Clinical Study Protocol

Protocol Pelle-926-301

A Multicenter, Randomized, Double-blind, Vehicle-controlled, Phase 3 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Subjects with Basal Cell Nevus Syndrome

Development Phase of Study:	3
Study design:	Multicenter, Double-Blind, Vehicle-Controlled Clinical Study
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Sponsor Representative:	[redacted]
Sponsor:	[redacted]
Version:	Original: 11 May 2018 Amendment 1: 06 Sep 2018 Amendment 2: 18 Jul 2019 Amendment 3: 04 Jan 2021

CONFIDENTIAL

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

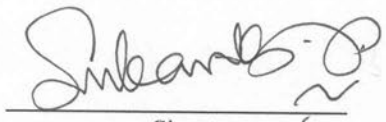
This protocol will be conducted in compliance with procedures outlined in this document, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. This study will not be initiated without the approval of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).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

Protocol Review and Approvals

A Multicenter, Randomized, Double-blind, Vehicle-controlled, Phase 3 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Subjects with Basal Cell Nevus Syndrome

Reviewed and approved:

Srikanth Pendyala, M.D.
VP, Clinical Development
PellePharm, Inc.



Signature

04-Jan-2021

Date

Principal Investigator Protocol Agreement Page

I have carefully read the protocol entitled: *"A Multicenter, Randomized, Double-blind, Vehicle-controlled, Phase 3 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Subjects with Basal Cell Nevus Syndrome"* and, I declare that, as a Principal Investigator, the clinical protocol was subject to critical review and is approved by PellePharm, Inc. (PellePharm).

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

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

Investigator Signature	Date
Printed Name	
Institution Name	
Address	
City, State/Country Zip or Postal Code	**Phone Number**

1 SYNOPSIS

Sponsor:	PellePharm, Inc. [redacted]
Title:	A Multicenter, Randomized, Double-blind, Vehicle-controlled, Phase 3 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Subjects with Basal Cell Nevus Syndrome (BCNS)
Short Title:	PATIDEGIB study
Protocol No:	Pelle-926-301
Study Regions:	United States (US), Canada, and European Union (EU)
Phase of Development:	Phase 3
Objectives:	**Primary Objective** • To assess the number of new BCCs in the 2 arms (Patidegib Topical Gel, 2%, and Vehicle) when applied twice daily to the face of subjects with Gorlin Syndrome **Secondary Objective** • To assess the safety and tolerability of Patidegib Topical Gel, 2%, in subjects treated twice daily for 12 months
Study Design:	This is a global, multicenter, randomized, double-blind, stratified, vehicle-controlled study of the efficacy and safety of Patidegib Topical Gel, 2%, applied topically twice daily to the face of adult subjects with Gorlin Syndrome. Subjects will be randomized ([redacted]) to receive either Patidegib Topical Gel, 2%, or Vehicle for 12 months. The assignment of subjects to the two groups will be stratified by gender, age [redacted]), and previous Hedgehog inhibitor (HHI) therapy. The primary endpoint is a comparison between the two treatment arms of the number of new BCCs that develop from Baseline to Month 12. BCCs will be imaged and tracked consistently throughout the study in order to identify new BCCs and new surgically eligible BCCs (nSEBs) All subjects who complete the Month 12/Exit Visit having demonstrated adequate compliance with application of the Investigational Product (IP) without major Protocol Deviations (PDs) during the study will be eligible for participation in the open-label extension study. All subjects will be contacted by phone approximately 30 days following the Exit or Discontinuation Visit to determine if the subject has experienced any new adverse events (AEs)/serious AEs (SAEs) since discontinuation/completion of study treatment.

Number of Subjects:	Approximately [redacted] subjects enrolled
Study Population:	Subjects of at least 18 years of age at the time of Screening with Gorlin Syndrome
Study Duration:	Study duration is approximately 14 months: up to 45-day Screening period, 12 months active treatment, and 30-day safety follow up. All subjects who complete the Month 12/Exit Visit having demonstrated adequate compliance with application of IP without major PDs during the study will be eligible for participation in the open-label extension study.
Criteria for Evaluation:	Key Inclusion criteria: 1. The subject must be at least 18 years old at the Screening visit. 2. The subject must meet diagnostic criteria for Gorlin Syndrome (Inclusion Criteria 3). 3. The subject must have had at least 10 (with at least 3 on the face) clinically typical BCCs present within 24 months prior to Randomization (Baseline/Day 1). Additionally, the subject must have at least 2 BCCs with longest diameter < [redacted] present on the face prior to randomization. 4. The subject must be willing to abstain from application of a non-study topical medication (prescription or over the counter) to facial skin for the duration of the trial. Key Exclusion criteria: 1. The subject has used topical treatment to the face or systemic therapies that might interfere with the evaluation of the study IP. 2. The subject is known to have a hypersensitivity to any of the ingredients in the IP. 3. The subject has uncontrolled systemic disease. 4. The subject has been treated for invasive cancer within the past 5 years excluding non-melanoma skin cancer, Stage I cervical cancer, ductal carcinoma in situ of the breast, or chronic lymphocytic leukemia (CLL) Stage 0. Full inclusion and exclusion criteria are presented in Section 7.1.
Investigational Product:	Patidegib Topical Gel, 2% (w/w), or Vehicle
Assessments:	Background and demographic assessments: Inclusion/exclusion criteria Demography Medical history Prior and concomitant medications Efficacy: BCC imaging (unmarked) BCC imaging marked (annotated) BCC identification and measurement

	Biopsy Quality of life assessments <u>Safety:</u> Dermal Safety and Tolerability Adverse Events (AEs) Safety Laboratory Tests Physical Examinations (PEs) Pregnancy tests
PK Assessment:	A single plasma sample will be collected prior to topical application of IP at the Baseline Visit and Months 3, 6, and 12 and assessed for circulating drug concentration of patidegib.
Genomic Testing (Optional):	A separate blood specimen will be collected at the Baseline Visit for genomic testing. This specimen may be used to study genetic and genomic mechanisms involved in Gorlin Syndrome pathogenesis, disease progression, and outcome. This sample should be collected at the Baseline Visit prior to dosing, but may be collected at any time during the study, if necessary. Genomic testing will not be available to study participants in Denmark due to country-specific regulations.
Statistical Methods:	**Determination of Sample Size** The sample size in this study was determined based on number of nSEBs as the original primary endpoint. In the UK Phase 2 study, the mean number of new BCC lesions at 6 months was 0.42 in the Patidegib Topical Gel, 2%, group with a standard deviation (SD) of [redacted], and a mean of [redacted] in the Vehicle group with a SD of [redacted]. The effect size was 0.81. It is assumed that at 6 months, the mean number of nSEBs in the Patidegib Topical Gel, 2%, group will be [redacted], with a SD of 0.94, while at 6 months the mean and SD in the Vehicle group will be the same as in the Phase 2 study at 6 months (see Table 4) for an effect size of [redacted]. At 12 months, it is assumed that the means and SDs will be twice those observed at 6 months. With these assumptions, 63 subjects in the Patidegib Topical Gel, 2%, group and 63 in the Vehicle group (for a total of 126 subjects) will give >90% power for a two-sided 0.05 level statistical significance. To account for a 16% drop-out rate, approximately [redacted] subjects will be randomized. Sample size was calculated based on a Wilcoxon-Mann-Whitney test, which is conservative if the underlying distribution is Negative Binomial. Given the change in primary endpoint requested by the FDA, it is acknowledged that the power for statistical significance in new BCCs may be different than what was projected before the initiation of the study, and based on nSEBs. We can however state that if the drug effect on new BCCs is the same proportion to its vehicle mean as is the drug effect on nSEBs to its vehicle mean, and if the coefficient of variations of new BCCs and nSEBs are similar, then the new BCC primary endpoint will have the same power as does nSEBs. **Statistical Analysis** The primary population for efficacy analyses will be the Intent-to-Treat (ITT) population, with the per-protocol (PP) population for supportive analyses. The

	primary endpoint is the number of new BCCs per subject that develop over 12 months. This endpoint will be analyzed using a negative binomial regression to compare treatment groups with number of BCCs at Baseline, Age [redacted] years), gender, prior HHI therapy, and geographic region as covariates. Secondary endpoints that are based on number of new BCCs or nSEBs will be analyzed similar to the primary endpoint. This includes the proportion of subjects with at least two new facial BCCs and the proportion of subjects with at least one new facial BCC. The primary method of dealing with missing data will be the multiple imputation method. Last Observation Carried Forward (LOCF) and observed case analyses will be done as sensitivity analyses. Safety endpoints will be summarized with means and standard errors, or proportions.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
aBCCdex	Advanced Basal Cell Carcinoma Index
AE	Adverse Event
ANCOVA	Analysis of Covariance
BCC	Basal Cell Carcinoma
BCNS	Basal Cell Nevus Syndrome
BID	Twice daily
CAPA	Corrective and Preventative Action Plan
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CLL	Chronic Lymphocytic Lymphoma
CMH	Cochran-Mantel-Haenszel
MP	Monitoring Plan
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol (Quality of Life) using 5 levels
EU	European Union
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HH	Hedgehog
HHI	Hedgehog inhibitor
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra-uterine device
IxRS	Interactive Web/Phone Randomization System
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Affairs
MI	multiple imputation
nSEB	New Surgically Eligible BCC
OMIM	Online Mendelian Inheritance in Man

Abbreviation or Specialist Term	Definition or Explanation
PD	Protocol deviation
PDT	Photodynamic Therapy
PE	Physical examination
PI	Principal Investigator
PP	Per protocol
PRO/ePRO	Patient Reported Outcome/electronic Patient Reported Outcome
PSCP	Primary Skin Care Physician
PTCH1	Patched Protein 1
QC	Quality Control/Quality Check
QD	Once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SEB	Surgically Eligible Basal Cell Carcinoma
TIV	Trial Initiation Visit
SMO	Smoothened
SoA	Schedule of Assessments
SPF	Sunscreen Protection Factor
PTV	Pre-Trial Visit
TEAE	Treatment-Emergent Adverse Event
US	United States
WOCBP	Woman of Child Bearing Potential

4 INTRODUCTION

Basal cell carcinomas (BCC) are slow growing tumors of the skin. They can be sporadic or inherited. Basal cell nevus (Gorlin) syndrome ([redacted][1]) (BCNS) is a rare autosomal dominant heritable disease characterized by numerous phenotypic abnormalities, most prominent among which is the development of numerous BCCs over a lifetime. Reports of its prevalence vary; the highest estimate is [redacted]. The burden of BCCs varies among Gorlin Syndrome patients. In general, Gorlin Syndrome patients have their BCCs treated as they become problematic (i.e., at risk of invasion of vital structures such as eyes, nose, or ears), large enough that scarring will be particularly noticeable if treatment is delayed, or large enough off the face such that they are uncomfortable, bleed).

