NCT04155190

Clinical Study Protocol

Protocol Pelle-926-203

A Multicenter, Randomized, Double blind, Vehicle-controlled, Phase 2 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Patients with Non-Gorlin High Frequency BCC

Development Phase of Study:	2
Study design:	Multicenter, Double-Blind, Vehicle-Controlled Clinical Study
IND #:	125,461
Eudra CT number:	2018-001462-42
Sponsor Representative:	[redacted]
Sponsor:	[redacted]
Version:	Original: 28 August 2019

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). Any changes to the protocol will be approved in writing by the IRB 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 2 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Patients with Non-Gorlin High Frequency BCC



Principal Investigator Protocol Agreement Page

I have carefully read the protocol entitled: *"A Multicenter, Randomized, Double blind, Vehicle-controlled, Phase 2 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Patients with Non-Gorlin High Frequency BCC"* 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) and the competent authority, if applicable.

I understand that any substantial changes to the protocol must be approved in writing by the IRB 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 2 Efficacy and Safety Study of Patidegib Topical Gel, 2%, for the Reduction of Disease Burden of Persistently Developing Basal Cell Carcinomas (BCCs) in Patients with Non-Gorlin High Frequency BCC
Short Title	PATIDEGIB Phase 2 study in non-Gorlin HF-BCC subjects
Protocol No	Pelle-926-203
Study Regions	United States (US) and Australia
Phase of Development	Phase 2
Objectives	**Primary Objective** • To assess the number of new surgically eligible BCCs (nSEBs) in patients treated with Patidegib Topical Gel 2% or Vehicle when applied twice daily to the face of subjects with non-Gorlin HF-BCC **Secondary Objective** • To assess the safety and tolerability of Patidegib Topical Gel, 2%, in subjects treated twice daily on the face
Study Design	This is a 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 non-Gorlin HF-BCC. Subjects will be randomized ([redacted]) to receive either Patidegib Topical Gel, 2%, or Vehicle for 9 months. Randomization will be stratified by gender. The primary endpoint is the number of nSEB that develop on the face over the 9 month period. The primary end point will be assessed by imaging and tracking of BCCs consistently throughout the study in order to identify nSEBs.
Number of Subjects	Approximately [redacted] subjects
Study Population	Subjects of at least 18 years of age at the time of Screening with non-Gorlin HF-BCC Non-Gorlin HF-BCC patients are defined as subjects whose BCCs are phenotypically similar to that in patients with Gorlin syndrome (basal cell nevus syndrome; BCNS) with respect to BCC development, but who do not meet the diagnostic criteria for Gorlin syndrome.
Study duration	Study duration is approximately 10.5 months: up to 14-day screening period, 9 months of active treatment, and a 30-day safety follow up.
Criteria for Evaluation	**Key Inclusion Criteria** 1. The subject must be at least 18 years old at the Screening Visit. 2. The subject must have had at least 10 (with at least 3 on the face) clinically typical BCCs present within 24 months prior to Screening and Randomization (Baseline/Day 1). Additionally, the subject must have at least 2 BCCs with longest diameter [redacted] present on the face prior to Screening and Randomization (Baseline/Day 1).

	3. 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. **Key Exclusion Criteria** 1. The subject has been previously diagnosed with Gorlin syndrome 2. On medical history, family history or clinical examination there is a suspicion that the patient has Gorlin syndrome. The diagnostic criteria for Gorlin syndrome are available in Appendix 17.3. 3. Patients with a family history of medulloblastoma 4. The subject has used topical treatment to the face or systemic therapies that might interfere with the evaluation of the study IP. 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. Full inclusion and exclusion criteria are presented in Section 7.1
Investigational Product (IP)	Patidegib Topical Gel, 2% (w/w), or Vehicle. The IP will be applied to the face.
Assessments	Background and demographic assessments Inclusion/exclusion criteria Demography Medical history Prior and concomitant medications Efficacy BCC imaging (unmarked) BCC imaging (marked) BCC identification and measurement Biopsy Quality of life assessments Safety Dermal safety and tolerability Adverse events Safety laboratory tests Physical examinations Pregnancy tests
PK Assessment	A single plasma sample will be collected at the Baseline Visit (predose) and at Months 3 and 6. Plasma will be assessed for circulating concentrations of patidegib and potentially, select metabolites.
Genomic testing	Blood will be collected for genomic testing for pathogenic variants of the (patched 1) PTCH1 gene and to identify mutations that may result in the development of a high frequency of BCC, such as mutations in DNA repair genes. BCC biopsy samples will be collected, stored and tested later, if warranted, to understand mechanisms leading to

