study, subjects will be assessed for the occunence 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 diug, con ective ti·eatment, outcome, and the Investigator's assessment of causality. AEs present at any visit will be followed to resolution (return to nonnal or to the baseline state) or until clinically stable as detennined by the Investigator.

Safety Laborato1y Tests: Routine safety laborato1y tests (complete blood count/differential minalysis, and sennn chemistry) will be perfonned at Screening, Week 6, Week 14, and Week 26. Any out-of-range laborato1y result that is considered clinically significant by the Investigator will be recorded as an AE and should be confmned by repeat testing at the discretion of the Investigator. Clinically significant laborato1y abnonnalities at any visit will be followed to resolution (retmn to n01mal or to the baseline state) or until clinically stable as detennined by the Investigator.

Physical Examinations: An abbreviated physical examination (including measmements of height, weight, and vital signs (blood pressme, hea1t rate, respiration rate, and oral temperatme) will be perfo1m ed at Baseline, Week 14, and Week 26.

Pregnancy Tests: All female subjects will have a pregnancytest perfo1med as specified visits dming the study. A semm pregnancy test will be perfonned at Screening and Weeks 6, 14, and 26.

Data Safety Management Board: Sho1tly after the last subject completes 14 weeks of h'eatment an independent data safety management board (DSMB) will evaluate all safety data as detailed in the DSMB chatter.

Efficacy Measurements:

The clinical efficacy of patidegib as defined by the percent decrease in greatest diaineter from Baseline of h'eatment targeted SEBs after 26 weeks of ti·eatment.

At Baseline and Weeks 2, 6, 10, 14, 18, 22, and 26, all visible BCCs will be identified by the

Investigator, circled in ink, photographed, measured, and recorded on a body diagram.
Biomarkers: A single baseline SEB designated as a treatment targeted tumor at Baseline will be biopsied with a 2 mm punch biopsy and at the end of 6 weeks of treatment for determination of GLI1 mRNA levels. In addition and whenever possible non-treatment targeted tumors or any tumor treated by surgical removal during the treatment phase of the trial will also be evaluated for GLI1 mRNA levels.

In addition, if non-treatment targeted tumors have been biopsied or any tumor treated by surgical removal during the trial are available they will be evaluated for GLI1 mRNA levels.

Subjects will complete the Dermatology Life Quality Index (DLQI) and the aBCCdex questionnaires at Baseline and Weeks 14 and 26.

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 1 confirmed dose of study drug, and have at least 1 post-baseline safety assessment will be included in the safety population.

Last observation carried forward (LOCF) will be used to impute efficacy data that are missing post-baseline through Week 26. No imputations will be made for missing safety data.

No adjustments for multiplicity will be made.

If determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers may be performed after the last subject completes 14 weeks of treatment.

Efficacy:

Efficacy Endpoints:

The efficacy endpoints are intended to compare 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:

- The primary efficacy endpoint is the decrease in tumor size defined as percent decrease in the sum of the greatest diameter of baseline treatment targeted SEBs at the Week 26.
- Change in GLI1 mRNA levels in drug-treated vs. vehicle-treated tumors after 6 weeks of treatment.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints include:

- Change in tumor size defined as percent decrease in the sum of the greatest diameter of baseline treatment targeted SEBs at Weeks 6, 10, 14, 18, and 22.
- Change in tumor size defined as percent change in greatest diameter from Baseline of

tumors located on the nose or periorbital area at Weeks 6, 10, 14, 18, 22 and 26.

- Number of new SEBs on the face at Weeks 6, 10, 14, 18, 22, and 26.
- Proportion of facial BCCs that at Baseline and/or Week 2 were less than 5 mm in greatest diameter but by Weeks 6, 10, 14, 18, 22, and 26 visit have become greater than 5 mm in greatest diameter.
- Proportion of baseline treatment targeted SEBs on the face that become less than 5 mm in greatest diameter and non-facial baseline treatment targeted SEBs that become less than 9 mm in greatest diameter at Weeks 6, 10, 14, 18, 22, and 26.
- The reduction in the HH signaling pathway after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 6 weeks to treatment-targeted SEBs.

Exploratory Efficacy Endpoints:

- The proportion of baseline treatment targeted SEBs that are evaluated as being clear or almost clear at Weeks 6, 10, 14, 18, 22 and 26 based on the ISGTA.
- DLQI and aBCCdex scores at Baseline and Weeks 14 and 26 as well as change from Baseline at Weeks 14 and 26.

Efficacy Analyses:

The sum of the greatest diameter of all treatment targeted SEBs for Baseline and post-baseline visits will be calculated.

The primary endpoint and secondary endpoints of change in tumor size, reduction in the HH signaling pathway, and the exploratory endpoint of change in GLI1 mRNA levels will be evaluated with an analysis of covariance (ANCOVA) with factors of treatment group and baseline value as a covariate. For the change in tumor size analyses, the covariate will be the sum of the baseline diameters. Pairwise comparisons will be performed using contrasts within the ANCOVA.

The number of new SEBs on the treated areas of the face will be analyzed with a Poisson Regression with factors of treatment group and the number of surgically eligible tumors at Baseline. Pairwise comparisons will be performed.

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

DLQI and aBCCdex scores will be summarized with descriptive statistics at Baseline and Weeks 14 and 26. Change from baseline will also be summarized at Weeks 14 and 26. DLQI responses of “not relevant” will be excluded from the change from baseline summaries.

Safety:

Safety Endpoints:

- Adverse Events
- Dermal Safety and Tolerability Including pain/burning, pruritus, erythema, edema, and scabbing/crusting.
- Patidegib concentration levels in plasma
- 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.

Plasma concentrations of patidegib will be summarized at Screening and Weeks 6, 14, and 26 by treatment group.

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 Baseline and Weeks 6, 14, and 26. 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:

Data from a trial of oral vismodegib (New England Journal of Medicine) given for 7 months resulted in a percent change in the sum of the greatest diameter of baseline treatment targeted SEBs of 69.2 and 13.7 with a standard deviation of 17 and 23 for treated and control subjects, respectively. A sample size of 6 subjects enrolled in each treatment group with a minimum of 5 SEBs will have greater than 95 percent power to detect a statistically significant difference at an alpha of 0.05.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
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
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
ET	Early Termination
GCP	Good Clinical Practice
GLI 1	Glioma-associated oncogene homolog 1
GRAS	Generally Recognized as Safe
HCl	Hydrogen Chloride
HH	Hedgehog
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
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
MHRA	Medicines and Healthcare Products Regulatory Agency
mRNA	Messenger Ribonucleic Acid
PSCP	Primary Skin Care Physician
QOL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SEB	Surgically Eligible Basal Cell Carcinoma

Abbreviation or Specialist Term	Definition or Explanation
SPF	Sunscreen Protection Factor
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
UK	United Kingdom
UV	Ultraviolet
WBC	White Blood Cell Count

4. INTRODUCTION

Patients affected by the BCNS (Gorlin syndrome, nevoid basal cell carcinoma syndrome; OMIM #109400), a rare autosomal dominant inherited disorder, have a dramatically increased risk of developing BCCs (developing hundreds to thousands of BCCs) as well as an increased risk of developing certain extra cutaneous tumors (e.g. medulloblastomas and rhabdomyosarcomas).