Several topically-applied drugs (e.g., imiquimod and 5-fluoruracil) are used in the treatment of sporadic BCCs. Both of these can cure approximately [redacted] of the superficial subtype of BCCs, which generally occur off the face. However, they generally are not useful for nodular BCCs, which are the more prevalent subtype, especially on the face. Surgery is the definitive treatment of choice for BCC which are refractory to other interventions.

Prevention of BCCs so far has been limited to admonitions to avoid sunlight, advice which is followed infrequently by patients at risk of developing sporadic skin tumors, and which has not been shown to produce a statistically significant reduction in BCC incidence.

In 1996, two groups identified the PTCH1 gene as the locus of the mutations that cause Gorlin Syndrome.[2-4] Patients with Gorlin Syndrome have one defective heritable copy of this gene, and sporadic loss of the second allele is crucial to the development of all of their BCCs. The PTCH1 gene encodes the primary inhibitor of the hedgehog (HH) signaling pathway, and its function is to inhibit signaling by the next "downstream" member of the HH pathway – [redacted] (SMO). All Gorlin Syndrome BCCs, unlike sporadic BCCs, thus far analyzed have loss of PTCH1 without activating mutations of SMO.[5] This signaling pathway is crucial to development of many organs during embryogenesis but in adult life functions in only a limited number of sites, among which is the hair follicle. The importance of aberrant HH signaling as the driver of BCCs was proved indisputably by the strong anti-tumor effect of small molecules that down-regulate this pathway.

Following identification of uncontrolled HH signaling as the driving molecular abnormality in all BCCs, several anti-HH drugs have been developed for oral treatment of BCCs. Two of these – vismodegib and sonidegib – have been approved for systemic treatment of advanced BCCs. The latter are defined as BCCs whose surgical excision likely would produce unsatisfactory results (i.e., "locally advanced") or those which have become metastatic[6]. Approximately 50% of such BCCs fail to respond initially, frequently due to mutations in the SMOOTHENED gene, which encodes the protein to which these drugs bind. Of those that do respond, a significant proportion

develop secondary resistance, often due to mutations in the drug binding pocket of the SMO protein.[7]

Vismodegib also has been studied for efficacy vs. BCCs in patients with Gorlin Syndrome.[8] Unlike results in advanced BCCs, essentially all Gorlin Syndrome non-advanced tumors respond by shrinking and eventually most disappear completely, both clinically and histologically. The BCCs in Gorlin Syndrome patients fail to develop resistance and, so long as Gorlin Syndrome patients continue to take the drug, no nSEBs develop. The combined result of shrinkage of existing BCCs and blockage of the development of nSEBs is that these patients have no need for surgical treatment of BCCs so long as they continue to ingest vismodegib. But because of detrimental class-specific side effects, most patients discontinue vismodegib, and most/all of the clinically and histologically cleared BCCs recur to the same size as before treatment.[8] Adverse events (AEs) seen with systemic hedgehog inhibitor (HHI) include muscle spasms, alopecia, dysgeusia, nausea, fatigue, weight loss, diarrhoea and decreased appetite [Vismodegib and Sonidegib USPI].

Patidegib is a semi-synthetic small molecule which when given orally has good therapeutic efficacy for advanced BCCs but produces the same types of AEs as do other systemic HH inhibitors.

PellePharm is developing Patidegib Topical Gel, 2%, for the reduction of BCC burden in subjects with Gorlin Syndrome. Patidegib Topical Gel, 2%, is manufactured with excipients generally accepted as safe, is stable in the developed gel formulation, and can be applied to mini-pig skin without irritation. Application of Patidegib Topical Gel, 2%, significantly reduces murine BCC tumor size in vivo and reduces GLI1 biomarker expression in vitro in human BCC tumor explants.

Patidegib gel has been evaluated in 1 phase 1 and 2 phase 2 studies (UK proof-of-concept study in patients with Gorlin syndrome; and US dose escalating study for sporadic BCCs). [redacted]) in the clinical development program, including [redacted]

The proof-of-concept trial in the UK (Pelle-926-201) evaluated the safety, tolerability and efficacy of Patidegib Topical Gel, 2% and 4%, compared to vehicle in Gorlin Syndrome patients. Two of 12 topical patidegib gel-treated subjects developed new tumors compared with [redacted]).

The goal of the US dose-escalating trial (Pelle-926-202) was to evaluate patidegib topical gel's safety, tolerability, and effects on the size of preexisting, sporadic, previously untreated, nodular BCCs in sporadic BCC patients. Subjects were enrolled into 1 of 4 sequential cohorts to receive [redacted] group experienced the largest median percent decrease in greatest

diameter of treatment targeted BCCs at Week 12 ([redacted] (Patidegib Topical Gel Investigator Brochure [IB]).

Overall patidegib has been found to be safe and well tolerated in previous studies. This trial will evaluate the safety and the ability of Patidegib Topical Gel, 2%, to reduce the development of BCCs in subjects with Gorlin Syndrome.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to assess the number of new BCCs in the 2 arms (Patidegib Topical Gel, 2%, and Vehicle) when applied twice daily to the face of subjects with Gorlin Syndrome.

5.2 Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of Patidegib Topical Gel, 2%, in subjects treated twice daily for 12 months.

6 OVERALL STUDY DESIGN AND PLAN

This is a global, multicenter, randomized, double-blind, stratified, vehicle-controlled study of the efficacy and safety of Patidegib Topical Gel, 2%, applied topically twice daily to the face of adult subjects with Gorlin Syndrome. Subjects will be required to apply the IP for 12 months. The primary endpoint is a comparison between the two treatment arms of the number of new BCCs that develop over the 12 month period. BCCs will be imaged and tracked consistently throughout the study in order to identify new BCCs and nSEBs.

An open-label extension safety and tolerability study is planned for at least 12 months duration following the end of this study. All subjects who complete the Month 12/Exit Visit having demonstrated adequate compliance with application of the IP without major Protocol Deviations (PDs) during the study will be eligible for participation in the extension study.

The principal investigator (PI) or designee will be responsible for the oversight of the study at their clinical trial site.

6.1 Rationale for Study Design

The key elements of the study design are choice of the primary endpoint, stratification, eligibility criteria, disease severity, a relatively longer treatment duration (12 months) than that in the Phase 2 Gorlin Syndrome study (treatment duration 6 months), the methodology for measurement of BCCs, and the use of imaging to track BCCs.

6.1.1 Choice of Primary Endpoint

The primary endpoint of the study is a comparison between treatment arms of the number of new BCCs per subject that develop over the 12 month period. BCC surgery has significant morbidity (e.g., scarring, functional loss of eyelid, nose, ear) and most BCCs in patients with Gorlin syndrome are ultimately removed by surgery. Reduction in the number of facial BCCs and in the number of resulting BCC surgeries are serious unmet medical needs and the number of BCCs and number of nSEBs are therefore considered appropriate correlating study endpoints.

Generally, a facial BCC of longest diameter [redacted] is considered a SEB.[8] In this study, a BCC is considered a nSEB if the diagnosis was verified histologically, it was not a SEB at Baseline, **and** post Baseline the BCC was either surgically removed because of the development of possible functional facial/health impairment, as determined by the Investigator **or** met objective size criteria (irrespective of whether or not it was surgically removed). These objective criteria are that post Baseline, the BCC has a longest diameter [redacted] mm in longest diameter from Baseline**.**

6.1.2 Stratification Parameters

The study design incorporates stratification to ensure that potential Baseline confounders of efficacy are distributed evenly across treatment arms. The assignment of subjects into the study is being stratified based on Gender, Age and previous HHI therapy.

Gender is a potential confounder as female subjects had more tumor response compared with male subjects in the prior Pelle-926-202 Phase 2 study. However, both females and male subjects treated with active treatment had fewer nSEBs compared with subjects treated with vehicle. Female subjects may have higher topical compliance as seen in other topical trials.[9] Gender will be used as a stratification factor in this Phase 3 trial.

Previous HHI therapy might also confound the assessment of efficacy. In the trial of oral vismodegib for subjects with Gorlin Syndrome, the rate of development of nSEBs was lower after vismodegib was discontinued ([redacted]) than it had been during placebo treatment prior to vismodegib treatment ([redacted]).[8] It is also likely that it is the subjects with more severe disease that are prescribed oral HHIs. For these reasons, previous HHI therapy is a stratification parameter.

Advanced age has been found to correlate with higher numbers of BCCs and new tumors in Gorlin Syndrome subjects from a natural history study.[10] Age is therefore a stratification factor to avoid confounding age-related rates of Baseline tumor progression across treatment groups.

6.1.3 Treatment Duration

The duration of treatment in the phase 2 UK study in Gorlin Syndrome patients (Pelle-926-201) was 6 months. A 12-month study increases the likelihood for the occurrence of new BCCs and nSEBs when compared to a 6-month study. This is also appropriate given that BCC are innately slowly developing tumors. A 12-month safety database will also further inform the overall benefit-risk of patidegib topical gel as a chronic therapy in Gorlin Syndrome.

6.1.4 BCC Tracking

The study design ensures that BCCs are tracked consistently throughout the study. The 12 months treatment duration necessitates the diligent tracking and photography of BCCs to assist the PI with tumor identification and measurement recall. This is accomplished by capturing standardized unmarked digital images of the face at every visit (unmarked). Marked (annotated) images will also be collected in addition to unmarked images at prespecified visits (see Table 1). Pelle-926-201 also included imaging to track BCCs.

At visits prior to IP application (i.e., Screening and Baseline), a second set of digital images (annotated images) will be captured, after the BCCs on the face have been identified, labeled, and numbered for tracking purposes. It is possible that in some instances at Screening and/or Baseline all BCCs cannot be tracked (labeled and numbered) due to limited space for stickering on the face. In such situations, the BCCs will be tracked in order of decreasing (longest) BCC diameter. It is of critical importance that **all** SEBs are identified in the images.