	a decreased response to hedgehog inhibitors (HHI). Genomic testing for PTCH1 gene is mandatory for all study participants with the rest being optional.
Statistical methods	**Analysis populations** The intent-to-treat (ITT) population will comprise all randomized subjects. The modified ITT (mITT) population will comprise all patients in the ITT population, excluding those who tested positive for pathogenic variants in the PTCH1 gene. The mITT population will be the primary efficacy analysis population. Safety analyses will be done on all randomized subjects who had at least one application of study treatment. **Sample size** The study is not powered for statistical significance. With [redacted] randomized subjects in the mITT population, the estimated effects will have the following precision (Standard Error): Number of new SEBs: It is assumed that in the active group, there will be [redacted] new SEBs per-subject, with a SD of [redacted]. The SE of the estimate will be [redacted]. The vehicle group is estimated to have [redacted] new SEBs per-subject, with an SD of [redacted]. The SE of the estimate will be [redacted]. These estimates are based on Gorlin patients in the phase 2 study Pelle-926-201. If the distribution of new SEBs is Poisson, then the actual SE may be smaller than estimated here. **Methods of analysis** The number of new SEBs will be analyzed using a poisson regression with treatment, baseline number of BCCs that are not SEBs, and stratification factors as covariates. If the Poisson assumption does not hold, a non-parametric analysis of covariance will be the primary method of analysis. Multiple imputations will be the primary method for dealing with missing post-baseline data for the primary endpoint

2 TABLE OF CONTENTS

1 SYNOPSIS 4
2 TABLE OF CONTENTS 7
3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 11
4 INTRODUCTION 13
5 STUDY OBJECTIVES 15
5.1 Primary Objective 15
5.2 Secondary Objective 15
6 OVERALL STUDY DESIGN AND PLAN 16
6.1 Rationale for Study Design 16
6.1.1 Choice of Primary Endpoint 16
6.1.2 Stratification Parameters 16
6.1.3 Treatment Duration 16
6.1.4 BCC Tracking 17
6.1.5 BCC Measurement 17
6.1.6 Eligibility Criteria and Disease Severity 18
6.1.7 Genomic testing 19
6.1.8 Contraception and duration of contraception 19
6.2 Dose Rationale 20
6.3 Benefit-risk Assessment 20
7 SELECTION AND WITHDRAWAL OF SUBJECTS 22
7.1 Inclusion/Exclusion Criteria 22
7.1.1 Subject Inclusion Criteria 22
7.1.2 Subject Exclusion Criteria 22
7.2 Concomitant Medications and Treatments 23
7.3 Study Drug Discontinuation 24
7.4 Subject Withdrawal Criteria 24
7.5 Study Discontinuation or Termination 24
8 STUDY PROCEDURES AND ASSESSMENTS 25
8.1 Study Procedures 26
8.1.1 Informed Consent 26
8.1.2 Inclusion and Exclusion 26
8.1.3 Randomization 26
8.1.4 Demographics 26
8.1.5 Medical History 26
8.1.6 Prior and Concomitant Medications 26

8.1.7 IP Application 26
8.1.8 Compliance 27
8.1.9 Unscheduled Visit 27
8.2 Efficacy Assessments 27
8.2.1 BCC Imaging 27
8.2.2 Biopsy 27
8.2.3 Quality of Life Assessments 28
8.3 Safety Assessments 31
8.3.1 Dermal Safety and Tolerability Events 31
8.3.2 Physical Examination and Vital Signs 33
8.3.3 Laboratory Assessments 33
8.3.4 Pregnancy Tests 33
8.4 Other Assessments 33
8.4.1 PK Assessments 33
8.4.2 Genomic Sample 33
9 TREATMENT PLAN 34
9.1 Methods of Assigning Subjects to Treatment Groups 34
9.2 Randomization and Blinding 34
9.3 Unblinding 34
9.4 Treatment Compliance 34
9.5 Protocol Deviations 35
10 INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT 36
10.1 Identity of the Investigational Product 36
10.2 Packaging and Dispensation of Investigational Product 36
10.3 Storage and Handling of Investigational Product 37
10.4 Application 37
10.5 Investigational Product Accountability and Disposal 38
11 SAFETY INSTRUCTIONS AND GUIDANCE 40
11.1 Adverse Events 40
11.1.1 Definition of Adverse Event 40
11.1.2 Documenting Adverse Events 40
11.1.3 Serious Adverse Events 41
11.1.4 Assessment of Severity 42
11.1.5 Assessment of Causality 42
11.1.6 Reporting of Serious Adverse Events 43
11.1.7 Emergency Contact 43
11.1.8 Expedited Serious Adverse Event Reports 44
12 STATISTICS 45

12.1 Analysis Population 45
12.2 Subject Disposition 45
12.3 Demographics and Baseline Characteristics 45
12.4 Protocol Deviations 45
12.5 Compliance 45
12.6 Assessment of Efficacy 45
12.6.1 Efficacy Summaries 45
12.6.2 Efficacy Analyses 46
12.6.3 Sample Size Determination 47
12.7 Assessment of Safety 47
12.7.1 Dermal Safety and Tolerability 47
12.7.2 Adverse Events 47
12.7.3 Physical Examination Including Vital Sign Results 48
12.7.4 Safety Laboratory Values 48
12.7.5 Pregnancy Tests 48
13 QUALITY CONTROL AND QUALITY ASSURANCE 49
13.1 Study Monitoring 49
13.2 Audits and Inspections 49
13.3 Data Quality Assurance 49
14 ETHICS AND ADMINISTRATIVE ISSUES 51
14.1 Ethical Conduct of the Study 51
14.2 Independent Review Board Review 51
14.3 Informed Consent 51
14.4 Subject Data Protection 51
14.5 Financial Disclosure 52
14.6 Investigator Obligations 52
14.7 Changes to the Protocol 52
14.8 Confidentiality 52
15 DATA HANDLING AND RECORD KEEPING 53
15.1 Inspection of Records 53
15.2 Retention of Records 53
15.3 Electronic Case Report Form Completion 54
16 REFERENCES 55
17 APPENDICES 57
17.1 Safety Laboratory Tests 57
17.2 Contraception 58
17.3 Diagnostic criteria for Gorlin syndrome 59