BCNS patients have multiple and frequent surgical removals of BCCs, with an average of 30 surgeries per year. Although this is problematic at all anatomical sites it is the greatest problem for facial tumors. While timely surgical removal of an *individual* BCC generally produces a cure and an acceptable cosmetic result, *repeated* surgeries can be uncomfortable, generally are disfiguring, and often cause functional impairment (e.g., of the eyelid, nose) and significant morbidity. The sponsor plans to develop topical patidegib to slow the progression of BCC disease in BCNS patients. "Progression" is defined as the development of increasing numbers of BCCs that are of a surgically-eligible size. Our focus on facial BCCs is based on the patients' need to minimize the number of facial surgeries with the consequent inevitable attendant scarring as well as to minimize impairment of function the lips, nose, eyelids, and ears. Surgical scarring on the trunk and extremities generally does not produce as much morbidity as does facial surgery. It may not be practical for patients to apply a topical product to their entire cutaneous surface, and treating the entire cutaneous surface would greatly increase the systemic exposure. Therefore in the present proof of concept trial non facial tumors will be treated only when needed to enable each patient to treat 5 baseline surgically eligible BCCs. SEBs are defined as tumors with a diameter of 3 mm or greater on the nose or periorbital skin, 5 mm or greater elsewhere on the face, and 9 mm or greater on non-facial skin in patients with BCNS. Illustrative of the potential of this pharmacologic inhibition of hedgehog signaling is a recently published trial of oral HH inhibitor vismodegib in which patients on active drug developed new SEBs at an annual median rate of 2 new SEBs and those on placebo at an annual median rate of 29 new SEBs.

Currently, 5-FU and Imiquimod are used as topical treatments for superficial BCCs. These are the easiest histologic subtype to treat but constitute only 20% of all BCCs. There are no topical drugs to prevent BCCs (except sunscreen) that are widely accepted. Oral retinoid treatment of BCNS patients can reduce their rate of development of BCCs but does so only at a dose that usually produces intolerable side effects.

Inhibition of HH pathway with the oral HH inhibitor, vismodegib, has been shown to prevent BCC development and to shrink existing BCCs in BCNS patients as well as to control some advanced BCCs[1]. In addition sonidegib another oral HH inhibitor has recently been approved for the treatment of locally advanced BCCs. However, oral HH inhibitors produce class-specific side effects such as hair loss, taste loss, weight loss, fatigue, and intense muscle cramps. The severity of the adverse events (AEs) associated with vismodegib is illustrated by the fact that 54% of

BCNS patients in an oral vismodegib clinical trial discontinued treatment because of AEs, despite clear efficacy.

PellePharm hopes to decrease the number of facial SEBs in BCNS patients by applying a topical HH inhibitor (patidegib) to produce good local effects without producing the side effects that occur with systemic administration of this class of drugs. PellePharm believes that there are two therapeutic effects that could decrease the patients' number of SEBs, namely (i) shrinking preexisting tumors and (ii) preventing the development of new tumors.

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 effect on 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 deposits significant amounts of drug in the dermis after topical application to human cadaver skin in Franz chamber assays. Topical application of patidegib significantly reduces murine BCC tumor size in vivo and reduces GLI1 biomarker expression in vitro in human BCC tumors.

The goal of the present trial is to evaluate topical patidegib's safety, tolerability, and effects on the size of preexisting SEBs and on the development of new SEBs. 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.

5. STUDY OBJECTIVES

The primary 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 Surgically Eligible basal cell carcinomas (SEBs) after 26 weeks of treatment [SEBs are defined as clinically diagnosed basal cell carcinoma (BCC) 5 mm or greater in diameter on the face excluding the nose and periorbital skin, and 9 mm or greater at sites other than the face].
2. The molecular efficacy of treatment as defined by reduction in the hedgehog (HH) signaling pathway target gene GLI1 after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 6 weeks to treatment-targeted SEBs.
3. The safety and tolerability of treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 26 weeks.

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

1. The clinical efficacy of treatment as defined by percent decrease in greatest diameter of baseline central facial SEBs (BCCs 3 mm or greater in diameter at Baseline located on the nose or periorbital area).
2. The frequency of new SEBs on the face. (A new SEB is defined as a SEB first noted at a visit after Week 2 and that developed at a site where there was no visible BCC of any size at the Baseline or the Week 2 visit.)
3. The proportion of non-central facial BCCs that at Baseline and/or Week 2 visit were less than 5 mm in greatest diameter but by the Week 6, 10, 14, 18, 22, or 26 visit have become greater than 5 mm in greatest diameter.
4. The proportion of baseline treatment targeted SEBs that at the end of 26 weeks of treatment are no longer large enough to be classified as SEBs (i.e., that is the proportion of baseline treatment targeted SEBs on the face that become less than 5 mm in greatest diameter and non-facial baseline treatment targeted SEBs that become less than 9 mm in greatest diameter).

Exploratory objective:

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

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This is a multicenter, double-blind, randomized; vehicle-controlled designed to assess the efficacy and safety of patidegib gel, 2% and 4% in comparison with vehicle. To be eligible for the study, subjects must be at least 18 years of age and meet the diagnostic criteria for BCNS.

Selection of dose levels and frequency of application for topically applied drug products is challenging. With systemic drugs it is possible to select the starting dose and frequency of dosing based on pharmacokinetics and pharmacodynamics obtained from animal studies and Phase 1 normal volunteer studies. Such data is simply not available for topically applied drugs, owing to several technical challenges. Foremost is a lack of in-vivo pharmacokinetic and pharmacodynamics data in skin following topical application of a drug product. In addition, the solubility of a drug often sets the limit for the highest concentration as it is preferable not to work with topical drugs in suspension. The reality is that the selection of doses for novel topical drugs is more an educated approximation than a calculation based on pharmacokinetics pharmacodynamics.

First and foremost in selecting the dose were safety considerations. As detailed in our Investigator's Brochure based on dermal application in mini pigs and oral administration in humans the proposed doses have a very large safety margin for both dermal tolerability and systemic safety. With these large safety margins the key question then in selecting the dose for this proof of concept clinical trial was choosing doses that had the greatest probability of showing biologic activity.

The selection of doses for patidegib gel was informed by in vitro skin penetration studies, in vitro treatment of excised and explanted human BCCs, in vivo treatment of tumors in mice and the upper limit the solubility of the drug. The penetration of patidegib into and through human skin was studied in-vitro with multiple formulations and concentrations of patidegib in Franz cells experiments. In these experiments formulated drug is applied to cadaver skin and drug levels in the skin are then measured. Patidegib gel at 4.87%, 0.75%, and 0.1% applied continuously in drug excess resulted in drug levels in the epidermis of 758 μM, 315 μM, and 35 μM and in the dermis of 341 μM, 59 μM, and 5 μM, respectively. BCCs are tumors of the epidermis that extend down into the dermis. While these levels represent only a small percentage of the applied dose they are well above the IC_{90} of 0.04 μM. It is not known how much of this drug is in the intracellular compartment and it should be noted that in Franz cell experiments formulated drug is applied in excess representing what is referred to as an infinite dose which is different than the clinical situation where a finite dose is applied. Because of these unknowns one

wants to be well above the IC_{90} as long as there are no safety concerns.

In trials of the oral formulation of patidegib for the treatment of BCC skin drug levels were measured. The levels of drug seen in vitro in the skin in Franz cells were 20 times higher than the skin levels seen in the skin following oral administration of 130 mg of patidegib to patients with BCCs. In mice with BCC allographs and in genetically modified mice with BCCs patidegib gel at 1% and 4% applied twice daily decreased tumor size and inhibited the GL1 biomarkers levels comparable to oral vismodegib. It is well known that drugs penetrate mouse skin much better than human skin. This is thought to be due to mouse skin being thinner and having far more large terminal hair follicles than human skin. In vitro in explanted human BCC tumors 5% patidegib gel was able to inhibit the GL1 biomarker after 5 days of treatment to levels comparable to those seen with oral vismodegib. In the process of developing the clinical formulation of patidegib the gel formation which showed the best in vitro skin penetration the solubility of the drug limited the highest concentration to 4%.