At prespecified post-Baseline visits, the PI will track and measure BCCs for a second set of (marked) images. For a given subject, each BCC will be given the same tracking number as

assigned prior to IP application, and all new tumors identified will be given new sequential numbers.

6.1.5 BCC Measurement

The primary endpoint requires that all Baseline BCCs be eliminated from consideration as new BCCs, and that all BCCs are identified and tracked for growth into nSEBs or for possible clinical resolution. At Baseline for all BCCs that have been tracked, the longest diameter will then be measured by the Investigator using a standardized method. SEBs identified at Baseline will not qualify to be called nSEBs.

At prespecified post-Baseline visits, the Investigator will identify (label and number) all BCCs that were tracked prior to IP application start and will identify any new BCCs that have appeared since start of IP application. At these pre-specified post-Baseline visits, the Investigator will review the BCCs and identify BCCs that may be approximately [redacted]) in size. The Investigator will measure the longest diameter for these BCCs, identify them as new or previously existing SEBs, and flag them on the label. Throughout the study for any given subject each BCC will have the same number.

Qualified, trained, and blinded Image Data Quality Reviewer (s) will examine each set of subject images (1) to determine the accuracy of mapping annotations, and (2) to rule out wild transcription or transposition reporting errors in BCC diameter. The Image Data Quality Reviewer (s) may query the Investigator, as appropriate. The Investigator may review the query and correct, as appropriate. The Investigator's decision of the BCC diameter and surgical eligibility is final.

6.1.6 Eligibility Criteria and Disease Severity

Patidegib topical gel is being evaluated in subjects with Gorlin Syndrome. Gorlin Syndrome is typically diagnosed clinically, based on the major and minor diagnostic criteria which are reflected in the inclusion criteria[6].

The protocol requires that the subject must have had at least 10 (with at least 3 on the face) clinically typical BCCs present within 24 months prior to Randomization (Baseline/Day 1). This is to ensure that subjects with moderate to severe Gorlin Syndrome who are most likely to benefit from treatment are enrolled.

Additionally the subject must have at least 2 BCCs with longest diameter <5 mm present on the face prior to Randomization (Baseline/Day 1). This increases the possibility for developing a nSEB during the study.

6.2 Dose Rationale

The PK data from the UK Phase 2 Proof-of-Concept (Pelle-926-201) study showed 1/6 subjects on Patidegib Topical Gel, 4% had a detectable patidegib concentration in plasma at Week 14 ([redacted]) and 1/6 subjects had a detectable concentration at Week 26 ([redacted]). No

subjects on Patidegib Topical Gel, 2% had detectable concentrations (Patidegib Topical Gel IB). The tumors treated with Patidegib Topical Gel, 2% had at least as much efficacy as the Patidegib Topical Gel, 4%. The Patidegib Topical Gel, 4% group had treatment-related application site AEs (e.g., rash, dermatitis, pain, facial alopecia) that were mild-moderate in 4/6 subjects. In contrast, no treatment related AEs were seen in the Patidegib Topical Gel, 2% group (data on file, clinical study report [CSR]).

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion/Exclusion Criteria

7.1.1 Subject Inclusion Criteria

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

1. The subject must be at least 18 years old at the Screening Visit.
2. The subject must provide written informed consent prior to any study procedures.
3. The subject must meet diagnostic criteria for the basal cell nevus (Gorlin) syndrome including major criterion #3a plus 1 additional major criterion or plus 2 additional minor criteria listed below.

   Major criteria:
   a. >2 histologically confirmed BCCs or 1 for subjects under age 20.
   b. Odontogenic keratocysts of the jaw confirmed histologically.
   c. ≥3 palmar and/or plantar pits seen at the Screening Visit.
   d. Bilamellar calcification of the falx cerebri present at less than 20 years old.
   e. Fused, bifid, or markedly splayed ribs.
   f. First degree relative with Gorlin Syndrome.
   g. PTCH1 mutation predicted to be of functional significance in normal tissue.

   Minor criteria:
   a. Macrocephaly.
   b. Congenital malformations including frontal bossing, cleft lip or palate, "coarse face", moderate to severe hypertelorism.
   c. Skeletal abnormalities detectable clinically: Sprengel deformity, marked pectus deformity, or marked finger syndactyly.
   d. Skeletal abnormalities detectable radiographically: bridging of the sella turcica; vertebral abnormalities such as hemivertebrae, fusion or elongation of the vertebral bodies; modeling defects of the hands and feet; flame shaped lucencies of the hands or feet.
   e. Ovarian fibroma.
   f. Medulloblastoma
   (*modification of criteria of V Kimonis et al Am J Med Genet 69: 299-308, 1997*[11])
4. The subject must have had at least 10 (with at least 3 on the face) clinically typical BCCs present within 24 months prior to Randomization (Baseline/Day 1). Additionally, the subject must have at least 2 BCCs with longest diameter <5 mm present on the face prior to Randomization (Baseline/Day 1).
5. The subject must be willing to have blood collected to measure circulating drug levels.
6. The subject must be willing to abstain from application of a non-study topical medication (prescription or over the counter) to facial skin for the duration of the trial except as prescribed by the Investigator. Moisturizers and emollients are allowed. Subjects will be encouraged to use their preferred sunscreen with a sunscreen protection factor (SPF) of at least 30 daily on all exposed skin sites.

7. If the subject is a woman of child bearing potential (WOCBP), she must be willing to use complete abstinence from sexual intercourse and/or she and her partner must be willing to use at least 2 highly-effective forms of birth control starting prior to Baseline, through the duration of the study, and for 12 months after last application of IP (Section 8.1).
8. If the subject is a male with a female sex partner who is a WOCBP, the subject must be willing to use condoms, even after a vasectomy, starting prior to Baseline, through the duration of the study, and for at least 8 months after the last application of IP.
9. The subject is willing for all facial BCCs to be evaluated and treatment recommendations made only by the Investigator.
10. The subject is willing to forego treatment of facial BCCs with anything other than the study IP except when the Investigator believes that delay of treatment of a facial BCC potentially might compromise the health of the subject. During the trial the only allowed form of treatment is surgical. Non-facial BCCs may be removed at the discretion of the Investigator or Primary Skin Care Physician (PSCP).

7.1.2 Subject Exclusion Criteria

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

1. The subject has previously participated in a clinical trial evaluating patidegib topical gel.
2. The subject has used topical treatment to the face or systemic therapies that might interfere with the evaluation of the study IP. Among these are use of the following:
   [redacted]
   c. [redacted]
   [redacted]
3. The subject is known to have a 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 to the study site for all study visits and tests.
5. The subject has uncontrolled systemic disease.
6. The subject has been treated for invasive cancer within the past 5 years excluding non-melanoma skin cancer, Stage I cervical cancer, ductal carcinoma in situ of the breast, or chronic lymphocytic leukemia (CLL) Stage 0.
7. The subject has current, recent (within five half lives of the experimental drug or if half life not known, within the past 6 months prior to the Screening Visit), or planned participation in an experimental drug study while enrolled in this study.
8. The subject is a WOCBP who is unwilling or unable to comply with pregnancy prevention measures.
9. The subject is pregnant or breastfeeding.

10. 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 may include a history of other skin conditions (e.g., severe facial eczema) or diseases, metabolic dysfunction, physical examination (PE) 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 subject at high risk from treatment complications.

7.2 Concomitant Medications and Treatments

All medications listed as exclusion criteria cannot be taken concomitantly during the study.

During the study, subjects will be allowed to use moisturizers and emollients and will be encouraged to use sunscreen of at least 30 SPF at least once daily on all exposed skin sites. Subjects must wait 30 minutes after IP application before applying any moisturizer, emollient, or sunscreen.

Facial BCCs may be removed at the discretion of the Investigator by the Investigator or a competent physician/surgeon at any time after the Baseline Visit if the Investigator believes that continued growth of the BCC might have deleterious effects on the health of the subject. Non-facial BCCs may be removed at the discretion of the Investigator or PSCP.

7.3 Study Drug Discontinuation

The Investigator has the right to permanently discontinue IP application of a subject at any time if in their opinion the continuation of the IP is deleterious to the subject's health or discontinuation is in the subject's best interest. If the subject becomes pregnant, IP will be discontinued immediately.

If, for any reason, a subject is discontinued during the treatment period prior to Month 12/Exit Visit, 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. At the 30 day follow up additional information may be collected. All data gathered on the subject will be made available to PellePharm.

7.4 Subject Withdrawal Criteria

The Investigator may consider discontinuing a subject with a major protocol violation or deviation (e.g., failure to meet study enrollment criteria, use of disallowed medications). However, an excessive rate of discontinuation can render the study uninterpretable; therefore, unnecessary discontinuation of subjects should be avoided. A protocol violation or deviation does not in itself necessarily constitute grounds for removal of the subject from the trial if the subject's safety is not compromised.

A subject has the right to withdraw from the study at any time for any reason, without prejudice, and is under no obligation to disclose the reason. Once a subject has withdrawn from the study, no additional information can be collected. All data gathered on the subject prior to withdrawal from the study will be made available to PellePharm.

7.5 Study Discontinuation or Termination

The study may be discontinued by PellePharm in any of, but not limited to, the following events:

- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties with subject recruitment that make it likely enrollment goals cannot be met.

8 STUDY PROCEDURES AND ASSESSMENTS

The study will be conducted as outlined in the schedule of assessments (SoA) (Table 1). All study visits will take place in person at the study site/clinic, except for the 30-day safety follow-up visit, which will be by phone call. All subject information and data obtained during the study visits will be recorded in the source documents, applicable study logs, and electronic case report forms (eCRFs), as appropriate.

