Clinical Study Protocol

Protocol Pelle-926-301E

A Phase 3, Multicenter, Open-Label Extension Study of Patidegib Topical Gel, 2% in Subjects with Gorlin Syndrome (Basal Cell Nevus Syndrome)

Development Phase of Study:	3
Study design:	Multicenter, Open Label Clinical Study
IND #:	125,461
Eudra CT number:	2020-000253-27
Sponsor Representative:	[redacted]
Sponsor:	[redacted]
Version:	Original: 25 November 2019 Amendment 1: 30 January 2020

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.

Principal Investigator Protocol Agreement Page

I have carefully read the protocol entitled: *"A Phase 3, Multicenter, Open-Label Extension Study of Patidegib Topical Gel, 2% in Subjects with Gorlin Syndrome (Basal Cell Nevus Syndrome)"* and, I declare that, as a Principal Investigator, the clinical protocol was subject to critical review and is approved by PellePharm, Inc. (PellePharm).

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

I understand that any substantial changes to the protocol must be approved in writing by the IRB/EC/REB 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

Title	A Phase 3, Multicenter, Open-Label Extension Study of Patidegib Topical Gel, 2% in Subjects with Gorlin Syndrome (Basal Cell Nevus Syndrome)
Short Title	PATIDEGIB Phase 3 OLE study in subjects with Gorlin syndrome
Protocol No	Pelle-926-301E
Study Regions	United States (US), UK, Canada, European Union
Phase of Development	Phase 3
Objectives	**Primary Objective** • To assess the safety and tolerability of Patidegib Topical Gel, 2% in patients who have completed PellePharm Study Pelle-926-201 or Pelle-926-301 **Secondary Objectives** • To assess the efficacy of Patidegib Topical Gel, 2% in patients who have completed PellePharm Study Pelle-926-201 or Pelle-926-301
Study Design	This is a multicenter, open label extension study evaluating the safety of Patidegib Topical Gel, 2%, applied topically twice daily to the face of adult subjects with Gorlin syndrome.
Number of Subjects	Maximum of about 200 participants (completers from PellePharm Studies 926-201 or 926-301).
Study Population	Patients with Gorlin syndrome who have completed PellePharm Study 926-201 or 926-301
Study duration	The treatment duration is 12 months, with potential extension beyond this period. Enrollment will close approximately after the last patient in Study 926-301 has completed their Study 926-301- related procedures.
Criteria for Evaluation	**Screening Visit** A screening visit is mandatory for all subjects. Subjects who fail a Screening Visit may be rescreened. All eligibility criteria at the Baseline visit must also be met at the Screening/Rescreening visit. Additionally, for women of child bearing potential (WOCBP) a serum pregnancy test must be negative, at the Screening visit. **Baseline Visit** **Key Inclusion Criteria (Section 7.1 for a complete list)** 1. The subject must have completed PellePharm Study 926-201 or 926-301. 2. Study Pelle-926-301 subjects must have completed the End of Treatment Visit in Study 301, prior to the Screening Visit in this study.

	They must also complete all Study 301 related procedures prior to the Baseline Visit of this study. 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. 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. 4. Female subjects must have a negative pregnancy test (serum pregnancy test at Screening Visit, urine pregnancy test at Baseline Visit). For Study 301 subjects a negative serum pregnancy test result from Study 301 is acceptable if the test was done within 7 days of the Screening Visit of this study. 5. 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 17.1). 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 6. 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. 7. The subject is willing for all facial BCCs to be evaluated and follow treatment recommendations made only by the Investigator. 8. 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 BCC potentially might compromise the health of the subject. In such instances, the only other allowed form of treatment is surgical. **Key Exclusion Criteria (**Section 7.1 **for a complete list)** 1. The subject has used topical treatment to the face or systemic therapies that might interfere with the evaluation of the study IP (Section 7.1 for details) 2. 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 (while enrolled in this study) participation in an experimental drug study (excluding Study 301). 3. The subject is a WOCBP who is unwilling or unable to comply with pregnancy prevention measures. 4. The subject is pregnant or breastfeeding.

Investigational Product (IP)	Patidegib Topical Gel, 2% (w/w). The IP will be applied to the face defined as the area extending from the anterior hairline to the jaw line (except the eyelids). 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.
Assessments	Background and demographic assessments Inclusion and exclusion criteria Demography Medical history Prior and concomitant medications Efficacy Count of facial lesions Surgery Biopsies Quality of life assessments Safety Skin tolerability Adverse Events Physical examinations Pregnancy tests
Genomic testing	There will be no genomic testing in this study.
Statistical methods	**Sample size** The study is not powered for statistical significance. **Analysis populations** The primary population for analysis of safety and efficacy will be the safety population. This population will comprise all patients who had at least one application of study treatment. Subgroup analysis will be done for subjects with history of oral or topical HHI in past 6 months – Yes/No. **Methods of analysis** All analysis will be descriptively summarized. There will be no hypothesis testing.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Definition or Explanation
aBCCdex	Advanced Basal Cell Carcinoma Index
AE	Adverse Event
BCC	Basal Cell Carcinoma
BSA	Body Surface Area
CAPA	Corrective and Preventive Action Plan
cGMP	Current Good Manufacturing Practices
CRO	Clinical Research Organization
DLQI	Dermatology Life Quality Index
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
HF-BCC	High-frequency Basal Cell Carcinoma
HH	Hedgehog
HHI	Hedgehog Inhibitor
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intra-uterine device
IUS	Intra-uterine system
MedDRA	Medical Dictionary for Regulatory Affairs
MUSE	Maximum Use Systemic Exposure
OLE	Open Label Extension
PD	Protocol Deviation
PDT	Photodynamic Therapy
PE	Physical Examination
PRO/ePRO	Patient Reported Outcome/electronic Patient Reported Outcome
PSCP	Primary Skin Care Physician
PTCH 1	Patched Protein 1
QA	Quality Assurance
SAE	Serious Adverse Event
SEB	Surgically Eligible Basal Cell Carcinoma
SoA	Schedule of Assessments
SAP	Statisatical Analysis Plan
SPF	Sunscreen Protection Factor
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