Based on the above observations PellePharm concluded that patidegib in the gel formulation at 2% and 4% applied twice daily would have a good probability of being effective treatment regimens. These concentrations also provide a large safety margin for both dermal and systemic safety. Assuming that this proof of concept trail demonstrates clinically meaningful activity future clinical trials will refine the treatment regimen in terms of drug concentration and/or frequency of application.

Approximately 18 subjects who meet the study entry criteria will be randomized in a 1:1:1 ratio to receive patidegib gel 2%, patidegib gel 4%, vehicle gel. One or two tubes of the assigned study drug will be dispensed to the subject at the Baseline visit. The study drug will be applied topically to the entire face as well as to treatment-targeted SEBs at other anatomical sites twice daily for 26 weeks of treatment. Subjects will apply their twice daily treatments at home as explained by the study coordinator or designee at each study center. The subject will apply the initial application under the supervision of the study staff. If a subject has a treatment targeted SEB 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 cannot be a woman of childbearing potential, and the person should apply the gel using a latex or vinyl glove. As BCNS 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.

At each post-baseline visit during the treatment period, (Weeks 2, 6, 10, 14, 18, 22, and 26) the subjects will be asked to return their tubes of study drug which will be evaluated for drug usage

compliance. It has been estimated that subjects will require 330 mg of gel to adequately cover their face and 20 mg of gel to adequately cover each non-facial SEBs. The Study Coordinator or designee at each study center will dispense new tube(s) of study drng to each subject at study center visits at Baseline through Week 22. The goal is that each subject will have an adequate supply of gel to last until the next clinic visit plus some extra in case of application enors and or delay in study visits. While individual usage rates of topical products have individual variability the use of dosing card should help limit the variation in dosing inherent with topical products. PellePhaim estimates that subjects ti·eating only the face, 1, 2, 3, 4, or 5 non-facial SEBs will consume 19.8 gm, 21 gm, 22.2 gm, 23.4 gm, 24.6 gm, and 25.8 gm of gel over the course of a 30 day month.

Table 1: Estimated Quantity of Study Drug Usage

Area Treated	Single Dose	Daily Dose	60 Doses	Face and SEB 60 Doses
Face	330mg	660mg	19.8 gm	
Non-Facial SEB				
0				19.8 gm
1	20mg	40mg	1.2 gm	21.0 gm
2	40mg	80mg	2.4 gm	22.2 gm
3	60mg	120mg	3.6 gm	23.4 gm
4	80mg	160mg	4.8 gm	24.6 gm
5	100mg	200mg	6.0 gm	25.8 gm

Upon completion of the 26-week ti·eatment period, all subjects will be asked to return to the investigational center for final evaluation. During the study, subjects will be allowed to use moisturizers and emollients and sunscreen. The Investigator will assess the areas affected at each study visit.

Non-facial baseline ti·eatment-tai·getedSEBs ai·e defined as SEBs identified at Baseline as ti·eatment tai·geted SEBs on skin other than skin of the face. While eyelids can be u-eated as paii of the applicationto the whole face, subjects need to be cautioned not to apply the gel to their eyes or the inner eyelids. Infonnation on repo1i ed and observed AEs will be obtained at each visit. An abbreviated physical exainination will be perfo1m ed at Baseline, Week 14, and Week 26.

At Baseline and Weeks 6, 10, 14, 18, 22, and 26, all visible BCCs will be identified by the Investigator, circled in ink, measured, and recorded on a body diagram. Treatment tai·geted SEBs

are defined as SEBs on the face and/or other anatomical areas identified at Baseline as SEBs and which were treated during the 6 month treatment phase.

Biomarkers: A single baseline SEB designated as a treatment targeted tumor at Baseline will be biopsied with a 2 mm punch biopsy and at the end of 6 weeks of treatment for determination of GLI1 mRNA levels. In addition and whenever possible non-treatment targeted tumors or any tumor treated by surgical removal during the treatment phase of the trial will also be evaluated for 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, Week 14, and Week 26. Plasma samples will also be collected at Screening and Weeks 6, 14, and 26 to determine plasma concentrations of patidegib and relevant metabolites.

Subjects who terminate study participation early will be asked to complete all Week 26 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 temporarily interrupt use of the study drug 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 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 from the study, due to clinically significant laboratory abnormalities or AEs will be asked to complete all Week 26 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 2: Schedule of Assessments

Assessments	Screening	Baseline (Within 6 weeks of Screening)	Week2	Week6	Week 10	Week 14	Week 18	Week22	**Week26/ ET3**
Day	-42 to 0	1	15	43	71	99	127	155	183
Window (days)			±2	± 3	±3	±3	± 3	± 3	±3
Info1med Consentb	X								
Eligibility Confnmation	X	X							
Demographics	X								
Medical Histo1y	X	X:							
Heigh t, We ight	X	Xd	X	X	X	X	X	X	X
Physical Examination (vital signs)	X					X			X
Laborato1y Testing (blood and urinee)	X			X		X			X
Semm Pregnancy Test	X			X		X			X
Randomization		X							
Quality of Life Questionnaires		X				X			X
Tasks to be Done by Physician									
Identify BCC to be Biopsied		X		X					
Identify 5 SEBs	X	X							
Application Site Evaluation		X	X	X	X	X	X	X	X
ISGTA		X	X	X	X	X	X	X	X
Measure and map visible BCCsf		X	X	X	X	X	X	X	X
Dete1mine Clinical Tumor Type		X							
Imagingg		X	X	X	X	X	X	X	X
Syste mic Symptoms		X	X	X	X	X	X	X	X
Patidegib Plasma Levels	X			X		X			X

Assess ments	Screening	Baseline (Within 6 weeks of Screening)	Week 2	Week6	Week 10	Week 14	Week 18	Week 22	Week 26 / ET
Day	-42 to 0	1	15	43	71	99	127	155	183
Window (days)			± 2	± 3	±3	± 3	± 3	± 3	±3
Patidegib *N* ehicle Applications		X	X	X	X	X	X	X	X
S tu dy chug review/In structions Dispensa tionh		X	X	X	X	X	X	X	
Co n co mitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Review Test Article Compliance/Accountability1		X	X	X	X	X	X	X	X

BCC= basal cell carcinoma; ET = early termination; ISGTA = investigator static global tumor assessment; SEB = surgically eligib le basal cell carcinoma

- For subjects who discontinue early dming the treatment period, all procedures outlined for the ET visit should be completed at the time of discontinuation.

b Must be signed prior to any study procedures.

c Medical histo1ywill be updated at Baseline visit.

d Height will be measured at Baseline only.

e The following blood samples for laborato1ytests will be collected: Alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), total bilimbin, 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/PercentLymphocyte count, Absolute/Percent Monocyte count, Absolute/Percent Eosinophil Count, Absolute/Percent Basophil Count. Urinalysis will include reflex microscopic examination. Clinically significant laborato1yfindings at Week 6, Week 14, or Week 26 will be repeated at the discretion of the Investigator, and the subjectwill be followed until resolution (retum to normal or to the baseline state) or until clinically stable as detennined by the Investigator.

f T umor s to be mea s ured and mapped include the 5 baseline treatment-targeted tumors as well as all other facial tumors including those on the eyelids and the nose. In addition, up to 10 non treatment-targeted non-facial tumors will also be measured and mapped.

[g] Imaging requirements are provided in the imaging manual.