17.4 Patient Reported Outcomes (PRO) Questionnaires 60
Appendix 17.4.1 aBCCdex 61
Appendix 17.4.2 DLQI 66
Appendix 17.4.3 EQ-5D-5L 68

List of Tables

Table 1: Schedule of Assessments 29
Table 2: Dermal Safety and Tolerability Scales 32
Table 3: Excipients of Patidegib Topical Gel, 2% (w/w) 36

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
aBCCdex	Advanced Basal Cell Carcinoma Index
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
BCNS	Basal Cell Nevus Syndrome
BUN	Blood urea nitrogen
CAPA	Corrective and Preventative Action Plan
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CLL	Chronic Lymphocytic Lymphoma
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
DNA	Deoxy ribonucleic acid
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol (Quality of Life) using 5 levels
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HH	Hedgehog
HHI	Hedgehog inhibitor
HF-BCC	High Frequency Basal Cell Carcinoma
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra-uterine device
IUS	Intra-uterine system
IxRS	Interactive Web/Phone Randomization System
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

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
PTV	Pre-trial visit
RBC	Red blood cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SEB	Surgically Eligible Basal Cell Carcinoma
SMO	Smoothened
SoA	Schedule of Assessments
SPF	Sunscreen Protection Factor
SuFu	Suppressor of fused
TEAE	Treatment-Emergent Adverse Event
TIV	Trial initiation visit
UK	United Kingdom
US	United States
UV	Ultraviolet
WBC	White blood cells
WHO	World Health Organization
WOCBP	Woman of Child Bearing Potential

4 INTRODUCTION

High Frequency Basal Cell Carcinoma (HF-BCC) is defined as the development of multiple basal cell carcinomas (BCCs) over a patient's lifetime. A high frequency of BCC development may be associated with Gorlin syndrome, or may occur in the absence of Gorlin syndrome, referred to hereafter as non-Gorlin HF-BCC.

Gorlin syndrome (also known as basal cell nevus syndrome; BCNS) is a rare autosomal dominant heritable disease characterized by numerous congenital malformations (macrocephaly, frontal bossing, cleft lip/palate etc.) and a postnatal predisposition to the development of numerous BCCs over a lifetime. In 1996, two groups identified the patched 1 (PTCH1) gene as the locus of the mutations that cause Gorlin syndrome[1,2,3]. Patients with Gorlin syndrome have one defective heritable copy of this gene (responsible for the congenital abnormalities). Sporadic loss of the second allele (likely frequently from ultraviolet light damage) 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). 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.

Non-Gorlin HF-BCC occurs in the absence of Gorlin syndrome. Non-Gorlin HF-BCC may be sporadic or associated either with a germ line mutation in DNA repair pathway or with other rare genetic syndromes. A cohort of 61 patients with HF-BCC (mean 11, range of 6 to 65 BCCs over ten years) were recently evaluated by Cho et al. Germline pathogenic mutations were seen in 12 genes in some of the patients. All 12 genes with pathogenic mutations were involved in the DNA repair pathway. The authors postulated that increased frequency of mutations in the DNA repair genes may underlie the greater susceptibility of these individuals to the environmental contribution of UV damage[4]. Non-Gorlin HF-BCC may also be associated with other rare genetic syndromes such as Bazex-Dupre-Christol and Rombo[5,6].

Irrespective of whether the BCCs are associated with Gorlin syndrome or otherwise, individual BCCs may be categorized as superficial, nodular, or of the mixed variety[7]. Several topically-applied drugs, in particular imiquimod and 5-fluorouracil, are approved for use in the treatment of BCCs[8]. Both of these topical products can cure approximately 80% of the superficial subtype of BCCs, most of which generally occur off the face. However, these treatments generally are not useful against nodular BCCs, which are the more prevalent subtype, especially on the face. In addition, both typically cause significant inflammation at sites of application. Oral retinoid treatment of patients with Gorlin syndrome can reduce the rate of development of BCCs, but does so only at a dose that usually produces intolerable side effects.

It is believed that the underlying molecular abnormality driving the development of all BCCs is aberrant up-regulation of the HH signaling pathway. Several anti-HH drugs have been developed

for oral treatment of BCCs, and two of these - vismodegib and sonidegib - have been approved for systemic treatment of advanced BCC. However, most patients discontinue vismodegib[9] because of class-specific side effects in particular hair loss, taste loss, and muscle cramps that negatively affect their quality of life.