4 INTRODUCTION

PellePharm, Inc. (PellePharm) is developing a topical formulation of patidegib for the mitigation of the disease burden of persistently developing basal cell carcinomas (BCCs) in patients with Gorlin syndrome and a high frequency of BCCs (HF-BCC). There are currently no approved therapies for Gorlin syndrome or HF-BCC. The continuous development of BCCs, especially on the face, can lead to seriously disfiguring scars and functional impairment, resulting in a significant decrease in quality of life. It is hoped that, by decreasing the number of surgeries that these patients require, their quality of life will be greatly improved.

Three clinical interventional studies of Patidegib Topical Gel have been completed by PellePharm, Inc. while a fourth study is ongoing. The safety of the oral formulation was characterized before the topical was advanced to the clinic (Patidegib IB).

Study Pelle-926-101 was a Phase 1 maximum use systemic exposure (MUSE) study in healthy volunteers. [redacted]

Study Pelle-926-201 was a Phase 2 double-blind randomized vehicle-controlled study [redacted]

Study Pelle-926-202 was a double-blind, dose escalating, randomized, vehicle-controlled Phase 2 study [redacted]

Patidegib Topical Gel appeared to be effective in the two Phase 2 studies. Additionally, based on the limited data from the three studies, Patidegib Topical Gel was found to be safe and tolerable. Patidegib Topical Gel is currently being evaluated in Study Pelle-926-301 – a Phase 3 double blind randomized vehicle controlled study in patients with Gorlin syndrome. [redacted]

[redacted]

[redacted]

This current study is an open label extension study offered to patients with Gorlin syndrome who participated in studies 926-201 or 926-301. The objective of this study is to evaluate safety and efficacy on an ongoing basis.

[redacted]

[redacted]

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability of Patidegib Topical Gel, 2% in patients who have completed PellePharm Study Pelle-926-201 or Pelle-926-301.

5.2 Secondary Objective

The secondary objective of the study is to assess the efficacy of Patidegib Topical Gel, 2% in patients who complete PellePharm Study Pelle-926-201 or Pelle-926-301.

6 OVERALL STUDY DESIGN AND PLAN

This is an open label study offered to all subjects who have completed Study 926-201 or Study 926-301. All study participants are treated with Patidegib Topical Gel 2% gel. This ensures that patients who were randomized to vehicle in the parent study 926-201 or 926-301receive Patidegib Topical Gel in the current study.

Safety and tolerability are the primary objectives of this study and will be evaluated by reviewing adverse events, treatment discontinuations and dermal safety and tolerability. The number of facial BCCs removed by surgery is considered an appropriate study endpoint as surgery has significant morbidity in Gorlin Syndrome (e.g., scarring, functional loss of eyelid, nose, ear).

Study visits will occur at quarterly intervals. However for WOCBP, study visits will occur monthly (Section 6.1 and Table 1)

6.1 Contraception and duration of contraception

Embryo-fetal toxicity was noted in non-clinical studies (Patidegib IB). This 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) (HMA CTFG guidelines). 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 (Patidegib IB). Nevertheless, as a matter of abundant caution, it is recommended that hormonal contraception be supplemented with a barrier method.

The mean half-life (Study 926-101) for patidegib after 2 weeks of dosing was [redacted] (Patidegib IB). Based on the longest observed half-life [redacted] in this study > [redacted] of the circulating drug will be gone from the body [redacted] after the last dose. In women, contraception must continue for a minimum [redacted] 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 (development of spermatozoa) after the last application of IP.

6.2 Benefit-risk Assessment

Mitigation of BCCs and SEB tumor burden has so far 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 (Tang et al., 2012). In 41 patients followed for a mean of 8 months (range, 1 to

15) after enrollment, the per-patient rate of new surgically eligible basal-cell carcinomas was lower with vismodegib than with placebo [redacted] But because of detrimental class-specific side effects, most patients discontinue oral HHI such as vismodegib (John and Schwartz, 2016). 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 (Patidegib IB). 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 3 study.

Notwithstanding the low systemic bioavailability of Patidegib Topical Gel, 2%, (Patidegib IB) the class effects seen with oral HHI are considered potential adverse events for Patidegib Topical Gel, 2%. These include muscle spasm, alopecia and dysgeusia (Patidegib IB, Lacouture et al., 2016). As observed with the oral HHI class, embryo-fetal toxicity has been observed in nonclinical studies of the oral formulation of patidegib (Patidegib IB).

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 (Patidegib IB). Cessation of growth in children treated with oral HHI has also been reported (Robinson et al., 2017). Pediatric patients are excluded from this study.

All formulation components of patidegib topical gel meet standard US or international compendial standards and are generally recognized as safe (Patidegib IB). 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).

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

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion/Exclusion Criteria – Baseline and when applicable, Screening

A Screening and Baseline visit is mandatory for all subjects. Subjects who fail a Screening visit may be rescreened.