[h] 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.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 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 written informed consent prior to any study procedures.
3. The subject must meet diagnostic criteria for BCNS including major criterion #3a plus one additional major criterion or major criterion #3a plus two of the minor criteria outlined below:

   Major Criteria:

   a. More than 2 histologically confirmed BCCs or one under the age of 20 years
   b. Odontogenic keratocysts of the jaw proven by histology
   c. Three or more palmar and/or plantar pits
   d. Bilamellar calcification of the falx cerebri (if less than 20 years old)
   e. Fused, bifid, or markedly splayed ribs.
   f. First degree relative with basal cell nevus syndrome (BCNS)
   g. PTCH1 gene mutation in normal tissue

   Minor Criteria

   a. Macrocephaly
   b. Congenital malformations: cleft lip or palate, frontal bossing, “coarse face”, moderate or severe hypertelorism
   c. Skeletal abnormalities: sprengel deformity, marked pectus deformity, or marked syndactyly of the digits
   d. Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame shaped lucencies of the hands or feet
   e. Ovarian fibroma
   f. Medulloblastoma

   (modification of criteria outlined by Kimonis et al, Am J Med Genetics 69:299- 308,

1997)

4. The subject must have a history of at least 10 BCCs in toto present at Baseline and/or treated within 24 months prior to screening.
5. The subject has at Baseline a total of at least 5 previously untreated SEBs (greatest diameter 5 mm or greater on the face excluding the nose and periorbital skin, 9 mm or greater on non-facial areas excluding the skin below the knees), as documented clinically by the Investigator at Baseline. Untreated is define as no previous surgical or topical or intralesional drug treatment. Previous treatment with systemically administered drugs more than 6 months prior to Baseline is not considered previous treatment as long as there was no clinical evidence of resistance to oral HH (e.g., vismodegib, patidegib, and sonidegib) inhibitors. Baseline treatment targeted SEBs must not exceed a diameter of > 2cm. At least one of these tumors must be appropriate for a 2 mm punch biopsy for biomarker analysis at Baseline and Week 6 visits. If a subject has 5 or more facial, excluding periorbital and nasal skin, SEBs at Baseline, non-facial SEBs will not be treatment targeted SEBs.
6. The subject is willing to have SEBs biopsied for biomarkers and plasma to be collected to measure drug levels as required in the protocol.
7. The subject is willing to abstain from application of non-study topical prescription and over the counter medications to facial skin and within 5 cm of treatment targeted SEBs at other anatomical areas 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.
8. Female subjects must have a negative serum pregnancy test at Screening.
9. 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. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months, must agree to use two effective methods of contraception for the duration of the study and at least 1 month after the last study drug application. 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.

10. 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.
11. The subject is willing to forego treatment of the treatment targeted baseline SEBs except when the Investigator and/or PSCP believes that delay in treatment potentially might compromise the health of the subject.

7.2 Subject Exclusion Criteria

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

1. The subject is a woman of childbearing potential. 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 in humans. A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months.
2. The subject has used topical products to the face or within 5 cm of a treatment targeted SEB 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) 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, and sonidegib) 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 return for all follow-up visits and tests.
5. The subject has uncontrolled systemic disease.

6. The subject has clinically important history of liver disease, including viral hepatitis, current alcohol abuse, or cirrhosis.
7. 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 an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk from treatment complications.
8. 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).
9. The subject has current, recent (within 4 weeks of Baseline visit), or planned participation in an experimental drug study while enrolled in this study.
10. Female sexual partner(s) of male subjects are unwilling or unable to comply with pregnancy prevention measures.

7.3 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 of non-permitted concomitant medication
- Lack of patient compliance
- Protocol violation - Contact PellePharm or designee before making decision.
- Disease progression
- 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 – Subject will discontinue study drug immediately, but 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 risk of continuing the subject in the study outweighs the benefit as determined by the Investigator. However, if treatment targeted SEBs requires treatment because of increase in size these tumors 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 26 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. In any case, no subject who has been included and has a study number assigned can be replaced by another if they discontinue prematurely for whatever reason.

If, for any reason, a subject is dropped during the treatment period prior to Week 26, all end of treatment study (i.e., Week 26) 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.

7.4 Study Drug Discontinuation

The Investigator may discontinue study drug administration for any patient 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 patient'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 patient.
- Pregnancy
- Disease progression

7.5 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 patients.

8. TREATMENT PLAN

8.1 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 randomized to 1 of the 3 study drug groups in a ratio of 1:1:1 (patidegib gel, 2%, patidegib gel, 4%, vehicle gel). 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 each investigational center.

8.2 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 entering the study within each investigational center. Study drug supplies will be distributed to the investigational centers to maintain the randomization ratio within each investigational center.

As a double-blinded study, the Investigators, the site staff, PellePharm, and the Clinical Monitors will not be aware of the treatment assigned to the individual study subjects.

Delegated staff members at each investigational center will dispense the study drugs and will collect and weigh all used and unused study drug tubes as scheduled.

8.3 Unblinding

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the treatment phase of the study. Specifically, the blind will be broken only after all data through Week 26 are verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; and the database is locked.

In the case of a medical emergency, the Investigator can break the blind for the subject involved. 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.

8.4 Prior and Prohibited Concomitant Medication or Therapy

Subjects must not have used topical products to the face or 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) 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, and sonidegib) topically or systemically within 6 months of entry into the study.

Subjects will not be allowed to use topical or systemic therapies that may affect treatment targeted SEBs and/or their development of new SEBs. 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.

8.5 Treatment Compliance

Each subject will be instructed on the importance of returning the study drug at each applicable study visit. If a subject does not return his or her study drug, he or she will be instructed to return it as soon as possible. The subjects will bring the tubes dispensed at each treatment visit to the next subsequent study visit. Each tube will be weighed by the Study Coordinator 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

8.6 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 the Medical Monitor and the Investigator, with appropriate documentation of 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 patients or a small group of patients and do not involve eligibility or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the subject or Investigator has failed to adhere

to significant protocol requirements (eligibility criteria) and the patient was enrolled without prior PellePharm approval, or when there is nonadherence to MHRA or local authority regulations and/or ICH GCP guideline.

The Investigator or designee must document and explain in the patients' 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 patients 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.

9. STUDY DRUG MATERIALS AND MANAGEMENT

The study drng will be dispensed by a trained qualified member of the study staff assigned by the Investigator to this task

Patidegib is generated from a plant source by the extraction of crnde cyclopamine. Cyclopamine is can ied through a series of synthetic steps to yield the well-characterized staii ing material for GMP conversion to patidegib.

Patidegib HCl active ingredient is found as a white free-flowingc1ystalline solid. Patidegib topical gel is a smooth clear viscous hydro alcoholic gel for topical administration. The gel is non-in itatingand easy to spread on the lesions as directed.

The following excipients are used in the fonnulation of patidegib topical gel: All components of patidegib gel meet standai·d US or international compendial standai·ds and are generally recognized as safe (GRAS).

Table 3: Excipients of Patidegib Topical Gel

Component	Monoeraph
Patidegib	*N/ A*
Transcutol P	USP, NF, PH. Eur.
Ethanol	USP,NF,JP, Ph. Eur.
Proovlene Glycol	USP, NF, Ph. Eur.
Purified Water *	USP, Ph. Eur.
Boric Acid *	Ph. Eur.
SodillllHydroxide *	NF, BP, JP, Ph. Eur.
Phenoxvethanol	Ph. Eur.
Hvdroxypropylcellulose HF	Ph. Eur.

