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CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

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

Sponsor Study Code: Pelle-926-301E

TFS Project Code: [redacted]

Sponsor	PellePharm, Inc.
Product/Compound/Device	Patidegib
Phase of the study	III
EudraCT number	2018-001462-42
Author	[redacted]
Company	TFS Trial Form Support
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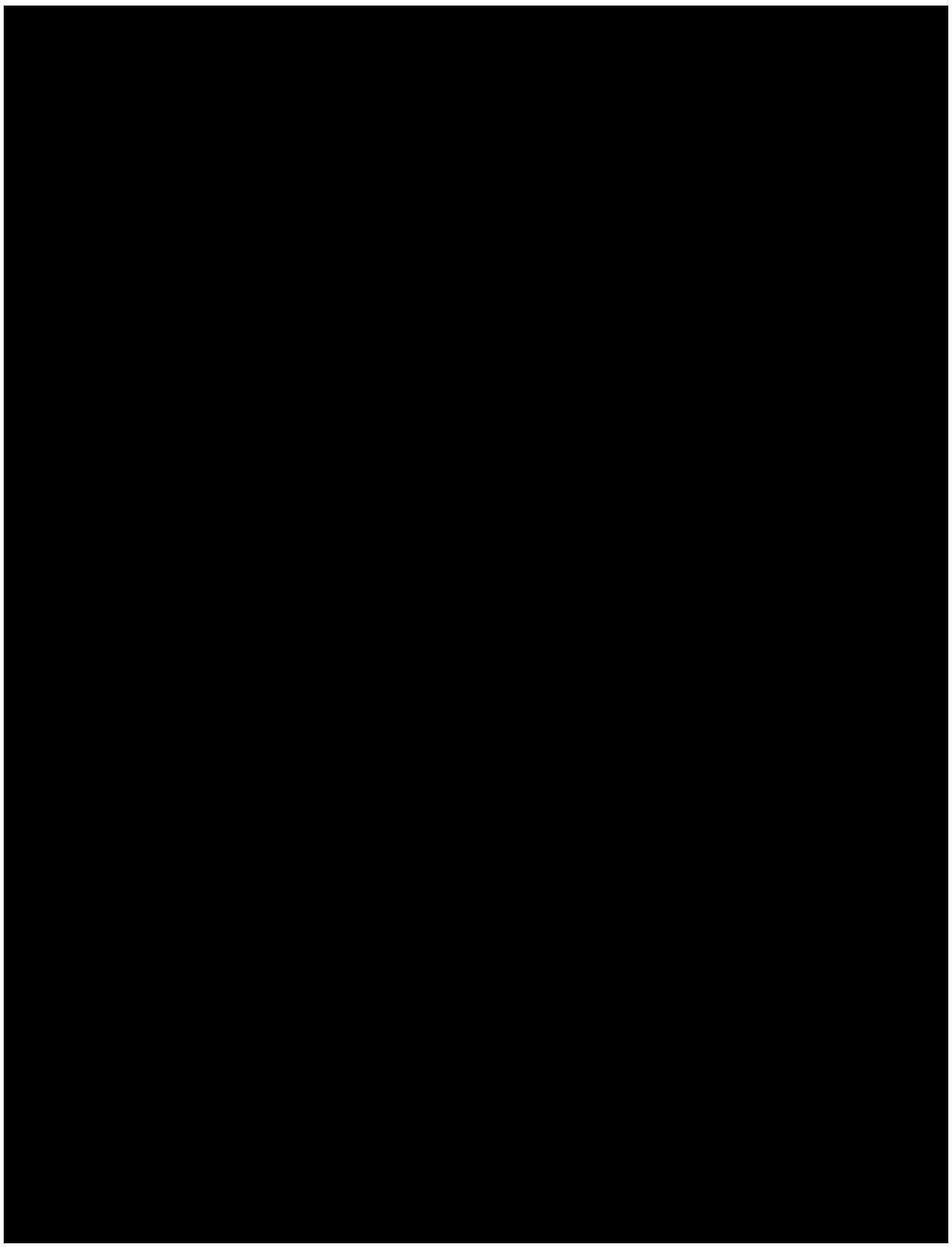
Protocol (amendment #)	25-NOV-2019