The most definitive treatment for BCCs in HF-BCC therefore is surgery. However surgery (particularly for facial BCCs) has significant morbidity (e.g., scarring, functional loss of eyelid, nose, ear). There is, therefore, an unmet need for a medication that will both preclude the need for surgery for BCCs, and that will be safe and well tolerated for chronic use.

Patidegib is a semi-synthetic small molecule that binds to SMO and blocks the hedgehog signaling pathway *in vitro*. Oral patidegib (IPI-926) has a good therapeutic effect on locally advanced and metastatic BCCs, but has the same types of clinically unacceptable adverse effects seen with all systemically administered HH inhibitors[10]. Topical patidegib is formulated with generally recognized as safe (GRAS) excipients and deposits significant amounts of drug in the epidermis and dermis after topical application in a human skin *in vitro* model. Patidegib gel has been evaluated in 1 phase 1 (Pelle 926-101) and 2 phase 2 studies (UK proof-of-concept study in patients with Gorlin syndrome – Pelle 926-201; and US dose escalating study for sporadic BCCs – Pelle 926-202). Based on the positive outcome from these studies, a Phase 3 study evaluating patidegib topical gel in patients with Gorlin syndrome is currently ongoing (Pelle 926-301).

Non-Gorlin HF-BCC patients who develop BCCs at a tempo similar to that seen in Gorlin syndrome patients have the same unmet medical need as do patients with Gorlin syndrome. Patidegib topical gel is therefore also being developed for the mitigation of disease burden (decrease number of BCCs that require surgery) in the non-Gorlin HF-BCC population. However, notwithstanding the similarities in the morphology, histology and the dependence on the HH pathway for BCCs in Gorlin and non Gorlin HF-BCCs, there remain some important differences between the two populations. Gorlin HF-BCC is a more homogeneous (predominantly germline PTCH1 mutation) population than non-Gorlin (sporadic, rare genetic syndromes or germline mutations in DNA repair pathway) HF-BCC. The two populations potentially may have different rates and standard deviations for the development of BCCs that require surgery; and different AE profiles. This phase 2 study is being conducted to characterize, for this more heterogeneous non-Gorlin HF-BCC population, an early safety profile, the event rate for BCCs that require surgery and to establish an initial proof of concept to inform further a Phase 3 evaluation.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to assess the number of nSEBs in patients treated with Patidegib Topical Gel 2% or Vehicle when applied twice daily to the face of subjects with HF-BCC.

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.

6 OVERALL STUDY DESIGN AND PLAN

This is a 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 HF-BCC. Subjects will be required to apply the IP or vehicle for 9 months. The primary endpoint is the number of nSEBs that develop on the face over the 9 month period. BCCs will be imaged and tracked consistently throughout the study in order to accurately identify nSEBs.

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 rationale for the key elements of the study design, including choice of the primary endpoint, stratification, eligibility criteria, disease severity, the methodology for measurement of BCCs, and the use of imaging to track BCCs are provided in the following sections.

6.1.1 Choice of Primary Endpoint

The primary endpoint is the number of nSEB that develop on the face over the 9 month period. Generally, a facial BCC of longest diameter [redacted] is considered a SEB[11]. 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] in longest diameter from Baseline.

Surgery has significant morbidity (e.g., scarring, functional loss of eyelid, nose, ear) and the number of nSEBs is therefore considered an endpoint that reflects the burden of disease.

6.1.2 Stratification Parameters

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[12]. Gender will be used as a stratification factor in this Phase 2 trial.

6.1.3 Treatment Duration

The rate of nSEB development in the non-Gorlin HF-BCC population has not been previously well studied. The duration of treatment in the phase 2 UK study in Gorlin patients (Pelle-926-201) was 6 months. Gorlin syndrome however, is relatively more homogeneous (predominantly germline PTCH1 mutation) when compared to non-Gorlin HF-BCC population (sporadic, rare genetic syndromes or germline mutations in DNA repair pathway). Therefore, in

this trial the treatment duration will be extended to 9 months, to more thoroughly evaluate the rate of nSEB development.

6.1.4 BCC Tracking

The study design ensures that BCCs are tracked consistently throughout the study. This is accomplished by capturing standardized unmarked digital images of the face at every visit and in addition, marked (annotated) images at prespecified visits (see Table 1).

At visits prior to IP application (i.e., Screening and Baseline), in addition to unmarked images, annotated/marked 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 applying stickers 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.