*Components for pH 7.5 borate buffer

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

Comoonent	4%*	2%*	Placebo
Patidegib	4.97	2.49	0.00
TranscutolP	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
Phenoxvethanol	1.00	1.00	1.00
HPC-HF**	1.00	1.00	1.00
TOTAL	**100.00**	**100.00**	**100.00**

*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 active pharmaceutical ingredient (API) lot

**Hydroxypropylcellulose –HF

9.1 Packaging and Labeling

Study drug will be packaged in tubes and provided in study drug kits. Each kit will contain 18 tubes, each containing 15 grams of study material. The subjects will be dispensed study medication as needed at Baseline and at all subsequent study visits, through Week 22. The tubes will be weighed prior to dispensing. The subject will bring the tubes to the next study visit, 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 between clinic visits. Each drug dispensation will be documented on the drug accountability log. Labels on the tubes will contain the following information:

- Protocol Number
- Name, address and telephone number of the sponsor, contract research organization or Investigator (the main contact for information on the product, clinical trial and emergency unblinding);
- Batch number
- Directions for use
- Period of use (expiry date), in month/day/year format and in a manner that avoids any ambiguity.
- Subject Number
- Space for entry of the subject initials
- Space for entry of date dispensed
- A statement reading, “For external use only. Avoid contact with eyes and lips”
- A statement reading, “Store at controlled room temperature 59°F to 86°F (15°C to 30°C). Do not refrigerate”
- A statement indicating the sponsor, PellePharm Inc.
- A statement indicating the quantity of product (15 grams)

- A statement reading, “for clinical trial use only”
- A statement reading, “Keep from breastfeeding or childbearing potential women”
- A statement reading, “Keep out of Reach and Sight of Children”

9.2 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 patient’s storage of dispensed tubes.

9.3 Administration

The investigational center staff member will instruct the subject to apply the study drug to the affected treatment areas identified at the Baseline visit by the Investigator. The staff member 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 the entire selected treatment area(s) as indicated on the body diagram twice daily up to the Week 26 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 child bearing 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.

9.4 Study Drug Accountability

Upon receipt of the study drug, the Investigator is responsible for ensuring that the designated study drug staff will 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.

10. STUDY PROCEDURES AND EVALUATIONS

The study will be conducted as outlined in the Schedule of Assessments (Table 2).

All subject information and data obtained during the study visits will be recorded in the 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 regulation. There are specific tasks that PellePharm requires be done by a physician. These include identification of SEBs, identification of the treatment-targeted tumor to be biopsied for biomarkrs, measuring and mapping of tumors, 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.

10.1 Schedule of Evaluations and Procedures

10.1.1 Screening Visit (Day -42 to Day 0)

Following written 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 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 verbal and written informed consent from the subject prior to performing any study related procedures. Give a signed copy to the subject.

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. Perform a brief physical exam including vital signs and weight.
9. The Investigator will identify 5 previously untreated non central facial SEBs one of which will be acceptable for biopsy for biomarker. The biomarker designated tumor will be biopsied with a 2 mm punch biopsy at Baseline and Week 6.
10. Verify that the subject meets the applicable inclusion/exclusion criteria as outlined in Sections 7.1 and 7.2.
11. Discuss the use of moisturizers and emollients with the subject.
12. Collect blood samples for routine laboratory analysis [complete blood count/differential (CBC/Diff), urinalysis, serum chemistry and serum pregnancy test on all female subjects] and plasma drug concentrations.
13. Record any AEs related to screening procedures on the AE eCRF.
14. Schedule subject to return for the Baseline/Day 1 visit. If the subject requires a washout, schedule the Baseline/Day 1 visit to occur after the washout is complete.

10.1.2 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 8.4.
3. Record changes in any concomitant medications since the previous visit in eCRF. Check for prior and concomitant therapies as per Section 8.4.
4. Verify that the subject continues to meet the applicable study eligibility criteria as outlined in Sections 7.1 and 7.2.

5. An abbreviated physical examination including measurements of height, weight, and vital signs (blood pressure, heart rate, respiration rate, and oral temperature).
6. Have the subject complete the DLQI and aBCCdex questionnaires.
7. The Investigator will perform the clinical evaluation to identify BCCs including the 5 baseline treatment-targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non-facial tumors will also be clinically classified as superficial, nodular, infiltrative, morpheic or sclerosing, pigmented, or micronodular/morpheaform, circle each tumor in ink, photographed, measured, and recorded on a body diagram. The 5 baseline treatment-targeted tumors will also be evaluated based on the ISGTA.
8. Obtain 2 mm punch biopsy from the baseline treatment targeted SEB that has been designated for biomarker evaluation. The 2 mm punch biopsies can be performed by the Investigator or designee as allowed by the clinical site's normal policies and procedures.
9. The Investigator or designee will assess each of 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. Each of the 5 treatment targeted-tumors, as well as the face in general, will be evaluated separately.
10. The Investigator will query the patient 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.
11. Randomize the subject to a treatment group and record the assigned kit number in the source document and in the eCRF.
12. The designated study drug staff will weigh each tube within the assigned kit and dispense them to the subject.
13. 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 twice daily at home.
14. Record any AEs reported spontaneously by the subject.
15. Schedule the next study visit at Week 2 (Day 15 ± 2 days).

10.1.3 Weeks 2, 10, 18, and 22

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 8.4.
2. Record any new AEs reported spontaneously by the subject or changes in any ongoing AEs.
3. Record subject weight.
4. The Investigator will perform the clinical evaluation of the 5 baseline treatment-targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non-facial tumors will be circled in ink, photographed, measured, and recorded on a body diagram. The 5 baseline treatment-targeted tumors will be evaluated based on the ISGTA.
5. The Investigator or designee will assess each of 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. Each of the 5 treatment-targeted tumors, as well as the face in general, will be evaluated separately.
6. 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.
7. The Study Coordinator or designee will collect and 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.
8. Any missed doses or deviations should be reported.
9. 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.
10. Schedule the next study visit.

10.1.4 Week 6, 14, and 26

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 8.4.
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 (*Weeks 14 and 26 only*).
4. Collect blood samples for routine laboratory analysis (CBC/Diff and serum chemistry) and plasma concentrations.

5. Perform a serum pregnancy test for all female subjects.
6. Have the subject complete the DLQI and aBCCdex questionnaires (Weeks 14 and 26).
7. Obtain a biopsy with a 2 mm punch at Week 6 from the single SEB designated as the biomarker treatment targeted tumor and previously biopsied at baseline. The 2 mm punch biopsies can be performed by the Investigator or designee as allowed by the clinical site's normal policies and procedures.
8. The Investigator will perform the clinical evaluation of the 5 baseline treatment-targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non-facial tumors will be circled in ink, photographed, measured and recorded on a body diagram. The 5 baseline treatment-targeted tumors will be evaluated based on the ISGTA.
9. The Investigator or designee will assess each of 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. Each of the 5 treatment-targeted tumors, as well as the face in general, will be evaluated separately.
10. 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.
11. The Study Coordinator or designee will collect and 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.
12. The Study Coordinator will verify study drug compliance. Any missed doses or deviations should be reported.
13. 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. The study drug should be applied after all clinical assessments.
14. Schedule the next study visit (*Weeks 6 and 14 only*).

10.1.5 Week 26 (Day 183 ± 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 8.4.
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) and plasma concentrations.
5. The Investigator or designee will assess each of 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. Each of the 5 treatment-targeted tumors, as well as the face in general, will be evaluated separately.
6. The Investigator will perform the clinical evaluation of the 5 baseline treatment-targeted tumors, as well as, all other facial tumors (including those on the eyelids and the nose). In addition, up to 10 non treatment-targeted non-facial tumors will be circled in ink, photographed, measured and recorded on a body diagram. The 5 baseline treatment-targeted tumors will be evaluated based on the ISGTA. 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.
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.

10.2 Evaluation of Tumors

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.

10.2.1 Assessment of BCCs

At Baseline and at Weeks 6, 10, 14, 18, 22, and 26, all visible BCCs will be identified by the Investigator. The Investigator will circle in ink, photograph, measure the greatest diameter, and record the BCCs on a body diagram.

Treatment targeted SEBs will be identified at Baseline on the face and/or other anatomical areas and will be treated during the 26 week treatment phase. The diameter of each SEB will be reported on the eCRF. New SEBs on the face will be reported on the eCRF at Weeks 2, 6, 10, 14, 18, 22, and 26.