Investigators (and any designee) must have appropriate, documented experience and training, or obtain approval from PellePharm based on experience (or through additional training organized and provided by PellePharm [or designee]). Sites will undergo a feasibility assessment, and a formal Pre-Trial Visit (PTV) conducted by the study Clinical Research Organization (CRO) (or designee). Sites that meet the requirements to conduct a study according to Good Clinical Practice (GCP) and applicable local and country regulatory requirements, as well as Investigator and site personnel with demonstrated experience and qualifications will be approved by PellePharm or designee to conduct the study. The CRO will continue the site activation process to assist sites to receive IRB approval and IP shipment and conduct of a Trial Initiation Visit (TIV) prior to the enrollment of subjects into the study for each site. In addition, at least one and preferably two site personnel will be trained in the image capture method by the imaging vendor as part of the site activation process. A back-up image capture site staff member should be available as needed.

At each study visit, every attempt should be made to ensure that the same Investigator assesses the same subject. PellePharm 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 PI. Tasks and responsibilities are delegated by the PI, and the PI is responsible for the conduct of the study at their site as well the training and oversite of all site personnel and other related non-site personnel. There are specific tasks that PellePharm requires be done by a licensed physician with appropriate experience. As outlined below and in the SoA (Table 1), these tasks include SEB biopsy procedure, assessment and reporting, BCC measurement and assessment, and recording application site reactions. The surgical excision of the BCC may be done by the Investigator or may be referred to a licensed physician with appropriate experience.

PellePharm also realizes that scheduling visits can be challenging and has allowed for flexibility with study visit days. It should be noted that the indicated visit day is in reference to the Baseline Visit. For example, the Month 8 visit is intended to be 8 months after the Baseline Visit. A month will be considered to have approximately 30 days.

8.1 Study Procedures

The SoA is provided in Table 1. Subjects should be seen for all visits on the designated day or as close as practically possible. The Baseline Visit may take place no more than 45 days after the Screening visit. If this period exceeds 45 days, subjects will need to be re-screened.

The assessments/procedures to be performed at the different visits are elaborated here.

8.1.1 Informed Consent

All subjects must provide written informed consent before any study related procedures are performed. Each subject will receive a copy of the signed consent form. Subjects may be pre-screened (chart review, etc.) for eligibility prior to any study related procedure.

8.1.2 Inclusion and Exclusion

Following provision of informed consent from each subject, the Investigator will determine whether subjects meet the inclusion/exclusion criteria.

A WOCBP is defined as a woman who (a) has not undergone hysterectomy or bilateral oophorectomy or (b) has not been naturally post-menopausal for at least 24 consecutive months (i.e., has had no menses in the 24 preceding months).

A WOCBP may be enrolled if she agrees to complete abstinence from sexual intercourse or the couple agrees to use at least 2 forms of birth control as defined by the use of a condom with spermicide in association with one of the following: 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 the Baseline Visit, or hormonal intra-uterine device (IUD) inserted at least 1 month prior to the Baseline Visit.

8.1.3 Randomization

Details on randomization are available in Sections 9.1 and 9.2.

8.1.4 Demographics

Subject's date/year of birth, gender at birth, race and ethnicity will be recorded in the eCRF, where allowed by local regulatory authorities. Race and ethnicity will not be collected in countries where prohibited.

8.1.5 Medical History

Subjects' relevant family history of Gorlin Syndrome and medical history pertinent to eligibility criteria will be collected. Information about medical conditions that resolved 2 or more years prior to Screening do not need to be recorded unless considered relevant by the Investigator.

8.1.6 Prior and Concomitant Medications

Prior and concomitant medications will be captured separately for BCC (facial) and other indications.

All medications ongoing in the 12 months prior to Baseline or ongoing at any time during the study will be recorded in the eCRF. The start date for all medications that were started during the study period must be reported. Likewise, the end date for all medications that were discontinued during the study period must be captured.

8.1.7 IP Application

For the first application, the subject will apply the IP at the study site under the direction of the Study Coordinator (or designee). The IP should be applied after all clinical assessments. Additional information on IP application is available in Section 10.4.

8.1.8 Compliance

The site pharmacist (or designated site personnel) will collect and weigh the previously dispensed IP tubes to assess compliance with IP dosing for the preceding month. The weight of the IP tubes will be recorded on the appropriate eCRF. See Section 9.4 and the Pharmacy Manual for full details on assessing compliance.

8.1.9 Unscheduled Visit

Subjects may return to the site for unscheduled visits in the event of an AE, SAE or as deemed necessary by the Investigator. The same procedures as described in the post-Baseline Visits may be conducted. For other subject care management, the Investigator may refer the subject to their primary care physician and/or their PSCP. Data collected will be reported in the 'Unscheduled Visit' eCRF page.

8.2 Efficacy Assessments

8.2.1 BCC Imaging

Digital imaging of the BCCs will be taken using a [redacted]. Subjects with facial hair should be encouraged to remove or at least to clip short any facial hair so that any BCCs present within the facial hair region will be easily identifiable on the captured images. Subjects must remove make-up prior to the facial exam. Photos will be taken to assess 5 views of the face in the same plane of an arc at a fixed distance from the face ([redacted]). The unmarked and marked digital facial images will uploaded to the imaging vendor portal for further review. Full details for image capture can be found in the Image Review Work Instruction.

8.2.1.1 BCC Imaging (Unmarked)

Take photos of the subject's unmarked face using the camera as described above for unmarked imaging.

8.2.1.2 BCC Imaging Marked (Annotated)

Following image capture of the subject's unmarked face, repeat the process and annotate the image by:

a. Identifying all BCCs, dot around border and place a sticker (1, 2, etc.). Record the measurement of the longest diameter of each BCC. BCCs in the region of the eyelids or posterior to the tragus are not numbered and tracked.
b. Marking each SEB ([redacted]) with a red dot on the sticker to indicate the BCC as a SEB or nSEB.

c. Taking a photo of face again with markings and stickers.
d. Uploading unmarked and marked digital facial images to the imaging vendor portal for further review.

8.2.2 Biopsy

All biopsies are to be done at the clinical trial site. Prior to the biopsy, the image data quality reviewer will confirm that the BCC has been tracked consistently throughout the study. However, if the surgeon or Investigator feels that continued growth of a nSEB can pose a significant problem, then it can be biopsied and removed at any time. The biopsy will be reviewed and reported by a licensed physician with appropriate experience. The biopsy diagnosis will be captured in the eCRF. The detailed report of the biopsy will be part of the source document. Additionally biopsy slides and photomicrographs will be retained at the site. The biopsy report, slides and photomicrographs must be made available for the study monitor or an audit by the Sponsor and/or Regulator.

If the Investigator feels that continued growth of a nSEB can pose a significant problem, then a biopsy can be done at anytime, followed by surgery as required.

8.2.3 Quality of Life Assessments

Patient reported outcome (PRO) or electronic PRO (ePRO) will be collected as outlined in Table 1. [redacted]

Table 1 provides the SoA for the study.

Table 1: Schedule of Assessments

Procedure	Pre-treatment	Treatment													F-Up
	Screening[c] (-45 days)	Baseline[a] (Day 1)	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	Mo 10	Mo 11	Mo 12	30 Days[b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 (Exit)**	**15**
Informed Consent[c]	X														
Inclusion/Exclusion	X	X													
Demographics	X														
Medical history[d]	X														
Current/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam **(including vital signs)**[e]	X	X	X		X			X			X			X	
Clinical laboratories and urinalysis	X	X	X		X			X			X			X	
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of contraceptive requirements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK sample collection[m]		X (predose)			X			X						X	
Genomic sample collection (Optional)[n]		X													
Digital imaging (unmarked)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Digital imaging (marked) and BCC measurement	X	X			X			X			X			X	
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
[redacted]		[redacted]						[redacted]						[redacted]	
[redacted]					X			X			X			X	
Randomization		X													
Dermal Safety and Tolerability	X	X			X			X			X			X	
Adverse events[h,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]													
[redacted]		[redacted]													
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense IP		X	X	X	X	X	X	X	X	X	X	X	X		

[a] The Baseline Visit may take place no more than 45 days after the Screening Visit. If this period exceeds 45 days, the subject will need to be re-screened.

[b] The safety follow-up phone call will be conducted 30 days following the subject's Exit or Month 12 visit.

[c] Before signing the informed consent, site staff will review/explain the nature of the study and subject expectations to ensure the subject meets study requirements .

[d] Review of systems (including the presence or absence of hair loss and change in frequency of shaving, dysgeusia, and muscle cramps), relevant family history of Gorlin Syndrome, and medical history pertinent to eligibility criteria.

[e] Physical examinations will include collection of vital signs and weight (and height at Baseline only). Additional PEs may be collected according to any signs/symptoms and/or positive findings at previous PE.

[f] WOCBP only: Serum pregnancy test at Screening and Month 12/Exit Visit, and serum or urine pregnancy tests at all other visits.

[g] SEB will typically be biopsied after confirmation that lesion has been tracked consistently. However, if the surgeon or Investigator feels that continued growth of a nSEB can pose a significant problem, then it can be biopsied and removed at any time.

[h] AEs that occurred after signing of the informed consent will be recorded.

[i] Subjects may return to the site for unscheduled visits in the event of an AE or SAE or as deemed necessary by the Investigator. The same procedures as described in the post-Baseline Visits may be conducted. For other subject care management, the Investigator may refer the subject to their primary care physician and/or their PSCP.
[j] Subjects will be trained on how to appropriately apply IP and comply with study procedures. Additional reminders may be provided at subsequent visits, as appropriate.
[k] IP is administered after all other assessments are completed and is followed by a 30-minute observation period.
[l] All IP tubes (used, partially used, and/or unused) will be returned and weighed. The weight will be recorded on the appropriate eCRF.
[m.] At Baseline, PK samples will be collected prior to the first dose and the date and time of the first dose will be recorded. Post-Baseline, the date and time of the last dose prior to collection of the PK sample must be recorded.
[n.] Genomic testing will not be available to study participants in Denmark due to country-specific regulations.
[o.] Patients who fail screen may be rescreened. The patient will need to meet all criteria at rescreen and baseline. Baseline should occur within 45 days of the rescreen.

8.3 Safety Assessments

The safety assessments in the study include vital signs, AEs, dermal safety, and laboratory assessments (Section 11.1).

8.3.1 Dermal Safety and Tolerability Events

Safety and tolerability will be evaluated through assessment of selected local signs and symptoms (pain/burning, pruritus, erythema, edema, and crusting) on the face. Any local skin reaction that requires use of a concomitant therapy or causes interruption or discontinuation of the IP should be reported as a dermal safety event. These events will be assessed for severity, relative to the skin reactions scale (Table 2).