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ABBREVIATIONS

aBCCdex	Advanced Basal Cell Carcinoma Index
AE	Adverse Event
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DLQI	Dermatology Quality of Life Index
DRM	Data Review Meeting
EQ-5D-5L	EuroQol (Quality of Life) using 5 levels
HHI	Hedgehog Inhibitor
ICF	Informed Consent Form
IP	Investigational Product
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per Protocol
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WOCBP	Women of Child Bearing Potential

1. VERSION HISTORY

Table 1. Summary of Major Changes in SAP

Version	Date	Summary of Changes
Initial version	16-APR-2020	[redacted]

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analysis and detailed methodology for the Clinical Study Report (CSR) of study Pelle-926-301E.

This SAP is based on Clinical Study Protocol (CSP) Version 2 dated January 30, 2020. This analysis plan overrides any statistical plans outlined in the protocol.

2.1. Study 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 Objective

- To assess the efficacy of Patidegib Topical Gel, 2% in patients who have completed PellePharm Study Pelle-926-201 or Pelle-926-301

2.2. 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. The treatment duration is 12 months, with potential extension beyond this period.

All study participants will be treated with Patidegib Topical Gel 2%.

A Screening visit will be mandatory for all subjects, with the possibility for rescreening for those who fail screen. Subjects will need to meet all I/E criteria at screening/rescreening visit. Completers from study Pelle-926-301 will have their Screening visit after the Study Pelle-926-301 End of treatment visit.

Study visits will occur at quarterly intervals. However for WOCBP, study visits will occur monthly. For the first application, the subject will apply the IP to the face at the study site under the direction of the Study Coordinator (or designee). The IP should be applied after all clinical assessments. Patients will be dispensed a diary to maintain a log of their IP application.

3. STUDY PROCEDURES AND ASSESSMENTS

3.1. Safety Assessments

- Physical Examination Including Vital Sign Results
- Pregnancy Tests

3.2. Efficacy Assessments

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

3.3. Exploratory Assessments Patient Reported Outcomes

Exploratory assessments will comprise the following Patient Reported Outcomes (PROs) of Quality of Life:

- Advanced Basal Cell Carcinoma index (aBCCdex)
- Dermatology Life Quality Index (DLQI)
- EuroQol Group 5-level EQ-5D (EQ-5D-5L)

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study, either '**study drug**', '**study treatment**' or '**Investigational product (IP)**' refer to Patidegib Topical Gel, 2%.

Start and end dates of study treatment:

The date/time of first dose of study treatment is the earliest date/time of non-zero dosing of the study drug.

The date/time of last dose of study treatment is the latest date/time of non-zero dosing of the study drug.

Definition of baseline:

In this study, baseline value will refer to the last assessment prior to the first dose.

3.4.2. Baseline characteristics

- Inclusion and exclusion criteria
- Demographic data
- Medical history
- Prior and concomitant medication

4. ANALYSIS POPULATIONS

Only patients who signed the Informed Consent Form (ICF) will be included in the analysis sets described below.

4.1. Safety Population

The safety analysis set will include all patients who had at least one application of study treatment. The primary population for analysis of safety and efficacy will be the safety population.

Subgroup analysis will be done for subjects with history of oral or topical HHI in past 6 months – Yes/No. This will be determined based on the group they were randomized in the parent study (i.e. either 201 or 301) and the previous and concomitant medication pages.