10.2.2 Messenger RNA (mRNA)

A single SEB designated as a treatment targeted tumor at Baseline will be biopsied with a 2 mm punch biopsy at Baseline as well as at the end of Week 6 for determination of GLI1 mRNA levels. It is preferable that the tumor selected for biopsy has the clinical features of a nodular BCC.

10.2.3 Investigator Global Static Tumor Assessment

The Investigator will assess and record each baseline treatment targeted SEBs at Weeks 6, 10, 14, 18, 22, and 26.

Table 5: Investigator Static Global Tumor Assessment

0	Clear - no evidence of residual tumor is seen or palpated, faint ill-defined macular erythema may be present; n01m al skin markings are seen
1	Almost clear - residual macular e1ythema is clearly seen but there is no palpable tumor, scale, erosions, ulcerations; n01mal skinmarkings are seen
2	Minimal residual tumor - macular e1ythemais clearly seen and slight palpable tumor with or without scale, erosions, ulcerations; n01m al 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; n01mal skin markings not seen

10.2.4 Subject Questionnaires

Subjects will complete the DLQI and aBCCdex questionnaires at Baseline and Weeks 14 and 26. The DLQI and aBCCdex questionnaires can be found in Appendix 16.2 and 16.3, respectively.

10.3 Evaluation of Safety

10.3.1 Dermal Safety and Tolerability

Safety and tolerability will be evaluated through assessments of selected local signs and symptoms (pain / bmnin g, pmritus, e1ythema, edema, and scabbing / cmsting). Each of the 5 treatment-targeted tumors, as well as the face in general, will be evaluated separately. Any local skin reaction requiring use of a concomitant therapy or is a cause for study diug intenu ption or discontinuation should be repo1i ed as an AE. The scales to be used for assessing local skin reactions follow:

Table 6: Dermal Safety and Tolerability Scales

Score	Grade	Description
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 Baselineor since the last visit at subsequent visits.		
0	None	No pain/bmning
1	Mild	Slight bmning/stinging sensation; not really bothersome

2	Mode rat e	Definite wa1m, bmning/stinging that is somewhat bothersome
3	Severe	Hot bmning/stinging sensation that causes definite discomfo1i and may intenupt daily activities and/or sleep
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.		
0	None	No prnritus
1	Mild	Slight prnritus, not really bothersome
2	Moderate	Definite prnritus that is somewhat bothersome
3	Severe	Intense prnritus that may intenu pt daily activities and/or sleep
E1ythema: as assessed by the Investigator at each site		
0	None	No e1yt hema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked e1yhema, bright red to dusky dark red in color
Edema: as assessed by the Investigatorat each site		
0	None	No edema
1	Mild	Slight, but definite edema
2	Moderate	Definite edema
3	Severe	Marked edema
Scabbing/Crusting:as assessed by the Investigator at each site		
0	None	No scabbing/crnsting
1	Mild	Slight, but definite scabbing/crnsting
2	Moderate	Definite scabbing/crnsting
3	Severe	Marked scabbing/crnsting

10.3.2 Medical History and Abbreviated Physical Examination

A medical histo1ywill be taken at Screening, and confnmed 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, Week 14, and Week 26. Height will be measured at Baseline only.

10.3.3 Safety Laboratory Tests

Routine safety laboratory tests as per Appendix 16.4 will be performed at Screening, Week 6, Week 14, and Week 26. 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.

10.3.4 Pregnancy Tests

All female subjects will have a pregnancy test performed at specified visits during the study. A serum pregnancy test will be performed at Screening and Weeks 6, 14, and 26.

10.3.5 Plasma Concentrations

A blood sample will be collected at Screening, Weeks 6, 14, and 26 to assess patidegib levels in plasma.

10.3.6 Adverse Events

10.3.6.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient 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.

10.3.6.2 Documenting Adverse Experiences

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.

10.3.6.3 Serious Adverse Events

All AEs will be assessed as either serious or nonserious.

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 patient 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 1 of the above listed outcomes

Note: A spontaneous abortion will be considered an SAE, and must be reported per Reporting of SAEs under Section 10.3.6.6.

10.3.6.4 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

10.3.6.5 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 patient'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 patient's clinical state or other modes of therapy administered to the patient.
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 patient's clinical state or other modes of therapy administered to the patient.
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

10.3.6.6 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.

Safety Reporting Contact	
Name:	Premier Research Phan nacovigilance
Facsimile:	+42 1268203713
Email	GlobalPV-Slovakia@12r e mi e r - r ese arch.com

If there are serious, unexpected AEs associated with the use of the study diug, PellePhaim will notify the appropriate regulato1yagency(ies) and all appropriate pa1iies 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 patients.

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 PellePhaim.

10.3.6.7 Emergency Contact

In the event of a medical emergency (i.e., an event that requires immediate attention regai·ding the treatm ent of a patient, operat ion of the clinical study , and/or the use of investigational di1lg), investigational site personnel must immediately contact the Medical Monitor.

Medical Monitor Contact	
Name:	rPD
T e lephon e :	rPD
F a cs imil e :	rPD
E m a il	rPD

10.3.6.8 Expedited Serious Adverse Event Reports

An AE, whether serious or nonserious, is designated unexpected (unlabeled) if it is not repo1i ed in the clinical safety section of the Investigator Brochure or if the event is of greater frequency, specificity or severity.

Expedited SAE reports ai·e those that document AEs that ai·e both unexpected based on the reference document (Investigator Brochure) and ai·e related (i.e ., the relations hip cannot be rnled out) to the study diug. These expedited repo1is ai·e s ubject to repo 1i ing 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.

10.3.6.9 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 patient 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

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.

11. STATISTICS

All statistical processing will be performed using Statistical Analysis System (SAS®) unless otherwise stated. If determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers may be performed after the last subject completes 14 weeks of treatment. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

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. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

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.

No adjustments will be made for multiplicity.

If determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers may be performed after the last subject completes 14 weeks of treatment.

Shortly after the last subject completes 14 weeks of treatment an independent data safety management board (DSMB) will evaluate all safety data as detailed in the DSMB charter.

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.

11.1 Analysis Populations

Efficacy analyses will be performed using the intent-to-treat (ITT) population. Safety analyses will be performed using the safety population.

All subjects who are randomized and dispensed study drug will be included in the ITT analysis set.

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.

11.2 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.

11.3 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.

11.4 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.

11.5 Compliance

No formal evaluations of compliance are planned.

11.6 Interim Analyses

If determined appropriate by the Sponsor, limited efficacy analysis on tumor shrinkage and biomarkers may be performed after the last subject completes 14 weeks of treatment.

11.7 Assessment of Efficacy

11.7.1 Efficacy Endpoints

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

11.7.1.1 Primary Efficacy Endpoints:

The primary efficacy endpoints include:

- Decrease in SEB size defined as percent decrease in the sum of the greatest diameter of baseline treatment targeted SEBs at the Week 26 visit.
- Change in GLI1 mRNA levels in drug-treated versus placebo-treated tumors after 6 weeks of treatment.

11.7.1.2 Secondary Efficacy Endpoints:

The secondary efficacy endpoints include:

- Change in tumor size defined as percent decrease in the sum of the greatest diameter of baseline treatment targeted SEBs at Weeks 6, 10, 14, 18, and 22.