Table 2: Dermal Safety and Tolerability Scales

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

**Enrollment in this table refers to both Screening and Baseline Visits*

8.3.2 Physical Examination and Vital Signs

Physical examinations (PEs) including vital signs (blood pressure, heart rate, respiration rate, and temperature) will be collected and reported. Height will be collected at the Baseline Visit only. Clinically significant changes from Baseline will be captured as AEs. Changes in BCC measurements and BCC count will be captured separately as efficacy (imaging and tracking) assessments and not as a PE assessment. Changes in BCC count or size will not constitute AEs.

PEs are also done at quarterly visits. Additional PEs at other visits may be collected according to any signs/symptoms and/or positive findings at previous PE.

8.3.3 Laboratory Assessments

Routine safety laboratory tests (complete blood count/differential, urinalysis, and serum chemistry) will be performed as per the SoA (Table 1) and Appendix 17.1. Any out-of-range laboratory result that is considered clinically significant by the Investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the Investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the Baseline state) or until clinically stable as determined by the Investigator until the study database is closed.

8.3.4 Pregnancy Tests

All WOCBP will have a serum pregnancy test as per the SoA (Table 1), and serum or urine pregnancy tests at all other study visits. If the WOCBP becomes pregnant during the course of the study, she must immediately stop applying the IP and report the finding to the Investigator. Potential teratogenicity should be discussed at each visit with WOCBP and with male subjects with partners who are WOCBP.

8.4 Other Assessments

8.4.1 PK Assessments

A plasma sample will be collected prior to application of IP per the SoA (Table 1). At Baseline, PK samples will be collected prior to the first dose and the date and time of the first dose will be recorded. Post-Baseline, the date and time of the last dose prior to collection of the PK sample must be recorded.

8.4.2 Genomic Sample

A separate, specific signature will be required to document a subject's agreement to provide additional samples for optional genomic research. From subjects who agree to participate and provide their additional, specific consent, a blood specimen will be collected at the Baseline Visit for genomic testing. This specimen will be used to study genetic and genomic mechanisms involved in Gorlin Syndrome pathogenesis, disease progression, and outcome. Stored specimens may also be used to evaluate the association of genetic and genomic

markers with study drug response, including metabolism and/or AEs and to determine future treatment predictions for patidegib topical gel and/or other approved or exploratory medications. This sample should be collected at the Baseline Visit prior to dosing, but may be collected at any time during the study, if necessary.

[redacted]

9 TREATMENT PLAN

9.1 Methods of Assigning Subjects to Treatment Groups

This is a double-blind study. The study site will assign each consented subject a unique [redacted] subject number consisting of the [redacted] study site number and the [redacted] chronological Screening order number, starting with [redacted] Site numbers will be assigned by country and/or region. Subjects who progress to enrollment in the study will retain their Screening number upon Randomization.

The IP accountability log will be completed by the site pharmacist (or qualified designee), and the IP tubes will be provided in a single boxed kit containing 3 tubes of IP gel. It is recommended that subjects use tubes consecutively, exhausting the first tube before opening and beginning use of subsequent tubes.

Subjects will be stratified for enrollment based on the following criteria:

1. [redacted])
2. Gender at birth
3. History of prior HHI therapy [redacted])

9.2 Randomization and Blinding

The IPs will be packaged and labeled identically, and the IP kits will be numbered and dispensed according to the subject's assigned randomization number for the study. IP supplies will be distributed to the study site to maintain the randomization ratio.

As a double-blinded study, the Investigators, the site staff, PellePharm, and the Clinical Monitor(s) will be blinded to the treatment assigned to individual subjects. Delegated staff members at the study site will dispense the IP and will collect and weigh all used and unused IP tubes, as scheduled.

9.3 Unblinding

In the case of a medical emergency, subject symptoms must be treated empirically. There is no known antidote for patidegib. In a medical emergency, unblinding may not necessarily improve the care of the subject.

Unblinding may be considered when there are two or more identical SAEs that are unexpected but considered related to study drug. Should the Investigator feel that unblinding is essential, the Investigator should endeavor to contact the PellePharm designated Medical Monitor to further discuss the situation.

9.4 Treatment Compliance

Subjects will be required to return the IP tubes that are used and/or unused. Each subject will be instructed on the importance of both the application of the IP and return of the used and

unused IP tubes. Each tube will be weighed when returned and the results will be entered on the source document and eCRF.

Any interruptions in the schedule of IP administration or use of prohibited concomitant medication will be recorded in the eCRFs.

9.5 Protocol Deviations

A PD is any change, divergence, or departure from the study design or procedures defined in the protocol. Major PDs are a subset of PDs that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.[12] If a major (important) PD has been identified, it should be communicated to and discussed with the Medical Monitor. A corrective and preventative action (CAPA) plan may be required to be instituted in the case of major PDs at the site. In the event of recurring major PDs, the site enrollment may be halted by the Medical Monitor, in consultation with PellePharm, until a CAPA plan has been instituted and the issue(s) resolved. PDs should be reported on at least an annual basis to the Central IRB or the site's local IRB/IEC.

that may compromise the IP shipment will require that the IP kits are quarantined until review by the Study Monitor.

For IP received undamaged, IP will be inventoried and the IP inventory/accountability log completed. IP will be stored in a [redacted] in a secure and restricted location.

Upon enrollment and randomization of a subject, the pharmacist (or designee) will select the IP kit based on the randomization number provided by the Interactive Web/Phone Randomization System (IxRS). The initial application of the IP will take place in the clinic under observation. No other IP applications at subsequent visits will be required to be observed in the clinic setting. However, where it is suspected that inappropriate amounts of IP are being applied by the subject (based on tube weights) further review of IP application in the clinic may be warranted.

The subject will return all IP gel tubes (used, partially used, and/or unused) at their subsequent study visit. If any IP gel tubes are lost or damaged between clinic visits, additional IP may be provided to the subject. The goal is to ensure that the subject has an adequate supply of IP to be able to administer all scheduled treatments.

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

10.3 Storage and Handling of Investigational Product

The IP tubes should be stored [redacted]

10.4 Application

The Investigator or site personnel will instruct the subject on how to apply the IP at the Baseline Visit and the subject will apply the IP at that visit under observation. The IP should be applied to the face, which will be defined as the area extending from the anterior hairline to the jaw line (except the eyelids) including the ears. If the anterior hairline is receding, application of IP to the forehead will extend no more than 9 cm above the eyebrow or superior orbital ridge.

The Investigator or site personnel 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, written and/or other media IP application instructions may be provided to the subjects.

Subjects should be encouraged to keep facial hair short enough to allow adequate application of IP to the face, and subjects must remove make-up prior to IP application.

Subjects will be instructed to wash their face and hands within approximately 10 minutes prior to IP application. Subjects will apply their first dose at the study site under observation.

Subjects will apply to the face an amount squeezed out as a specified amount on a laminated dosing card ([redacted]), avoiding the eyelids (as described above and in the Pharmacy Manual). If no observable AEs are noted within a [redacted] observation period after their first application, subjects can leave the site. Subjects will be advised to minimize exposure to direct sunlight while in the study and to wash their hands before and after application of the IP.

[redacted]. If an IP application has been missed or delayed such that there would be [redacted] between applications, the subject should not apply that dose of IP and just wait to apply the next dose. The importance of IP compliance should be discussed with the subject during each site visit.

Subjects will be instructed to store their IP in a secure location away from children. WOCBP should not come in contact with the gel unless avoiding pregnancy.

The amount of IP used by the subjects will be monitored by weighing each returned IP tube at all applicable study visits. If it is suspected that inappropriate amounts of IP are being applied by the subject (based on tube weights) further review of IP application in the clinic may be warranted.

10.5 Investigational Product Accountability and Disposal

Upon receipt of the IP, the Investigator (or designee, e.g., study center pharmacist) will acknowledge receipt of the IP after reviewing the shipment's content and condition. The Investigator (or designee) is responsible for ensuring that the designated study site staff conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. The Investigator (or designee) must agree to keep all study materials in a secure location with restricted access. The Investigator (or designee) will keep a record of the inventory and dispensing of all IPs. This record will be made available to the Study 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 of IP administered at the study center will be administered by qualified study center staff. At each site visit, IP compliance will be discussed with the subject.

At the end of the study, following final IP inventory reconciliation by the monitor, the study site will dispose of and/or destroy all supplies (including used, partially used, and/or unused tubes of IP) where possible, in compliance with the site's SOPs for IP disposal/destruction. In the event that the site is unable to dispose of and/or destroy IP supplies, the Sponsor will be notified and a third-party vendor may be contracted to manage destruction of IP supplies.

Refer to the Pharmacy Manual for additional details about IP accountability procedures, including the IP accountability log.

11 SAFETY INSTRUCTIONS AND GUIDANCE

11.1 Adverse Events

11.1.1 Definition of Adverse Event

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

Subjects will be questioned about any concurrent illness or systemic sign or symptom. Any incidence of these systemic signs or symptoms will be reported on the AE eCRF.

Vital signs and laboratory 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). A laboratory abnormality that is part of an efficacy endpoint (e.g., histologic confirmation of BCC on a biopsy) is not to be reported as an AE.

An unexpected AE is one that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.

11.1.2 Documenting Adverse Events

It is the responsibility of the Investigator to document in the eCRF all AEs/SAEs that occur during the course of the study. AEs/SAEs should be collected after the informed consent form is signed and usually at the Screening visit. The AEs/SAEs should be documented as a single medical diagnosis. When this is not possible, the AE/SAEs 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/SAEs occurring after the subject signs the informed consent through the last study visit must be reported, regardless of whether or not the AEs/SAEs are considered drug-related. All AEs/SAEs, 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 requiring a concomitant therapy or discontinuation from the study will be reported as an AE/SAE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)

- Onset date and end date
- Maximum severity
- Seriousness
- Action taken regarding IP
- Corrective treatment, if given
- Outcome

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

It is not necessary to capture multiple occurrences of an AE separately if the event recurs at short intervals. In such instances the end date of the AE is the date when the event resolved last and did not recur. If however the event recurs after long intervals, then the subsequent event may be captured as a separate event. The PI may use his discretion to determine what constitutes a long or short interval between events and which event is reported once versus more than once. Furthermore, protocol defined end points (e.g new BCCs on the face, nSEBs on the face and BCC surgeries on the face) will be summarized as efficacy parameters and are not to be reported as AEs/SAEs.