All eligibility criteria at the Baseline visit must also be met at the Screening/Rescreening visit. Additionally, at the Screening visit a serum pregnancy test must be negative.

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.
2. The subject must provide written informed consent prior to any study procedures.
3. The subject must have completed PellePharm Study 926-201 or 926-301 with adequate compliance
4. Study 926-301 subjects must have completed the End of Treatment Visit in Study 301, prior to the Screening Visit in this study. They must also complete all Study 301 related procedures prior to the Baseline Visit of this study.
5. The subject must meet diagnostic criteria for Gorlin (basal cell nevus) syndrome, including major criterion #a plus 1 additional major criterion or plus 2 additional minor criteria listed in Appendix 17.2
6. The subject must be willing to abstain from application of a non-study topical medication (prescription or over the counter) to facial skin for the duration of the trial except as prescribed by the Investigator. Moisturizers and emollients are allowed. Subjects will be encouraged to use their preferred sunscreen with a sunscreen protection factor (SPF) of at least 30 daily on all exposed skin sites.
7. Female subjects must have a negative pregnancy test (serum pregnancy test at Screening Visit, urine pregnancy test at Baseline Visit). For Study 301 subjects, a negative serum pregnancy test result from Study 301 is acceptable if the test was done within 7 days of the Screening Visit of this study.
8. 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 17.1). 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
9. 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.
10. The subject is willing for all facial BCCs to be evaluated and follow treatment recommendations made only by the Investigator.

11. 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 BCC potentially might compromise the health of the subject. In such instances, the only other allowed form of treatment is surgical.

7.1.2 Subject Exclusion Criteria

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

1. 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]
2. The subject has a known hypersensitivity to any of the ingredients in the study IP formulation.
3. The subject is unable or unwilling to make a good faith effort to return to the study site for all study visits and tests.
4. 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 (excluding Study 926-301) while enrolled in this study.
5. The subject is a WOCBP who is unwilling or unable to comply with pregnancy prevention measures.
6. The subject is pregnant or breastfeeding.
7. The subject has any condition or situation which, in the Investigator's opinion, may put the subject at significant risk, could confound the study results, or could interfere significantly with the subject's participation in the study. This 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 systemically or applied on the face concomitantly during the study. This includes the use of drugs indicated for the treatment of superficial BCCs such as imiquimod, 5-fluorouracil. Topical agents may be applied on anatomical sites other than the face.

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.

BCCs may be removed at the discretion of the Investigator in consultation with the patient, by the Investigator or a competent physician/surgeon at any time after the Baseline Visit.

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 the Exit Visit, evaluations should be performed at the time of early termination and the reason for termination should 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 for medical or ethical reasons affecting the continued performance of the study

8 STUDY PROCEDURES AND ASSESSMENTS

The study will be conducted as outlined in the schedule of assessments (SoA).

8.1 Study Procedures

The SoA is provided in Table 1.

Study 301 subjects will have their Screening visit after Study 926-301 End of Treatment visit. This can be on the same day as the Study 301 End of Treatment visit. Study 301 End of Treatment visit assessments may be used for Screening or rescreening assessments in this study if the visit in this Study occurs within 7 days of the End of Treatment/Exit visit of Study 301. The Baseline Visit may take place no more than 30 days after the Screening/Rescreening visit. If this period exceeds 30 days, subjects will need to be re-screened.

For most patients, following the Baseline Visit, study visits will occur at quarterly intervals. IP will be dispensed to cover 3 months supply. However for WOCBP, post Baseline visits will occur every month. Only after pregnancy is ruled out at these visits will IP be dispensed.

Subjects should be seen for all visits on the designated day or as close as practically possible.

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, acceptable contraceptive measures and their duration are provided in the inclusion and exclusion criteria and in Appendix 17.1.

8.1.3 Randomization

This is an open label study. Subjects will not be randomized. All subjects will receive Patidegib Topical Gel.

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 including that 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

At the Baseline visit, the number of lesions on the face that are suspicious for BCC will be recorded. Additionally, the number of lesions on the face that are suspicious for BCC and that the patient consents to have removed in accordance with PI recommendation will also be recorded. These will be removed prior to the next Post-baseline quarterly visit.

At all quarterly visits, the number of lesions on the face that are suspicious for BCC will be recorded. Additionally, the number of lesions on the face that were suspicious for BCC and removed since the last visit will be recorded. Finally the number of lesions on the face that were suspicious for BCC, removed and confirmed on histology to be BCC will be recorded.

The count of facial lesions will exclude lesions on the face where IP should not be applied (i.e eyelids). Face is defined as in Section 10.4**.**

8.2.1 Biopsy

This is a mandated study procedure for all lesions suspicious for BCCs that were removed (irrespective of the treatment modality). All biopsies need to 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.

8.2.2 Surgery

During the study, only lesions that the patient consents to have removed in accordance with the PI recommendation will be removed.

Per local standard of care, the PI may decide to biopsy the lesion first and remove it based on histopahtologiuc confirmation. Alternately, this may be a one step procedure where the lesion is removed and biopsied at the same time.