- Change in tumor size defined as percent change in greatest diameter from Baseline of tumors located on the nose or periorbital area at Weeks 6, 10, 14, 18, 22 and 26.
- Number of new SEBs on the face at Weeks 6, 10, 14, 18, 22, and 26.
- Proportion of facial BCCs that at Baseline and/or Week 2 were less than 5 mm in greatest diameter but by Weeks 6, 10, 14, 18, 22, and 26 visit have become greater than 5 mm in greatest diameter.
- Proportion of baseline treatment targeted SEBs on the face that become less than 5 mm in greatest diameter and non-facial baseline treatment targeted SEBs that become less than 9 mm in greatest diameter at Weeks 6, 10, 14, 18, 22, and 26.
- The reduction in the HH signaling pathway after treatment with patidegib gel 2% or 4% or vehicle applied twice daily for 6 weeks to treatment-targeted SEBs.

11.7.1.3 Exploratory Efficacy Endpoints:

- The proportion of baseline treatment targeted SEBs that are evaluated as being clear or almost clear at Weeks 6, 10, 14, 18, 22 and 26 based on the ISGTA.
- DLQI and aBCCdex scores at Baseline and Weeks 14 and 26 as well as change from Baseline at Weeks 14 and 26.

11.7.2 Efficacy Analyses

The sum of the greatest diameter of all treatment targeted SEBs for Baseline and post-baseline visits will be calculated.

The primary endpoint and the secondary endpoints of change in tumor size, reduction in the HH signaling pathway, and the exploratory endpoint of change in GLI1 mRNA levels will be evaluated with an analysis of covariance (ANCOVA) with factors of treatment group and baseline value as a covariate. For the change in tumor size analyses, the covariate will be the sum of the baseline diameters. Pairwise comparisons will be performed using contrasts within the ANCOVA.

The number of new SEBs on the treated areas of the face will be analyzed with a Poisson Regression with factors of treatment group and the number of surgically eligible tumors at Baseline. Pairwise comparisons will be performed.

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

DLQI and aBCCdex scores will be summarized with descriptive statistics at Baseline and Weeks 14 and 26. Change from baseline will also be summarized at Weeks 14 and 26. DLQI responses of "not relevant" will be excluded from the change from baseline summaries.

11.8 Assessment of Safety

11.8.1 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.

11.8.2 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.

11.8.3 Plasma Concentrations

Plasma concentrations of patidegib and any major metabolites will be summarized descriptively at Screening and Weeks 6, 14, and 26 by treatment group.

11.8.4 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 Baseline and Weeks 6, 14, and 26. 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.

11.8.5 Pregnancy Tests

Pregnancy test results will presented in a data listing.

11.8.6 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.

11.8.7 Multicenter Issues

The study will be conducted at multiple investigational centers in the United Kingdom with the intention of pooling the results for analysis.

11.8.8 Multiplicity Issues

Since this is a Phase 2 study, no adjustments have been made for multiplicity.

11.9 Sample Size Determination

Data from a trial of oral vismodegib[1] given for 7 months resulted in a percent change in the sum of the greatest diameter of baseline treatment targeted SEBs of 69.2 and 13.7 with a standard deviation of 17 and 23 for treated and control subjects, respectively. A sample size of 6 subjects enrolled in each treatment group with a minimum of 5 SEBs will have greater than 95 percent power to detect a statistically significant difference at an alpha of 0.05.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Monitoring

An Investigator Meeting or an initiation visit will be conducted with the Principal Investigator and Study Coordinators 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 study monitors/clinical research associates 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.

12.2 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.

12.3 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.

13. ETHICS AND ADMINISTRATIVE ISSUES

13.1 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.

13.2 Ethics 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.

13.3 Written Informed Consent

Written 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 subjects' medical record 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.

13.4 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.

13.5 Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMB) will meet after subjects complete 10 weeks of treatment, and on an as needed basis, to review and evaluate the ongoing study safety data.

Details for the Data Safety Monitoring Committee can be found in the DSMB charter.

13.6 Financial Disclosure

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

13.7 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).

13.8 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.

13.9 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 MHRA or other regulatory body, without written consent from the sponsor.

14. DATA HANDLING AND RECORD KEEPING

14.1 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 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.

14.2 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 MHRA, 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 MHRA or other local authority regulations.

14.3 Electronic Case Report Form Completion

eCRFs will be completed for each enrolled patient. 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 patient status.

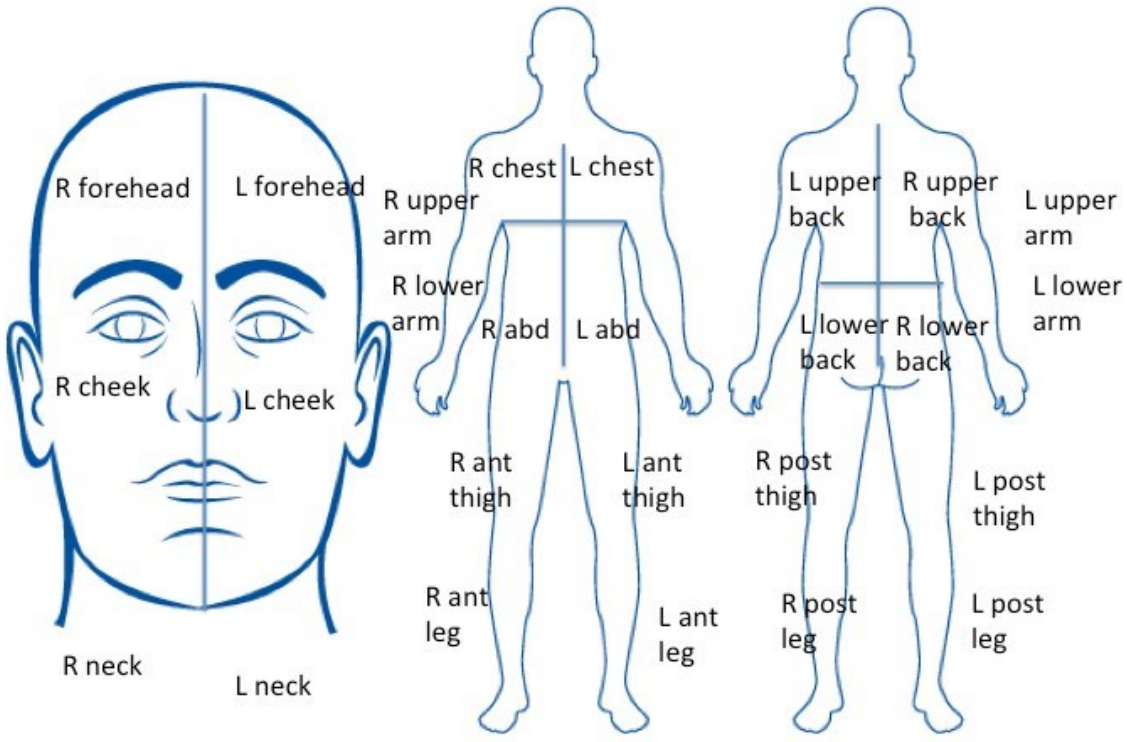
Investigators will maintain copies of the eCRFs at the clinical site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate eCRF.

15. REFERENCES

Tang, J.T., et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. 2012. *N. Engl. J. Med.* 366(23):2180-2188.