In the clinical database, all AEs including SAEs are to be followed for a minimum up to the 30 day follow up visit. In the source documents, any and all AEs including SAEs must be thoroughly documented to conclusion or in the opinion of the investigator, the event has resolved or stabilized.

11.1.3 Serious Adverse Events

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

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

- Results in death
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a condition present at Screening is not considered an AE)
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent any of the above listed outcomes

If the BCC surgery requires as per standard of care, that the patient be hospitalized, then this hospitalization is not an SAE.

Note: A spontaneous abortion will be considered an SAE and must be reported per Reporting of SAEs under Section 11.1.6. Pregnancy in and of itself is not an SAE, but a subject who becomes pregnant must discontinue IP application immediately and the pregnancy will be followed to term (and ideally the child will be followed afterward if the subject consents) or termination. Any birth defect or other serious issue that may arise during the pregnancy or due to fetal exposure will be considered an SAE.

11.1.4 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

11.1.5 Assessment of Causality

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

- Positive temporal relationship to IP, such as if the IP was discontinued 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 IP 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. **Not Related**: No relationship between the experience and the administration of IP; related to other etiologies such as concomitant medications or subject's clinical state.
2. **Unlikely**: The current state of knowledge indicates that a relationship is unlikely.

3. **Possibly**: A reaction that follows a plausible temporal sequence from administration of the IP and follows a known response pattern to the suspected IP. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
4. **Probably:** A reaction that follows a plausible temporal sequence from administration of the IP and follows a known response pattern to the suspected IP. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
5. **Definitely**: A reaction that follows a plausible temporal sequence from administration of the IP and follows a known response pattern to the suspected IP and can be confirmed with a positive re-challenge test or supporting laboratory data.

11.1.6 Reporting of Serious Adverse Events

SAEs will be captured in both the clinical and safety database.

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signs the informed consent) and throughout the duration of the study and for 30 days following the last IP application will be captured in the clinical database via the eCRFs (Section 11.1.2).

SAEs also will be captured in the safety database. An initial SAE Report must be completed for all SAEs (irrespective of relatedness) with an onset date within 30 days from the date of last IP application. An initial SAE Report must also be completed for Related SAEs (possibly, probably or definitely) regardless of the time elapsed from the last dose (even if the study has been closed).

When new, significant information for an SAE is obtained, as well as when the outcome of an SAE is known, the Investigator must submit a Follow-Up Report. If the subject was hospitalized, a copy of the discharge summary must be included as part of the subject's medical file. For related events, the Investigator should monitor the subject until the outcome of the SAE is known. This may require periodic Follow-Up Reports.

PellePharm and the study CRO must be notified of all SAEs (regardless of causal relationship to IP) within 24 hours of the Investigator's knowledge of the event by faxing or emailing a completed SAE report to the CRO Medical Monitor.

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

11.1.7 Emergency Contact

In the event of a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of

investigational drug), investigational site personnel should endeavor to contact the Medical Monitor to discuss the situation.

11.1.8 Expedited Serious Adverse Event Reports

An AE, whether serious or non-serious, is designated unexpected if it is not reported in the reference safety section of the IB or if the event is of greater frequency, specificity or severity than so reported.

PellePharm will notify regulatory authorities of unexpected related SAEs and all participating study sites in writing for submission by the Investigator to the IRB/IEC. This notification will be in the form of a Safety Update to the IB (i.e., “15-day letter”).

Upon receiving such notices, the Investigator must review and retain the notice with the IB 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.

12 STATISTICS

All statistical processing will be performed using SAS® unless otherwise stated. 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, standard deviation (SD), median, minimum, and maximum.

The multiple imputation (MI) method will be the primary method for dealing with missing data. Last Observation Carried Forward (LOCF) and observed case analyses will be done as sensitivity analyses.

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.

12.1 Analysis Population

The primary population for efficacy analyses will be the Intent-to-Treat (ITT) population, defined as all subjects who were randomized. Subjects will be assigned to treatment groups as randomized. The per-protocol (PP) population will be used for supportive efficacy analyses. Subjects will be assigned to treatment groups as treated (not as randomized). The Safety population will consist of all subject who have applied IP at least once.

12.2 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.

12.3 Demographics and Baseline Characteristics

Subject demographic data and Baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT population.

12.4 Protocol Deviations

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

12.5 Compliance

Compliance will be tracked throughout the study. Results of compliance assessments (weight of returned drug, etc.) will be tabulated, and descriptive statistics will be used to compare the 2 groups. For the per protocol population, a sensitivity analysis will be conducted based on compliance.

12.6 Assessment of Efficacy

12.6.1 Efficacy Summaries

The efficacy endpoints are intended to compare twice daily application of Patidegib Topical Gel, 2%, and Vehicle. Efficacy assessments will be summarized descriptively by treatment group and visit.

12.6.1.1 Primary Endpoint

The primary endpoint is the number of new BCCs per subject by Month 12.

12.6.1.2 Secondary Endpoints

The secondary efficacy endpoints are:

1. The number of nSEBs per subject by Month 12.
2. The proportion of subjects developing ≥2 facial new BCCs by Month 12.
3. The proportion of subjects developing ≥1 facial new BCCs by Month 12.
4. The number of new BCCs per subject by Month 9.
5. The number of new BCCs per subject by Month 6.
6. aBCCdex change in Lesion Symptoms scale score from Baseline to Month 12.

An nSEB is a histologically verified BCC that was surgically removed because of possible functional facial/health impairment as determined by the Investigator.

Also, nSEBs are facial BCCs with a longest diameter of [redacted] that:

a. were not surgically eligible BCCs (SEBs) at Baseline,
b. have grown by [redacted] in longest diameter from Baseline, and
c. have been verified histologically.

12.6.1.3 Exploratory Endpoints

The exploratory endpoints are:

1. The proportion of SEBs that undergo clinical resolution at Month 12.
2. The number of BCC surgeries from Baseline to Month 12.
3. Change in aBCCdex Worry About Future Lesions scale score from Baseline to Month 12.
4. Change in aBCCdex Mental Health scale score from Baseline to Month 12.
5. Change in aBCCdex Social/Relationships scale score from Baseline to Month 12.
6. Change in aBCCdex Life Impact scale score from Baseline to Month 12.

12.6.2 Efficacy Analyses

The primary endpoint is the number of new BCCs per subject that develop from baseline to Month 12. The number of new BCCs that develop from Baseline to Month 12 will be analyzed using a negative binomial regression to compare treatment groups with number of BCCs at Baseline, Age [redacted]), gender, prior HHI therapy, and geographic region strata (North America, Europe) as covariates. PROC GENMOD of SAS will be used with distribution=Negbin.

In order to assess the impact of parametric assumptions, a non-parametric rank analysis of covariance (ANCOVA, Stokes et al) will be provided as a sensitivity analysis with number of BCCs at Baseline, prior HHI therapy, gender, age [redacted]), and geographic region as covariates.

The Negative Binomial regression was selected as the primary method of analysis to account for the potential for overdispersion. Using the Negative Binomial model, the power will be somewhat higher than the one calculated using a non-parametric Wilcoxon-Mann-Whitney test. The proposed sensitivity analysis, Rank ANCOVA, was selected to corroborate the results from the Negative Binomial model. If the distribution is markedly different from Negative Binomial (and unknown to sufficiently allow a different parametric regression model), then the non-parametric ANCOVA gives type-1 error closer to the nominal level.

The number of nSEBs that develop from Baseline to Month 12 will be analyzed using a Negative Binomial regression to compare treatment groups with number of BCCs at Baseline, Age [redacted]), gender, prior HHI therapy, and geographic region as covariates. Secondary endpoints that are based on number of new BCCs will be analyzed similar to the primary endpoint. The proportion of subjects with at least two new BCCs lesions and the proportion of subjects with at least one new BCC lesion will be analyzed using a logistic regression to compare treatment groups with number of BCCs at Baseline, Age [redacted]), Gender, and prior HHI therapy and geographic region as covariates. Change in aBCCdex will be analyzed using an ANCOVA model with treatment group as a main effect, Baseline aBCCdex, prior HHI therapy, gender, age strata, and geographic region as covariates. Testing of secondary endpoints will be done sequentially at a two-sided 0.05 level.

The primary method for dealing with missing data will be the MI method discussed in detail in Section 12.7.6.

LOCF and observed case analyses will be done as sensitivity analyses.

12.7 Assessment of Safety

Safety results will be summarized with means and standard errors, or proportions. Treatment-emergent AEs (TEAEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Previous and Concomitant drugs will be coded using the WHO-Drug dictionary.

12.7.1 Dermal Safety and Tolerability

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

12.7.2 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 IP, corrective treatment, outcome, and Investigator's assessment of causality. All AEs will be recorded and classified using terminology from the MedDRA. All reported TEAEs, defined as any AE with an onset on or after the date of first IP application, or worsening of an AE with an onset prior to first IP application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to IP. When summarizing TEAEs by severity or relationship to IP, 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 IP.

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 IP, corrective treatment, outcome and relationship to the IP. 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.

12.7.3 Physical Examination Including Vital Sign Results

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

12.7.4 Safety Laboratory Values

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

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Screening to Baseline (Day 1) and at Months 1, 3, 6, 9, and Month 12/Exit Visit. Normal ranges established by the local laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment

time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each Investigator and reported as an AE accordingly. In addition, a listing of all clinically significant laboratory test results will be provided.

12.7.5 Pregnancy Tests

Pregnancy test results will be presented in a data listing.

12.7.6 Handling of Missing Data

The primary method for dealing with missing data will be the MI method. The MI model will be detailed in the SAP. One hundred imputations will be generated using PROC MI of SAS. Fully Conditional Specification (FCS) model will be used with either new BCCs or nSEBs at prior post-Baseline visits, treatment group, number of BCCs at Baseline, prior HHI therapy, gender, age strata, and geographic region as covariates to impute the data. The seed to be used is 20180330. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

LOCF and observed case analyses will be done as sensitivity analyses.