8.2.3 Quality of Life Assessments

Patient reported outcome (PRO) or electronic PRO (ePRO) will be collected [redacted]

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

Table 1: Schedule of Assessments

Procedure	Pre-treatment	Treatment												F-Up
	Screening/Rescreening[a] (-30 days)	Baseline[b] (Day 1)	M 1	M 2	M 3	M 4	M 5	M 6	Mo 7	Mo 8	Mo 9	M 10	M 11	M 12[c]	30 Days[d]
Visit[e]	**1**	**2**	**2.1**	**2.2**	**3**	**3.1**	**3.2**	**4**	**4.1**	**4.2**	**5**	**5.1**	**5.2**	**6**	**7**
Informed Consent	X	X													
Inclusion/Exclusion	X	X													
Demographics	X	X													
Medical history	X	X													
Current/concomitant medications	X	X			X			X			X			X	
Physical exam (including vital signs)[f]	X	X			X			X			X				X
Pregnancy test - WOCBP[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of contraceptive requirements - WOCBP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy assessments[h]		X			X			X			X			X	
[redacted]															
		X						X			X			X	
Dermal safety and tolerability		X			X			X			X			X	
Adverse events[i]	X	X			X			X			X			X	X
[redacted]															
					X			X			X			X	

[a] The Screening Visit is mandatory for all subjects. Patients who fail screen may be rescreened. The patient will need to meet all I/E criteria at rescreen. Study 301 subjects will have their Screening visit after the Study 301 End of treatment visit. This can be on the same day as the Study 301 End of treatment visit. Study 301 End of treatment visit assessments may be used for Screening or rescreening assessments in this study if the visit in this Study occurs within 7 days of the End of Treatment/Exit visit of Study 301. All Screening/Rescreen assessments will need to be data entered into the database for this study.

[b] The Baseline Visit is mandatory for all subjects. Study 301 participants will have to complete all Study 301 related procedures before the Baseline Visit for this Study. Baseline visit will need to occur within 30 days of the Screening or rescreen visit.

[c] End of treatment/Exit Visit. This visit occurs at the end of treatment which may be after Month 12 (if the treatment period is extended beyond Month 12).

[d] Safety/Follow Up Visit will be conducted 30 days following the subject's End of treatment/Exit Visit

[e] WOCBP subjects will have monthly visits. Other subjects will have quarterly visits. If the treatment period is extended beyond 12 months, these visits will recur until the end of treatment visit. Additionally any subject may be evaluated at an unscheduled visit as needed.

[f] 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.
[g] Serum pregnancy test at Screening and End of treatment/Exit Visit. For Study 301 subjects a negative serum pregnancy test result from Study 301 is acceptable if the test was done within 7 days of the Screening Visit of this study. Urine pregnancy test at all other visits.
[h] Efficacy assessments include – number of lesions removed by surgery since last assessment and count of BCCs. Lesions may be removed at any time per PI convenience but before the subsequent visit. Lesions identified at the End of treatment/Exit Visit, must be removed within 15 days of this visit.
[i] AEs that occurred after signing of the informed consent will be recorded.
[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.

8.3 Safety Assessments

The safety assessments in the study include vital signs, AEs and dermal safety 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. These assessments will be performed prior to the application of IP. Any local skin reaction that requires use of a concomitant therapy or causes interruption or discontinuation of the IP should be reported as a 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 count will be captured separately as efficacy assessments and not as a PE assessment. Changes in BCC count or size will not constitute AEs.

8.3.3 Pregnancy Tests

All WOCBP will have a pregnancy test done at all visits, as per the SoA (Table 1). 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.

9 TREATMENT PLAN

9.1 Methods of Assigning Subjects to Treatment Groups

This is an open label study where all patients will receive Patidegib Topical Gel 2%.

9.2 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.

Patients will be dispensed a diary to maintain a log of their IP application. Any interruptions in the schedule of IP administration or use of prohibited concomitant medication will be recorded in the eCRFs.

9.3 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 (FDA sheets and notices). 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]

For IP received undamaged, IP will be inventoried and the IP inventory/accountability log completed.

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 under controlled room temperature at 20-25 °C (68-77 °F) with excursions allowed from 15-30 °C.

10.4 Application

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 initial application of the IP will take place in the clinic under observation. 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 Investigator or site personnel will instruct the subject on the proper use of laminated dosing cards during the Baseline Visit. Subjects will apply to the face an amount squeezed out as a specified amount on the laminated dosing card [redacted] avoiding the eyelids (as described above and in the Pharmacy Manual). If no observable AEs are noted within a [redacted] observation period after their first application, subjects can leave the site. No other IP applications at subsequent visits will be required to be observed in the clinic setting.

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 may 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 be advised to minimize exposure to direct sunlight and to wash their hands before and after application of the IP.

[redacted] If an IP application has been missed or delayed such that there would be [redacted] between applications, the subject should not apply that dose of IP and just wait to apply the next

dose. The importance of IP compliance should be discussed with the subject during each site visit.

Subjects will be instructed to store their IP in a secure location away from children. WOCBP should not come in contact with the gel unless using contraception as specified in this protocol.

If it is suspected that inappropriate amounts of IP are being applied by the subject 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

PellePharm will notify regulatory authorities of unexpected related SAEs and all participating study sites in writing for submission by the Investigator to the IRB, EC or REB. 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/EC/REB, according to local regulations. The Sponsor, Investigator and IRB//EC/REB will determine if the informed consent requires revision. The Investigator should also comply with the IRB//EC/REB procedures for reporting any other safety information.

12 STATISTICS

12.1 Analysis Population

The primary population for analysis of safety and efficacy will be the Safety population. This population will comprise all patients who had at least one application of study treatment. Subgroup analysis will be done for subjects with history of oral or topical HHI in past 6 months – Yes/No.