Marked (annotated) images will also be captured at prespecified post-Baseline visits. The PI will identify, label and number BCCs at these visits. 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 SEBs be eliminated from consideration as nSEBs, and that small BCCs are also 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, preferred (ruler, caliper etc.) method. The same method will be used for a given patient throughout the study. 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 all BCCs present and identify BCCs that may be [redacted] in their longest diameter in size. The Investigator will measure the longest diameter for these BCCs and report lesions [redacted] as nSEBs, if appropriate. 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 HF-BCC without Gorlin syndrome. Gorlin syndrome is typically diagnosed using some combination of medical history, clinical examination, genetic testing, x-rays and/or tomography[13]. In the diagnostic evaluation for Gorlin syndrome, genetic testing is perhaps the most sensitive. The genes known to be involved with Gorlin syndrome are PTCH1 and suppressor of fused (SuFu), with PTCH1 pathogenic variants being far more common than SuFU. The proportion of probands with a pathogenic variant detectable by sequence or gene targeted deletion/duplication analysis for the PTCH 1 gene are 50 to 85% and 6 to 21% respectively. The proportion for the same methods for the SuFU gene are 5 % and 1 % respectively. The PTCH1 and SuFu pathogenic variant Gorlin syndromes cannot be differentiated clinically. However, the risk of developing medulloblastoma is substantially higher in individuals with a SuFu pathogenic variant (33%) than in those with a PTCH1 pathogenic variant (2 %). In the genetic evaluation of Gorlin syndrome a family history of medulloblastoma and proband testing for PTCH1 are critical[14].

In this study, all subjects who have been previously diagnosed with Gorlin syndrome will be excluded. Patients will also be excluded if there is a clinical suspicion of Gorlin syndrome. In order to exclude as many patients as possible, with the rare SuFu mutation, subjects with a family history of medulloblastoma will also be excluded (Section 7.1.2). The patients thus enrolled in the study will form the basis for the Intent to Treat population. These patients in the ITT population will have genetic testing for pathogenic variants in PTCH1, results for which may become available in weeks to months during the study conduct. ITT subjects with a PTCH1 pathogenic variant will be excluded from the modified ITT (mITT) population, which will be the primary efficacy analysis population (Section 12). Patients in the ITT population (including those with a pathogenic variant in PTCH1) will remain in the study, as patidegib topical gel in patients with Gorlin syndrome in this ITT population is expected to have the same benefit-risk profile to that in patients participating in the Phase 3 study in Gorlin syndrome patients, Pelle-926-301.

The protocol requires (as for the ongoing Phase 3 study in Gorlin subjects) 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 Screening and Randomization (Baseline/Day 1). This is to ensure that subjects with a moderate to severe frequency of BCC development, who are likely to benefit most from therapy, are enrolled. This also ensures that the patients have an unmet need similar to that of patients with Gorlin syndrome participating in ongoing Protocol Pelle-926-301.

Additionally the subject must have at least 2 BCCs with longest diameter <5 mm present on the face. This increases the likelihood of the subject developing a nSEB during the study.

6.1.7 Genomic testing

Genomic testing will comprise mandatory testing for PTCH1 pathogenic variants and optional testing to identify mutations that may result in the development of a high frequency of BCC and decreased response to HHI.

6.1.7.1 Mandatory testing for Gorlin syndrome

All patients enrolled into the study will need to consent for genetic testing for PTCH1 pathogenic variants. Patients who test positive for pathogenic variants in the PTCH1 gene will be excluded from the mITT population (Section 6.1.6).

6.1.7.2 Optional testing

Germline pathogenic mutations in DNA repair pathways were seen in some subjects with HF-BCC[4]. In order to better understand the different pathogenic mechanisms for non Gorlin HF-BCC, all patients who give additional consent will also be tested for mutations that may result in the development of a high frequency of BCC (such as mutations in DNA repair genes).

Upregulation of the HH pathway plays a significant role in the pathogenesis of BCC. It is possible that any nSEBs that develop despite the use of patidegib may have mutations that render them less susceptible to HHI. For patients who consent, nSEB biopsy samples will be collected and stored for future testing. It is possible that these tests may help understand better the role of other genes and pathogenetic pathways in HF BCC.

These optional tests are for research purposes and will not guide therapy in the study. The results will not be shared with study participants and will not be available with the core study report but may form the basis of a supplementary report or publication.

6.1.8 Contraception and duration of contraception

Embryo-fetal toxicity was noted in non-clinical studies[15]. The study therefore has stringent recommendations on the choice of and duration of contraception.

Highly effective contraception (defined as a failure rate of < 1%) is mandated for women of child bearing potential (WOCBP)[16]. For women on oral contraceptives, the likelihood of any clinically significant drug-drug interaction of topical patidegib gel is remote due to the absence of first pass metabolism as well as the extremely low patidegib systemic exposure following topical administration[15]. Nevertheless, as a matter of abundant caution, it is recommended that hormonal contraception be supplemented with a barrier method.

The mean half-life for patidegib after 2 weeks of dosing was 52 ± 32% (range 30 - 87) hours[15]. Based on the longest observed half-life of 87h in this study > 99.5% of the circulating drug will be gone from the body 30 days after the last dose. In women, contraception must continue for a minimum of 30 days after the last application of IP.

Patidegib is not genotoxic. For males with a WOCBP partner, it is also not anticipated that relevant systemic exposures will be obtained in the WOCBP partner. Nevertheless male subjects with a WOCBP partner are required to use a condom from prior to application of the IP and continue for a minimum of three months (life of a spermatocyte) after the last application of IP.