12.7.7 Multicenter Issues

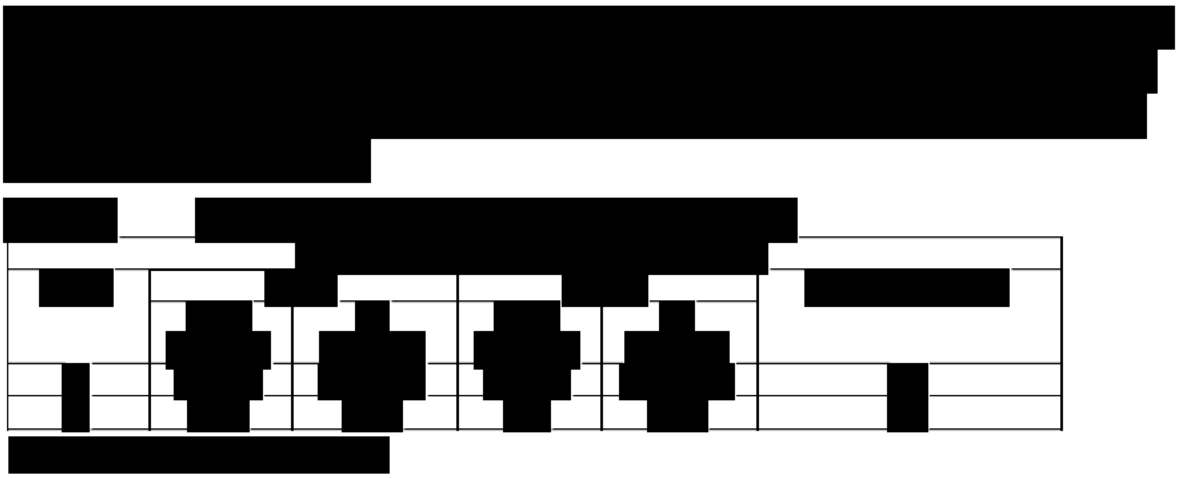
For the purpose of the summaries and analyses, the term ‘Center’ will be used to define each study site. All data collected from participating Centers will be monitored and reviewed as specified in this protocol.

Approximately 50 Centers are planned in this study to enable a sufficient number of subjects to be enrolled. In the event that a Center has low numbers of subjects enrolled, pooling of results for Centers may be performed. The algorithm for pooling of Centers will be described in the SAP. Descriptive summary statistics will be generated including Center and pooled-Center (when appropriate) by primary and secondary efficacy endpoints.

12.7.8 Multiplicity Issues

Testing of secondary endpoints will be done sequentially at a two-sided 0.05 level.

12.8 Sample Size Determination



secondary (original primary) endpoint of number of nSEBs per subject at Month 12 may be affected by follow-up time. Based on the Phase 2 study, it is projected that the power calculated above will be substantially similar in this Phase 3 study population to that observed in the Phase 2 trial unless marked differences are seen between the treatment arms in follow-up time. The power calculation is based on a Wilcoxon-Mann-Whitney test which is conservative if the underlying distribution is Negative Binomial.

Given the change in primary endpoint requested by the FDA, it is acknowledged that the power for statistical significance in new BCCs may be different than what was projected before the initiation of the study, and based on nSEBs. We can however state that if the drug effect on new BCCs is the same proportion to its vehicle mean as is the drug effect on nSEBs to its vehicle mean, and if the coefficient of variations of new BCCs and nSEBs are similar, then the new BCC primary endpoint will have the same power as does nSEBs.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study Monitoring

An Investigator Meeting and/or a TIV will be conducted with the PI, Sub-Investigator(s), Study Coordinator(s) and other site personnel present. During the TIV the following items will be reviewed/discussed: IB review; key elements of the protocol including but not limited to the eligibility criteria, safety monitoring, endpoints, and image capture (with additional training and review by the imaging vendor); site personnel roles and responsibilities; all study procedures; source documents; IP application; compliance monitoring; and eCRFs completion.

Use of the image capture system will require training and qualification by the Imaging Vendor prior to site personnel being allowed to capture subject facial images.

The CRAs will be trained to the protocol and undergo CRO-specific training. Specific monitoring guidelines (Monitoring Plan [MP]) and procedures to be followed during monitoring visits will also be utilized. During the course of the study, source documents will be verified by the CRAs and the percentage of Source Data Verification detailed in the MP. All subject source records must be made available to the CRAs.

The conduct of the study will be closely monitored by PellePharm following GCP guidelines. A risk assessment and mitigation plan will be prepared in collaboration with PellePharm and the study CRO prior to enrollment of the first subject at the Baseline Visit. PellePharm will also provide Vendor and CRO oversight as part of PellePharm's responsibilities.

In addition, inspections or on-site audits may be carried out by local authorities or by PellePharm. The PI will allow members of PellePharm, the study CRO, and any regulatory agency access to examine all study records, corresponding subject medical records, clinical dispensing records and storage area, and any other documents considered source documentation. The PIs agree to assist the representative(s) as required.

13.2 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 the study CRO and/or PellePharm's QA Department or designee.

PellePharm 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, PellePharm will be responsible for securing agreement from all involved parties to ensure direct access to all study sites, source data/documents, eCRFs, and reports for the

purpose of monitoring and auditing by PellePharm, and inspection by domestic and foreign regulatory authorities.

13.3 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 PellePharm or designee. Subjects will be identified in the eCRFs by their assigned subject number only.

The Investigators must read the protocol thoroughly and must follow the instructions. Any deviations should be agreed to by prior discussion between PellePharm 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 PellePharm.

14 ETHICS AND ADMINISTRATIVE ISSUES

14.1 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.

14.2 Independent Review Board Review

This protocol, proposed informed consent form and other information provided 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 PellePharm and Investigator prior to study initiation. The name and occupation of the chairman and members of the IRB/IEC will be supplied to PellePharm. The Investigator will provide required progress reports and report all SAEs to the IRB/IEC as required by the IRB/IEC.

14.3 Informed Consent

An IRB-approved Informed Consent Form (ICF) that displays the version and date of approval is required for completion by signature from each subject prior to conduct of any study procedures under this protocol, including Screening tests and evaluations. The ICF, as specified by the investigational site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 Code of Federal Regulations Part 50.

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

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

14.4 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. Any individual data listings required to be presented to comply with regulatory requirements will be de-identified prior to disclosure.

14.5 Financial Disclosure

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

14.6 Investigator Obligations

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

14.7 Changes to the Protocol

The Investigators must read the protocol thoroughly and must follow the instructions. Waivers for enrollment should be avoided, and PellePharm does not plan to provide any waivers. Any amendment to the protocol containing major modifications 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 PellePharm.

14.8 Confidentiality

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 study CRO, FDA or other regulatory body, without written consent from PellePharm.

15 DATA HANDLING AND RECORD KEEPING

15.1 Inspection of Records

Investigators must maintain detailed records on all 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 study CRO and/or PellePharm. Source documents include subject medical records, hospital charts, site 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 study CRO and/or PellePharm, 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 the ICF 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 IP accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion or until the event has stabilized in the opinion of the Investigator
- 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, PellePharm, or PellePharm's designee concerning the study must be recorded or kept on file. All source documents must be made available to PellePharm and PellePharm's designated monitor upon request.

15.2 Retention of Records

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

The Investigator will allow representatives of PellePharm's monitoring team, the governing IRB/IEC, the FDA or other applicable local authorities to inspect all study records, eCRFs, and corresponding portions of the subject's study site 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 eCRF, and compliance with FDA or other local authority regulations.

15.3 Electronic Case Report Form Completion

eCRFs will be completed for each enrolled subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status. The eCRFs should be completed within 48 hours of the subject visit.

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

16 REFERENCES

1. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib: a syndrome. New England Journal of Medicine 1960;262:908-12.
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8. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. New England Journal of Medicine 2012;366:2180-8.
9. Harper J, et al. The efficacy and tolerability of dapsone 5% gel in female versus male patients with facial acne vulgaris: Gender as a clinically relevant outcome variable. Poster Presented at the Fall Clinical Dermatology Conference. Las Vegas, NV. October, 2010.
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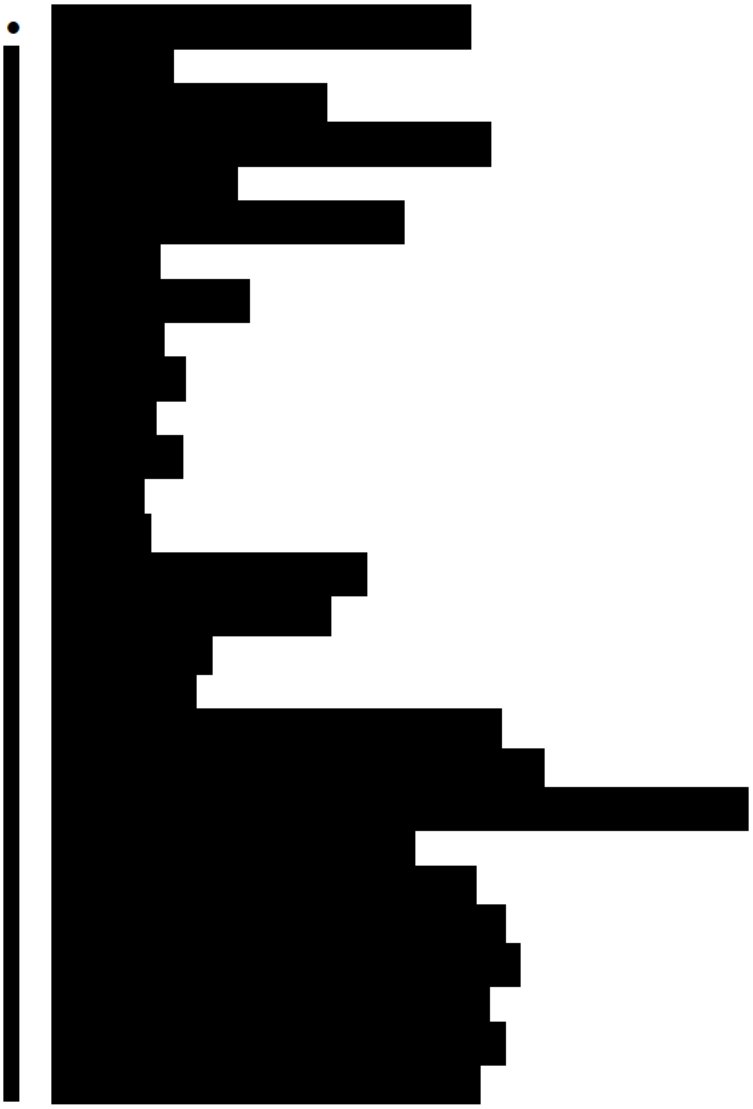
17 APPENDICES

17.1 Safety Laboratory Tests

The following blood samples for laboratory tests will be collected:



Urinalysis with microscopic examination.