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 using descriptive statistics for the Safety population.

12.4 Protocol Deviations

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

12.5 Compliance

Compliance will be determined from the use of diary cards.

12.6 Assessment of Efficacy

12.6.1 Efficacy Endpoints

The efficacy endpoints are as follows:

1. The number of facial BCCs removed by surgery (per Investigator determination) and histologically verified as BCC; from Baseline to Month 12
2. The number of facial BCCs removed by surgery (per Investigator determination) and histologically verified as BCC; from Baseline to Month 6.
3. The number of facial BCCs removed by surgery (per Investigator determination) from Baseline to Month 12.
4. The number of facial BCCs removed by surgery (per Investigator determination) from Baseline to Month 6.
5. Change from Baseline to Month 12 in the total number of facial lesions suspicious for BCC
6. Count of facial lesions suspicious for BCC over time
7. aBCCdex change in lesion score from Baseline to Month 12

12.6.1.1 Exploratory Endpoints

Additional endpoints will be listed in the Statistical Analysis Plan (SAP).

12.6.2 Efficacy Analyses

All analysis will be descriptively summarized. There will be no hypothesis testing. Additional information, including the handling of missing data will be provided in the SAP.

12.6.3 Sample Size Determination

This study is not powered for efficacy. All eligible subjects from Study 201 and 301 will be enrolled into this study.

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 visit.

12.7.2 Adverse Events

Subjects will be assessed for the occurrence of new and ongoing AEs. Listings 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, 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, 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 at all applicable study visits.

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

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

17.2 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:

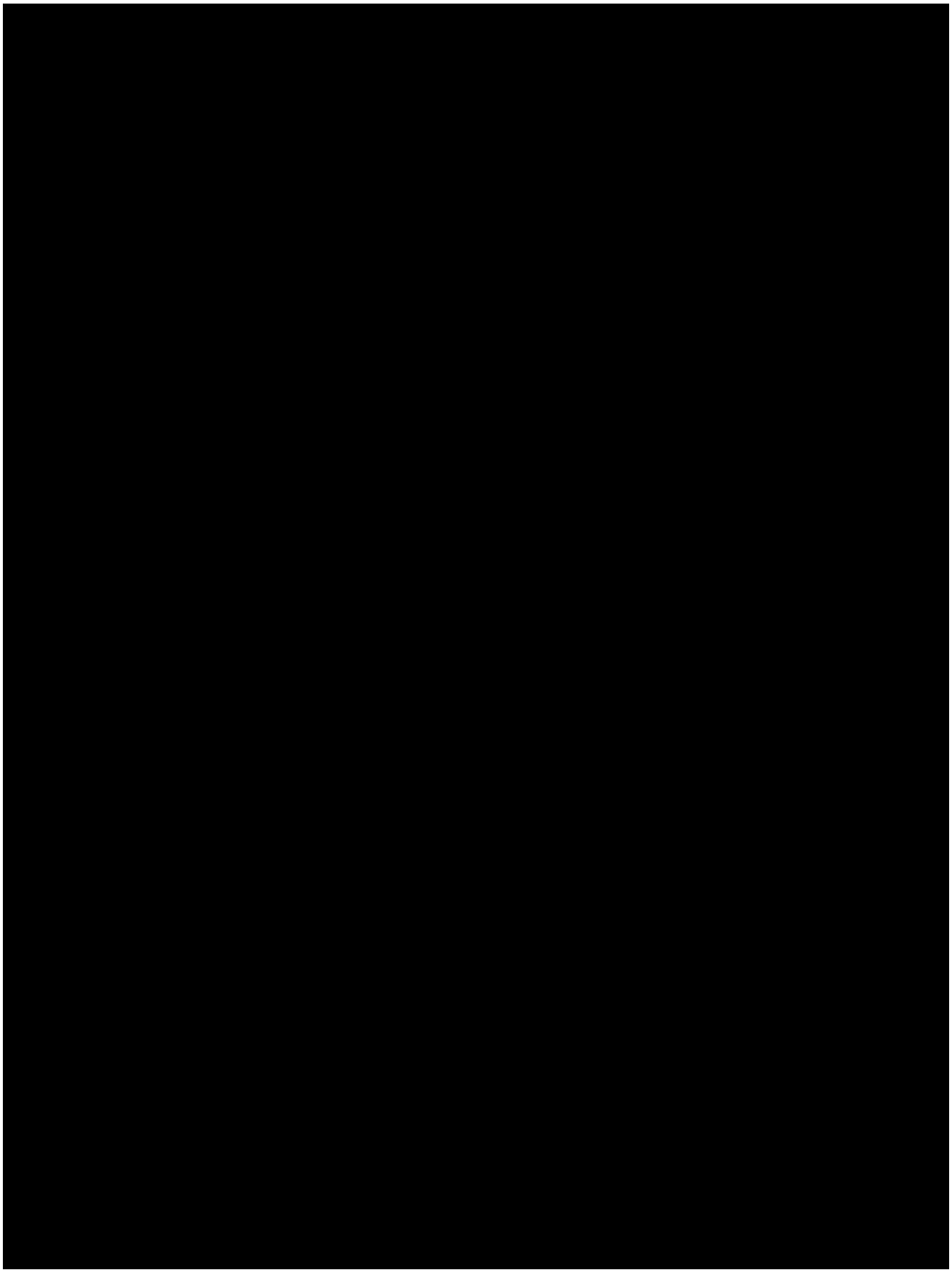
a. >2 histologically confirmed BCCs or 1 for subjects under age 20.
b. Odontogenic keratocysts of the jaw confirmed histologically.
c. ≥3 palmar and/or plantar pits seen at the Screening Visit.
d. Bilamellar calcification of the falx cerebri present at less than 20 years old.
e. Fused, bifid, or markedly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