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 ([redacted]) patidegib concentration in plasma at Week 14 ([redacted] and [redacted] subjects had a detectable concentration at Week 26 ([redacted]). No subjects on Patidegib Topical Gel, 2% had detectable concentrations[15]. 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 [redacted] subjects. In contrast, no treatment related AEs were seen in the Patidegib Topical Gel, 2% group (data on file, clinical study report [CSR]).

Therefore, Patidegib Topical Gel, 2% has been selected for further development under both the ongoing Phase 3 study Pelle-926-301 in Gorlin syndrome patients and this Phase 2 study in non-Gorlin HF-BCC patients.

6.3 Benefit-risk Assessment

Mitigation of BCCs and SEB tumor burden has so far has been limited to avoiding sunlight, advice which is followed infrequently by patients at risk of developing sporadic skin tumors. Vismodegib, an orally bioavailable HHI has been studied for efficacy vs. BCCs in patients with Gorlin syndrome[11]. Unlike results in advanced BCCs, essentially all Gorlin syndrome non-advanced tumors respond by shrinking and eventually most disappear completely, both clinically and histologically. But because of detrimental class-specific side effects, most patients discontinue oral HHI such as vismodegib[17]. Surgery is currently the definitive treatment for BCCs in patients with HF-BCC. Surgery has significant morbidity (e.g., scarring, functional loss of eyelid, nose, ear). Meanwhile, in Study Pelle-926-201, Patidegib Topical Gel, 2 % has shown promise to potentially mitigate tumor burden, without the systemic toxicity of oral HHI in patients with Gorlin syndrome.

The safety evaluation in the two clinical studies of the topical 2% and 4% formulations (Pelle-926-201, and Pelle-926-202) have shown that patidegib topical gel in repeated QD and BID doses appears to be safe and well-tolerated[15]. Based on clinical and non-clinical studies for the topical product there are no known (expected) adverse events for the topical product. Adverse events and dermal safety and tolerability will nevertheless be monitored throughout the Phase 2 study.

Notwithstanding the low systemic bioavailability of Patidegib Topical Gel, 2%, class effects seen with oral HHI are considered potential adverse events for Patidegib Topical Gel, 2%. These

include muscle spasm, alopecia and dysgeusia[15, 18]. As expected with the oral HHI class, embryo-fetal toxicity has been observed in nonclinical studies of the oral formulation of patidegib[15].

In non-clinical studies, changes in growth plate were observed in mice and young dogs treated at high doses. In skeletally mature adult dogs, there were no adverse bone changes[15]. Cessation of growth in children treated with oral HHI has also been reported[19]. Pediatric patients are excluded from this study.

The vehicle gel contains the same inactive ingredients as patidegib topical gel, but lacks the active ingredient. All formulation components of patidegib topical gel meet standard US or international compendial standards and are generally recognized as safe[15]. Nevertheless, subjects known to have a hypersensitivity to any of the ingredients in the study medication formulation are excluded from the study (Section 7.1.2). Subjects randomized to the vehicle arm benefit from the close monitoring of their BCCs in the study.

The current benefit-risk profile is therefore deemed acceptable to support the continued development of patidegib topical gel in non-Gorlin HF-BCC patients.

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 have had at least 10 (with at least 3 on the face) clinically typical BCCs present within 24 months prior to Screening and Randomization (Baseline/Day 1). Additionally, the subject must have at least 2 BCCs with longest diameter <5 mm present on the face prior to Screening and Randomization (Baseline/Day 1).
4. The subject must be willing to have blood collected to measure circulating drug levels.
5. 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.
6. If the subject is a woman of child bearing potential (WOCBP), she must be willing to use birth control methods which may be considered highly effective (Appendix 17.2). Hormonal contraception must be supplemented with a barrier method (preferably condom). Birth control must start prior to Baseline, continue through the duration of the study, and for 30 days after last application of IP
7. 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 3 months after the last application of IP.
8. The subject is willing for all facial BCCs to be evaluated and treatment recommendations made only by the Investigator.
9. 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 treated with topical agents or 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 been previously diagnosed with Gorlin syndrome

2. On medical history, family history or clinical examination there is a suspicion that the patient has Gorlin syndrome. The diagnostic criteria for Gorlin syndrome are available in Appendix 17.3.
3. Patients with a family history of medulloblastoma
4. The subject has previously participated in a clinical trial evaluating patidegib topical gel.
5. 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:
   a. [redacted]
6. The subject is known to have a hypersensitivity to any of the ingredients in the study medication formulation.
7. The subject is unable or unwilling to make a good faith effort to return to the study site for all study visits and tests.
8. The subject has uncontrolled systemic disease.
9. 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.
10. 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.
11. The subject is pregnant or breastfeeding.
12. 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 or applied 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 9/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 including the 30-day safety follow-up visit. 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 oversight 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 14 days after the Screening visit. If this period exceeds 14 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.

The study has stringent recommendations on the choice of and duration of contraception. The rationale for this is provided in Section 6.1.8, acceptable contraceptive measures and their duration are provided in the exclusion criteria and in Appendix 17.2

8.1.3 Randomization

Details on randomization are available in Sections 9.1 and 9.2.