17.2 Patient Reported Outcomes (PRO) Questionnaires

- Appendix 17.2.1 Advanced Basal Cell Carcinoma index (aBCCdex) (4 pages)
- Appendix 17.2.2 Skindex-16 administration (2 pages)
- Appendix 17.2.3 Dermatology Life Quality Index (DLQI) (2 pages)
- Appendix 17.2.4 EuroQol Group 5-level EQ-5D (EQ-5D-5L) (3 pages)

General Instructions:

Please answer each question to the best of your ability.

There are no right or wrong answers.

These questions ask you about your symptoms and your functioning and well-being. For each question, please choose the response that best describes your experience during the past week.

Your responses will be confidential and will be summarized with other study participant's responses.

[redacted]

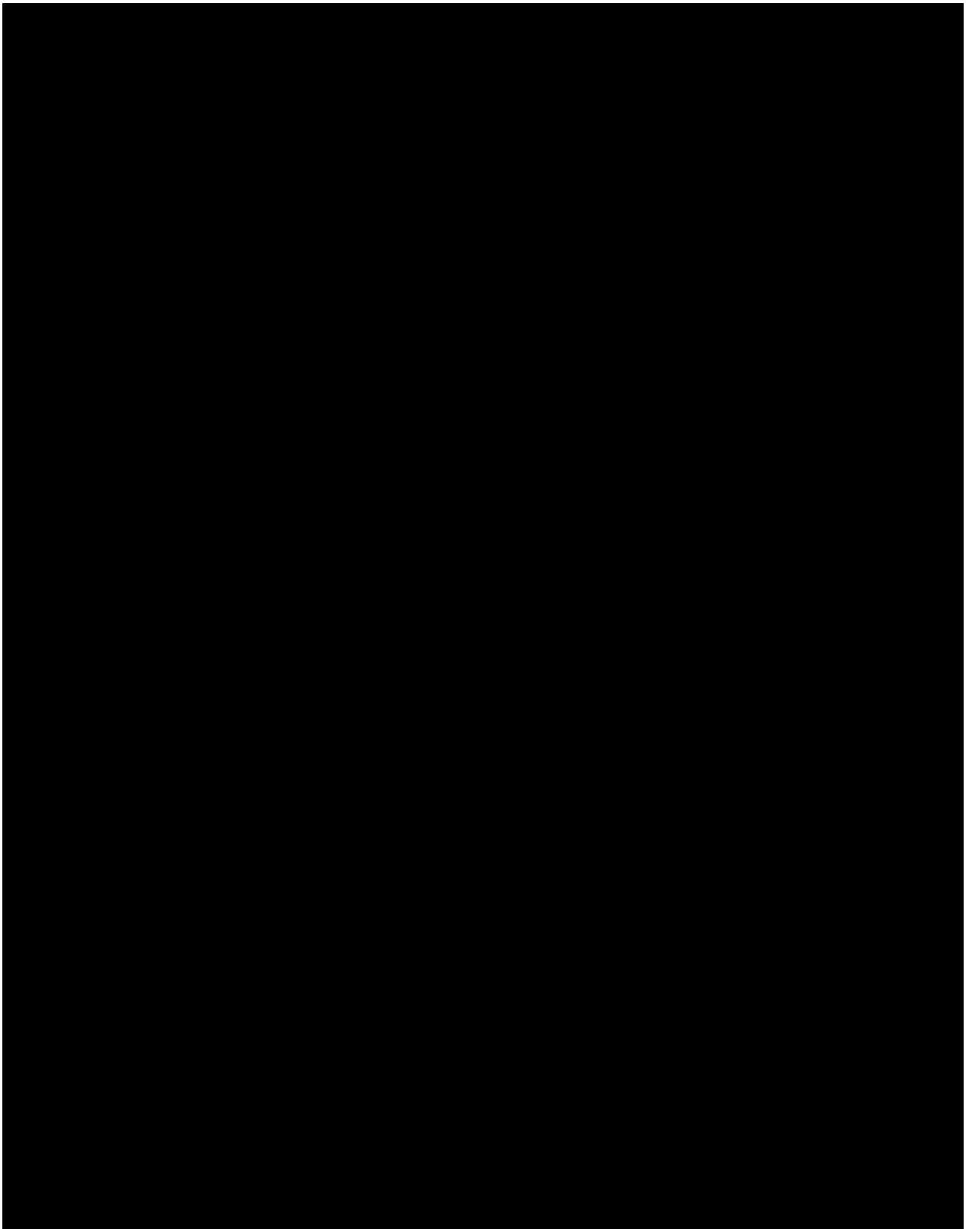
2. People sometimes experience **<u>different emotions</u>** because of their condition. Please indicate **how much of the time** you had these emotions during the **<u>past week</u>** as a result of your advanced BCC [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]						
[redacted]						

3. Please circle the <u>one number</u> that comes closest to indicating **how worried** you were about the following issues in the **<u>past week</u>** as a result of your advanced BCC or BCCNS.

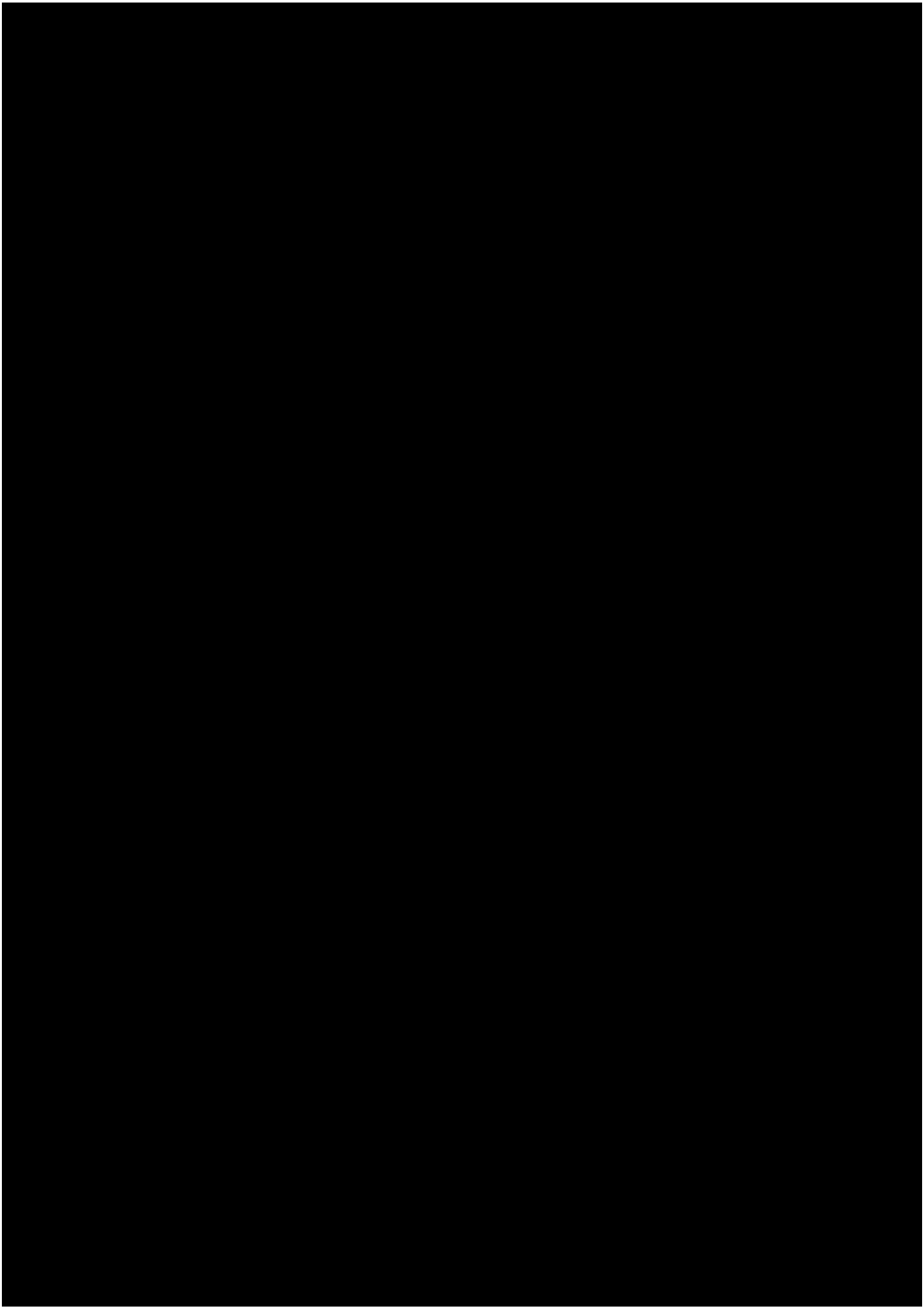
4. Many people make changes to their lifestyle <u>as a result of their condition</u>. Please indicate **how often** you **AVOIDED** each of the following activities in the **<u>past week</u>** as a result of your advanced BCC or BCCNS.

5. Advanced BCC and BCCNS can affect many aspects of a person's life. In this next section, please indicate **how much** you **agree or disagree** with each statement.



[redacted]

Have you answered every item? Yes ☐ No ☐



DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

[redacted]

of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

[redacted]

REFERENCES

Finlay AY and Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19:**210-216.

Basra MK, Fenech R, Gatt RM, Salek MS and Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159:**997-1035.

Hongbo Y, Thomas CL, Harrison MA, Salek MS and Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *J Invest Dermatol* 2005; **125:**659-64.

There is more information about the DLQI, including over 85 translations, at www.dermatology.org.uk. The DLQI is copyright but may be used without seeking permission by clinicians for routine clinical purposes. For other purposes, please contact the copyright owners.

Health Questionnaire

English version for the USA