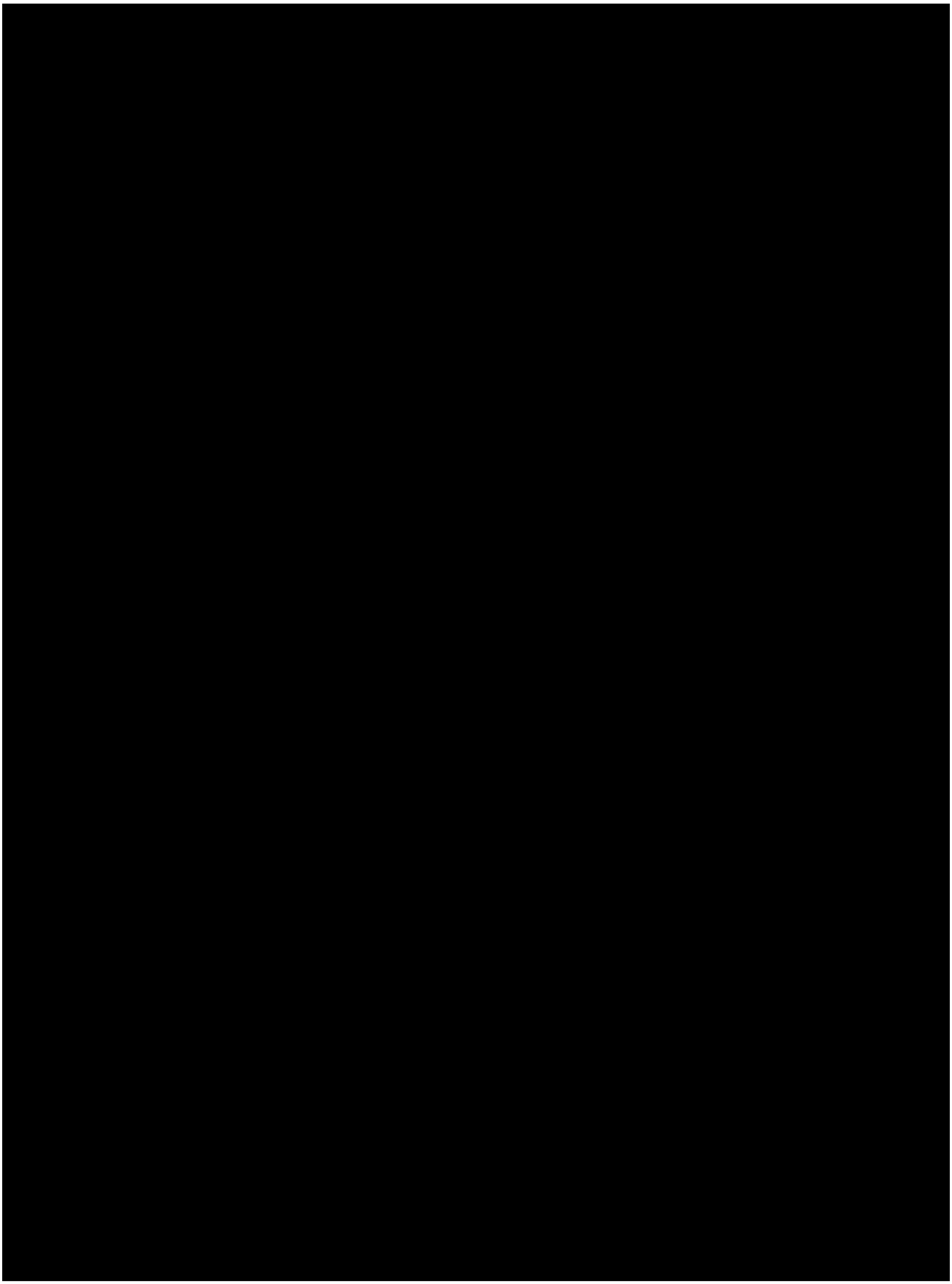
Minor criteria:

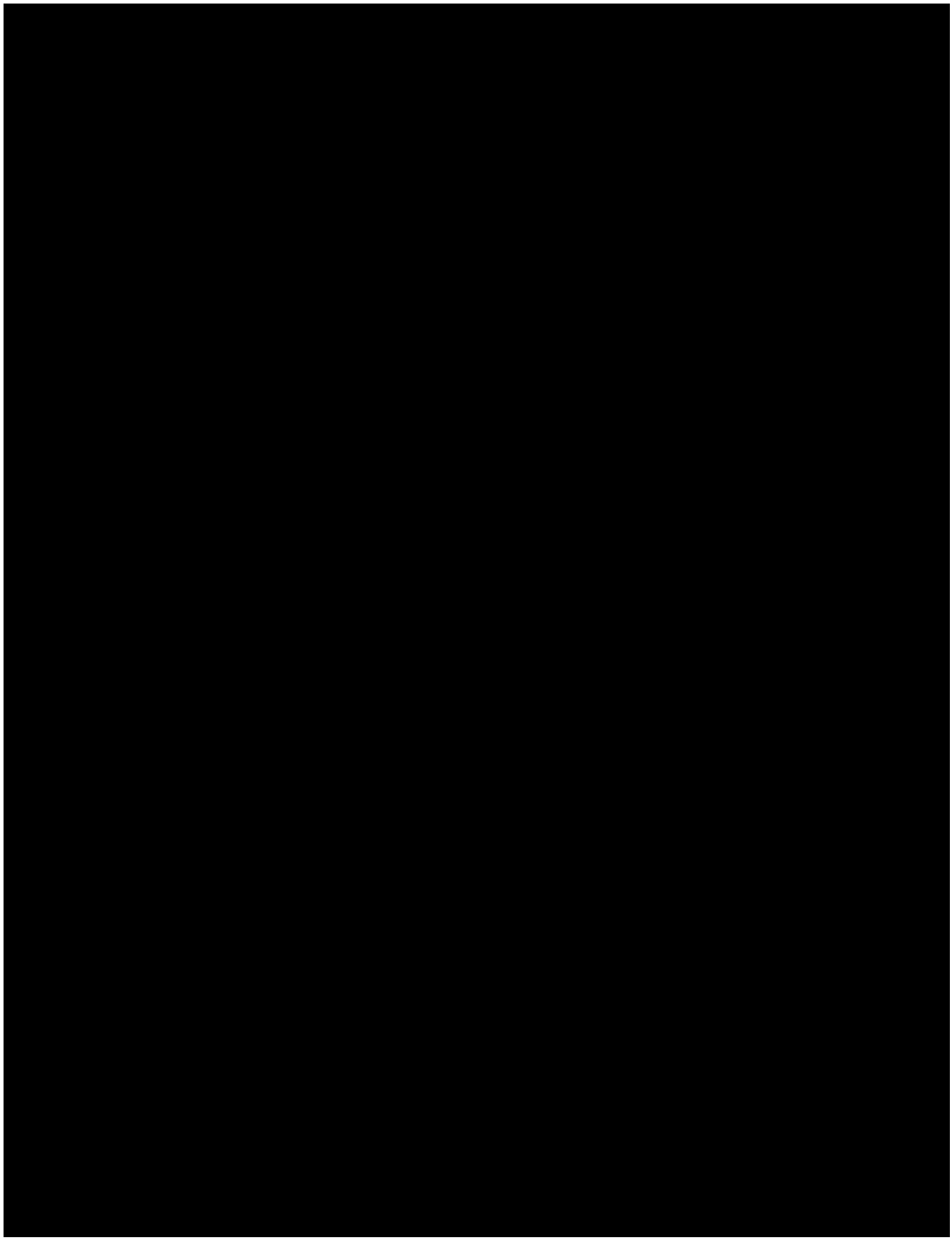
a. Macrocephaly.
b. Congenital malformations including frontal bossing, cleft lip or palate, "coarse face", moderate to severe hypertelorism.
c. Skeletal abnormalities detectable clinically: Sprengel deformity, marked pectus deformity, or marked finger syndactyly.
d. Skeletal abnormalities detectable 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*)

17.3 Patient Reported Outcomes (PRO) Questionnaires

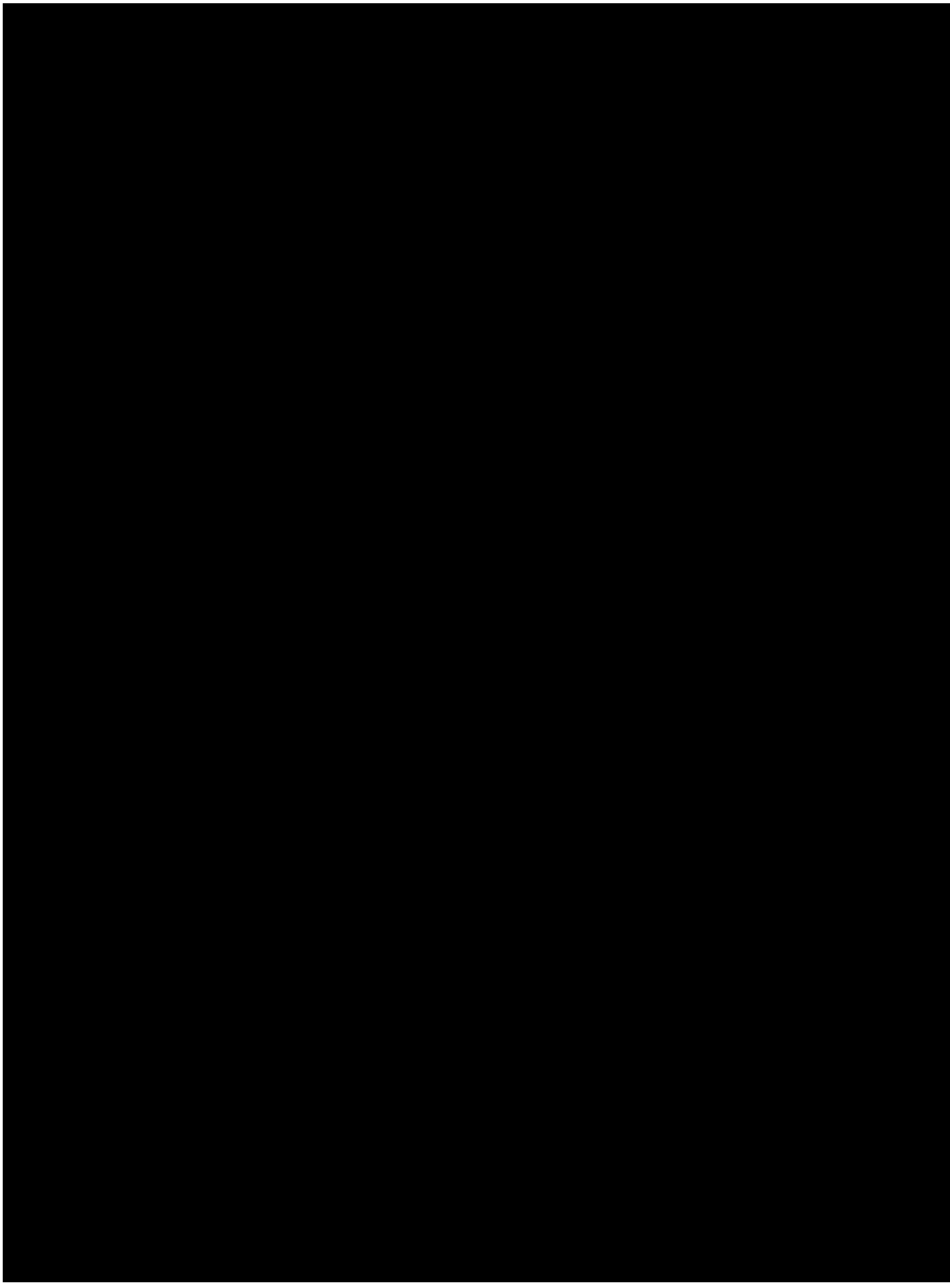
Appendix 17.3.1 [redacted]