8.1.4 Demographics

Subject's date of birth, gender at birth, race and ethnicity will be recorded in the eCRF.

8.1.5 Medical History

Subjects' relevant family history 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

Patients will be dispensed a diary to maintain a log of their IP application.

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 be uploaded to the imaging vendor portal for further review. Full details for image capture can be found in the Imaging Review Charter.

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.). BCCs in the region of the eyelids or posterior to the tragus are not numbered and tracked. Record the measurement of the longest diameter of each BCC.
b. Taking a photo of face again with markings and stickers.
c. 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.

8.2.3 Quality of Life Assessments

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

- [redacted]
- [redacted]
- [redacted]

Table 1 provides the SoA for the study.

Table 1: Schedule of Assessments

Procedure	Pre-treatment	Treatment										F-Up
	Screening[n] (-14 days)	Baseline[a] (Day 1)	Mo 1	Mo 2	Mo 3	Mo 4	Mo 5	Mo 6	Mo 7	Mo 8	Mo 9	30 Days[b]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed Consent[c]	X											
Inclusion/Exclusion	X	X										
Demographics	X											
Medical history[d]	X											
PTCH1 mutation testing	X											
Current/concomitant medications	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	
Pregnancy test[f]	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
PK sample collection[m]		X (predose)			X			X				
Genomic sample collection		X										
Digital imaging (unmarked)	X	X	X	X	X	X	X	X	X	X	X	
[redacted]												
[redacted]												
[redacted]												
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
Dermal safety and tolerability	X	X			X			X			X	
Adverse events[h,i]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
[redacted]												
[redacted]												
[redacted]			X	X	X	X	X	X	X	X	X	
Dispense IP		X	X	X	X	X	X	X	X	X		

[a] The Baseline Visit may take place no more than 14 days after the Screening Visit. If this period exceeds 14 days, the subject will need to be re-screened.
[b] The safety follow-up visit will be conducted 30 days following the subject's Exit or Month 9 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), 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 9/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 after the Baseline Visit.
[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 time and date of the last dose prior to collection of the PK sample must be recorded.
[n] Patients who fail screen may be rescreened. The patient will need to meet all criteria at rescreen and baseline. Baseline should occur within 15 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), weight 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 performed 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 time and date of the last dose prior to collection of the PK sample must be recorded.

8.4.2 Genomic Sample

Blood will be collected at the baseline visit from all patients for testing for mutations in the PTCH1 gene. Blood will also be collected at the baseline visit from patients who have consented to genetic testing for mutations in DNA repair genes. BCC biopsy tissue samples from patients who have consented will be stored for subsequent testing to identify mutations that might render lesions less susceptible to HHI.

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 3-digit chronological Screening order number, starting with [redacted] 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 gender.

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 discuss the situation further.

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.

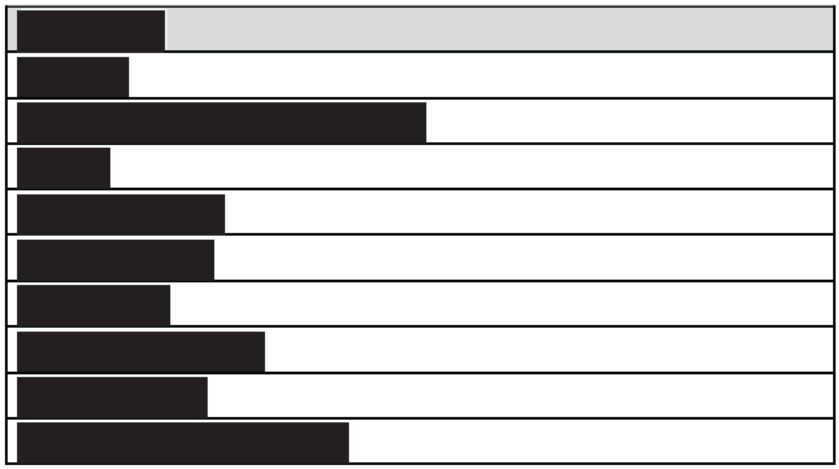
Any interruptions in the schedule of IP administration or use of prohibited concomitant medication will be recorded in the eCRFs.

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[20]. 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.

10 [redacted]

[redacted]



[redacted]

and assessed for damage and/or temperature excursions. Damage or other issues 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. Make-up should not be applied any sooner than 30 minutes after the application of IP. If feasible the application of make-up maybe be deferred for as long as possible.

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 (avoiding the eyelids (as described above and in the Pharmacy Manual). If no observable AEs are noted within a 30-minute observation period after their first application, subjects can leave the site. Subjects will be advised to minimize exposure to direct sunlight and to wash their hands before and after application of the IP.

If an IP application has been missed or delayed such that there would be 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 using contraception as specified in this protocol.

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 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, 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 sign or symptom. Any incidence of these 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 assessments 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/her discretion to determine what constitutes a long or short interval between events and which event is reported once versus more than once. Protocol defined endpoints (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, information pertaining to all AEs including SAEs are to be recorded 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 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. 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, according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information.