16. APPENDICES

16.1 Body Diagram



Appendix: Photographs of tumors and sequence of regional photos

1. Identify the 5 treatment targeted SEBs with labels
2. Measure greatest diameter of each tumor, perform ISTA 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
2. R cheek
3. R neck
4. L forehead
5. L cheek
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

16.2 Subject Questionnaire- DLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hosp ital No: Date:

N am e: Score: D

Add r ess : Dia gnos is :

PD

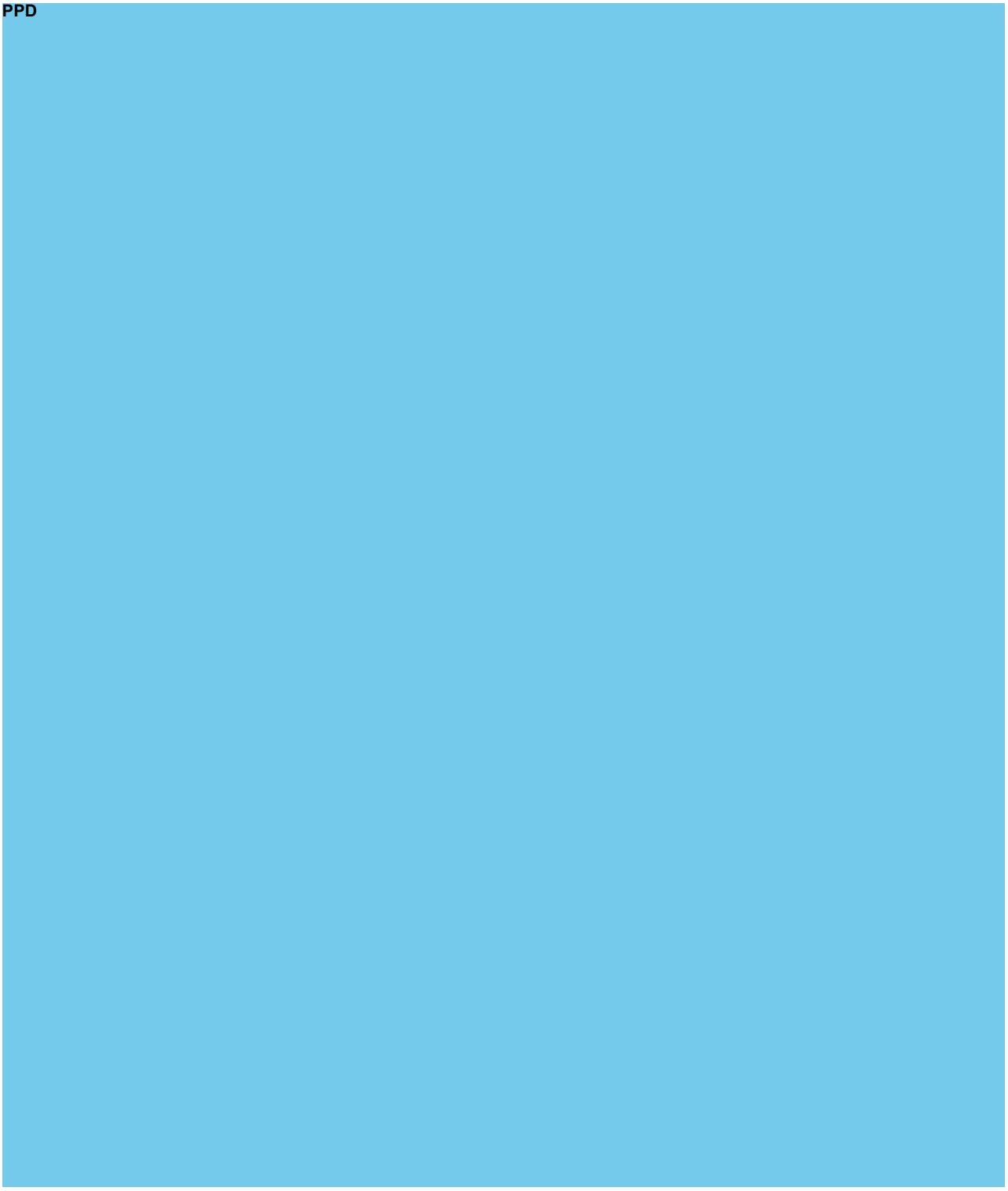
Piease cDec.11: y o u D av e a n swer e a"r; VE K Y qu esti on . J Dan.11: y o u .

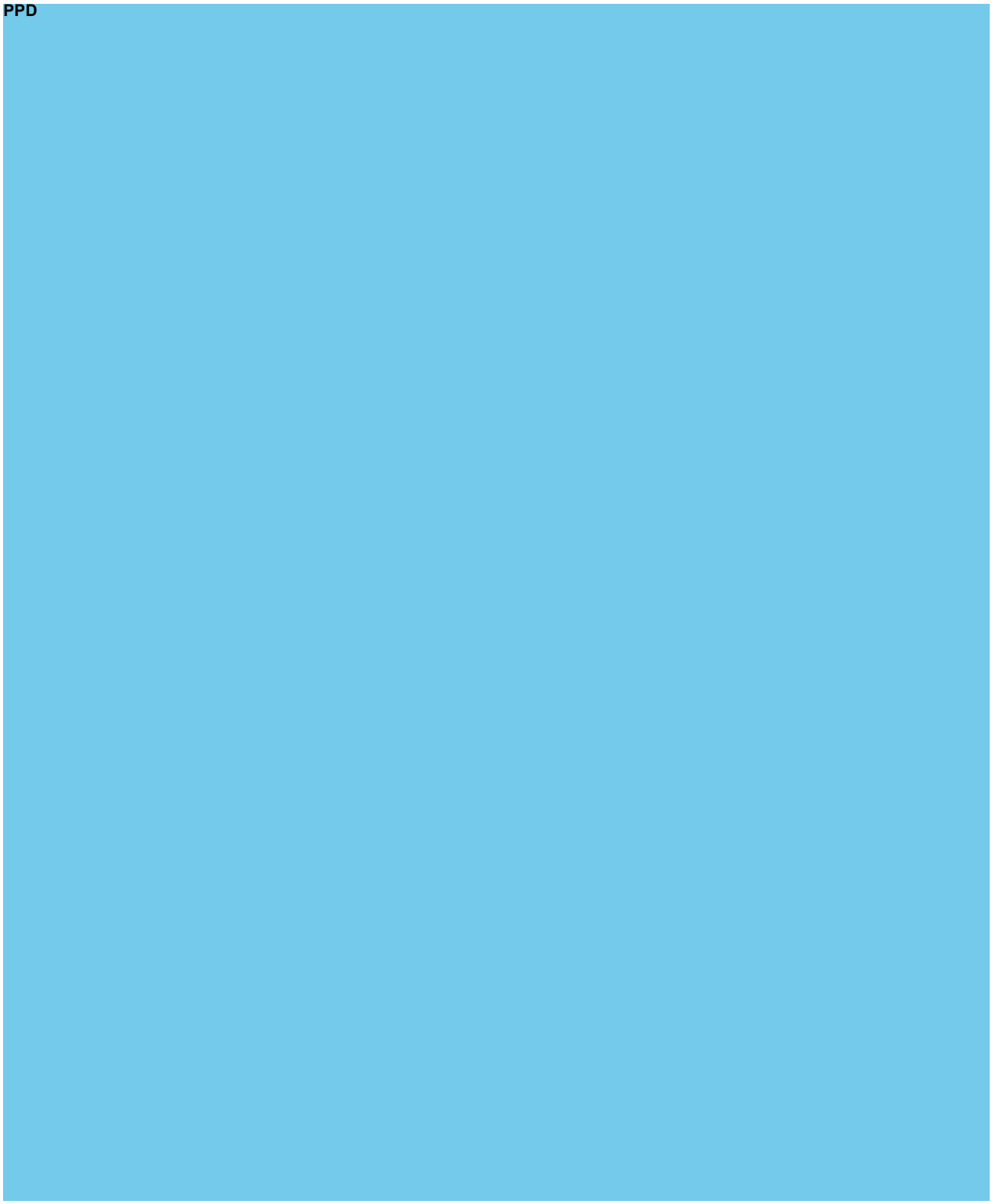
AY Finlay, OK Khan, April I 992 unw,d•rma tol= .org.uk, this must n:,t b ooq,iod witm ut h • permiuion oflh•autho<.

16.3 Subject Questionnaire – aBCCdex

General Instructions:

PPD


PPD



PPD

16.4 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.