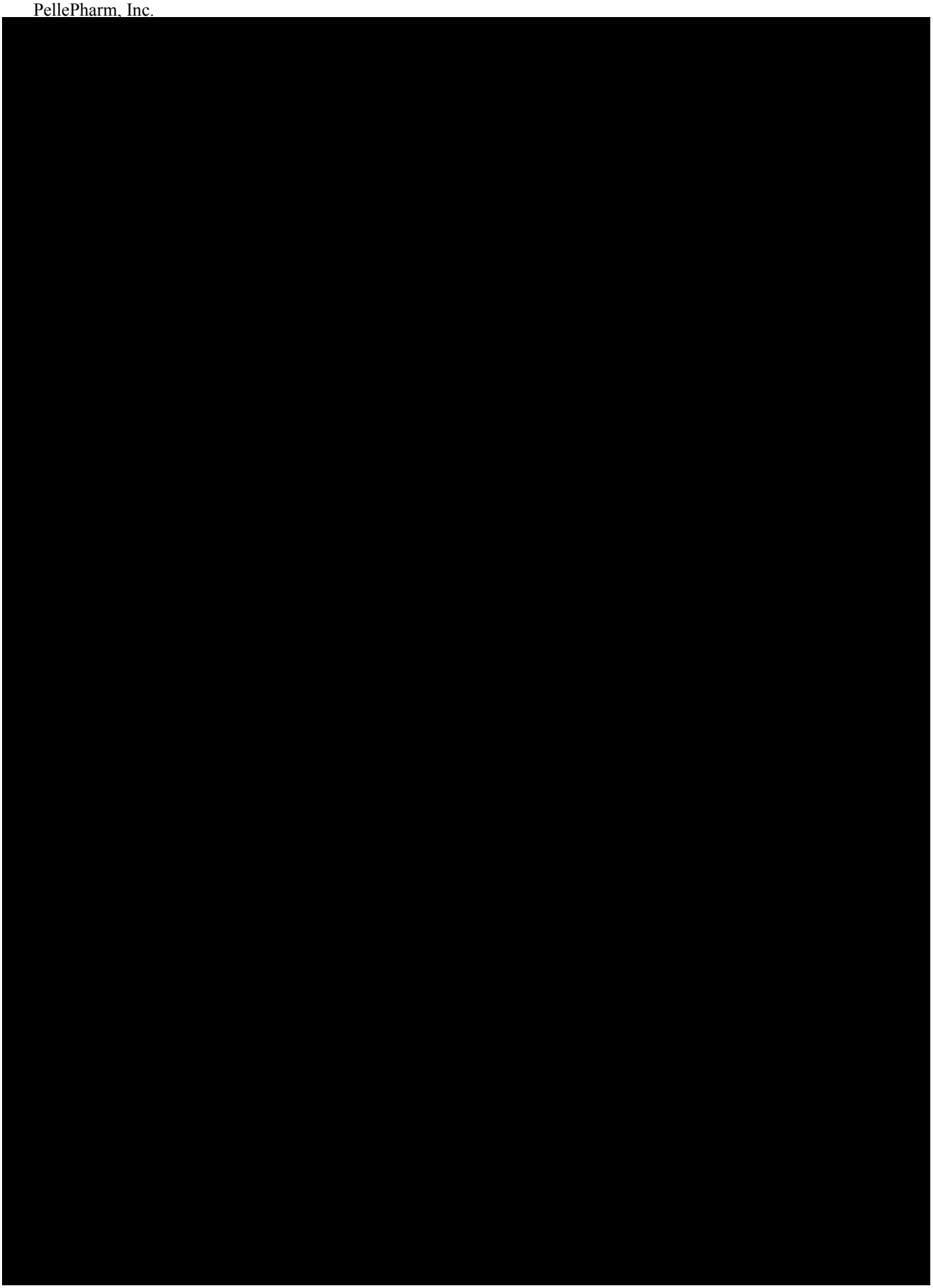






Appendix 17.3.2 [redacted]





Appendix 17.3.3 [redacted]