12 STATISTICS

12.1 Analysis Population

The intent-to-treat (ITT) population will comprise all randomized subjects. The modified ITT (mITT) population will comprise all patients in the ITT population, excluding those who tested positive for pathogenic variants in the PTCH1 gene. The mITT population will be the primary efficacy analysis population. Subjects will be assigned to treatment groups as randomized. The per-protocol (PP) population will be used for supportive efficacy analyses. The Safety population will consist of all subjects who have applied IP at least once. For the PP and Safety populations, subjects will be assigned to treatment groups as treated (not as randomized).

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.

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 determined from the use of diary cards.

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 nSEBs per subject by Month nine.

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.

12.6.1.2 Secondary Endpoints

The secondary efficacy endpoints are:

1. The number of new BCCs that develop from Baseline to Month 9.
2. The proportion of subjects developing ≥2 facial nSEB(s) by Month 9.
3. The proportion of subjects developing ≥1 facial nSEB(s) by Month 9.
4. The number of BCC surgeries from Baseline to Month 9.
5. The number of qualifying nSEBs per subject at Month 6.
6. aBCCdex Change in Lesion scale score from Baseline to Month 9.

12.6.1.3 Exploratory Endpoints

The exploratory endpoints are:

1. Time to first new SEB
2. The proportion of SEBs that undergo clinical resolution by Month 9.
3. Change in aBCCdex Worry About Future Lesions scale score from Baseline to Month 9.
4. Change in aBCCdex Mental Health scale score from Baseline to Month 9.
5. Change in aBCCdex Social/Relationships scale score from Baseline to Month 9.
6. Change in aBCCdex Life Impact scale score from Baseline to Month 9.

12.6.2 Efficacy Analyses

The primary endpoint is the number of qualifying (i.e. histologically verified as BCC) nSEBs per subject over 9 Months. The number of new SEBs will be analyzed using a Poisson regression with treatment, baseline number of BCCs that are not SEBs, and stratification factors as covariates. Multiple imputations (MI) will be the primary method for dealing with missing post-baseline data for the primary endpoint. The Poisson assumption will be evaluated, and if it appears that it does not hold, a non-parametric rank analysis of covariance (ANCOVA) will be used as the primary method of analysis.

Secondary efficacy endpoints that are similar to the primary endpoint will be analyzed similarly. Other categorical endpoints will be analyzed using logistic regression or Cochran-Mantel-Haenszel (CMH). Continuous endpoints will be analyzed using ANCOVA models.

No adjustment due to multiplicity will be made.

Additional details will be available in the statistical analysis plan (SAP).

12.6.2.1 Handling of Missing Data

The primary method for dealing with missing data will be the MI method.

For the MI model, 100 imputations will be generated using PROC MI of SAS. Fully conditional specification (FCS) model using the regression method will be used with the number of SEBs at prior post-baseline visits, treatment group, number of BCCs that are not SEBs at baseline, gender as covariates to impute the data. The ROUND and MINIMUM options will be utilized to ensure imputed values are non-negative integers. 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.

Additional details will be available in the statistical analysis plan (SAP).

12.6.2.2 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.

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.

12.6.3 Sample Size Determination



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, and Month 9/Exit Visit. Normal reference ranges 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.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study Monitoring

The Sponsor or designee will be responsible for the monitoring of the study. Study monitors will contact and visit the Investigators at regular intervals throughout the study to verify adherence to the protocol, and assess the completeness, consistency, and accuracy of the data by comparing patients' medical records with entries in the eCRF.

The study monitor must be allowed access to laboratory test reports and other patient records needed to verify the entries on the eCRF, provided patient confidentiality is maintained in accordance with local requirements. These records, and other relevant data, may also bereviewed by appropriate qualified personnel independent from the Sponsor or designee, who is appointed to audit the study. Patient confidentiality will be maintained at all times.

By agreeing to participate in this research study, the Investigators agree to co-operate with the study monitor to ensure that any problems detected during the monitoring visits are promptly resolved.

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. A signed and dated notification of the IRB approval will be provided to PellePharm and Investigator prior to study initiation. The name and occupation of the chairman and members of the IRB will be supplied to PellePharm. The Investigator will provide required progress reports and report all SAEs to the IRB as required by the IRB.

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, 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 and by the study CRO and/or PellePharm or designee. The ICF must not be altered without the prior agreement of the relevant IRB 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, 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.

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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 Contraception

1. Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered a woman of childbearing potential (WOCBP) after the initiation of puberty following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women are considered to be in a post-menopausal state when there has been a cessation of previously occurring menses for $\geq$12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measure is insufficient.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2. Contraception Requirements

a. Contraception Requirements for Female Subjects

Hormonal contraception must be supplemented with a barrier method (preferably condom).

Highly effective forms of birth control include (but are not limited to) the following:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

17.3 Diagnostic criteria for Gorlin syndrome

Diagnostic criteria for Gorlin syndrome includes major criterion #a 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*[21])

17.4 Patient Reported Outcomes (PRO) Questionnaires

[redacted]