The following efficacy assessments will be analyzed for the forementioned subgroups:

- The number of facial BCCs removed by surgery (per Investigator determination) and histologically verified as BCC; from Baseline to Month 12
- The number of facial BCCs removed by surgery (per Investigator determination) from Baseline to Month 12
- Change from Baseline to Month 12 in the total number of facial lesions suspicious for BCC

4.2. Other Population

4.2.1. Per-protocol Population

The Per-Protocol set (PPS) will include all subjects in the Safety population who have no major Protocol Deviations (PDs). The final criteria for the PPS will be determined when all data on PDs are available through a Data Review Meeting (DRM). Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database (i.e. Database Lock) and classifications will be documented per TFS's (or Sponsor's) standard operating procedures. Patients who meet any of the following criteria may be excluded from the PP analysis set:

- Patient with any major protocol violations in regards to inclusion/exclusion criteria
- Patient not completing 12 months of treatment with 80% - 120% treatment compliance (see Section 6.3.3)
- Patient taking any prohibited concomitant medications.

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

4.2.2. PK Population

Not Applicable.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Sample size determination

As stated in the CSP, this study is not powered for statistical significance. Eligible subjects (completers) from PellePharm Studies 926-201 and 926-301 will be enrolled into this study up to a maximum of about 200 participants.

5.2. General Methods

Endpoints will be summarized based on either the Safety or the PP analysis sets.

5.2.1. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values [i.e., n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages based on number of available observations. Missing data will not be summarized as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.2. Definition of study day

Start day of study treatment is the day of the first IP application of study treatment.

The study day for assessments occurring on or after the start of study treatment will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first IP application of study treatment will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.3. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first IP application of study treatment to last IP application of study treatment + 30 days.

Safety data collected outside the on-treatment period as well as data from unscheduled visits will be listed and flagged in listings but not summarized.

5.2.4. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)
  - In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The

rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. E.g., 3.1 to 3.4 will be rounded to an integer of 3, and 3.5 to 3.9 will be rounded to an integer of 4.

5.2.5. Unscheduled visits

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 per any other post-Baseline Visits may be conducted. Data collected will be reported in the 'Unscheduled Visit' eCRF page.

Data from unscheduled visits will be summarized by assigning to closest visit within a 6-week window. If two unscheduled visits occur in a row the last one will be assigned (Last Observation Carried Forward approach).

All unscheduled visits info will be listed, flagging those that have been assigned to a pre-scheduled visit.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

No missing data imputation is planned. All summaries will use observed data only. Missing statistics, e.g. when they cannot be calculated, should be presented as 'ND' or 'NA'.

5.3.2. Handling of incomplete dates

5.3.2.1. Adverse events

Incomplete AE-related dates will be imputed in a conservative manner, as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/NOV/2014, and study treatment start date is 14/NOV/2014, then the imputed AE onset date will be 14/NOV/2014.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2013, and study treatment start date is 18/JAN/2013, then the imputed AE onset date will be 18/JAN/2013.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only) if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.

- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off then the outcome of AE will be ongoing at cut-off.

5.3.2.2. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/NOV/2014, and study treatment start date is 15/NOV/2014, then the imputed medication start date will be 15/NOV/2014.
- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2013, and study treatment start date is 20/JAN/2013, then the imputed medication start date will be 20/JAN/2013.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only) if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.3. Exposure

No imputation will be done for first IP application date. Date of last IP application of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the date of last contact will be the last IP application date
- If the last date of study drug is completely or partially missing and there is an End of Treatment eCRF page available (within the cut-off date), then imputed last IP application date is:

  = 31DECYYYY, if only Year is available and Year < Year of EOT date

  = Last day of the month, if both Year and Month are available and Year = Year of EOT date and Month < the month of EOT date

  = EOT date, for all other cases

5.3.3. Imputation rules for date of last contact

The date of last contact will be derived for patients at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory), vital signs, performance status)
- AE start and end dates
- Study drug start and end dates
- Randomization date
- Withdrawal of consent date

Only dates associated with actual examinations of the patient will be used in the derivation.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Safety and Tolerability.

Safety and tolerability are the primary objectives of this study and will be evaluated by reviewing adverse events (see Section 6.4.2), treatment discontinuations and dermal safety and tolerability (see Section 6.4.1).

6.1.1.1. Primary analysis

No inferential tests will be performed. Data will be summarized through descriptive statistics only.

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

See Section 6.4.

6.2.2. Efficacy endpoints

The efficacy endpoints are:

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.

All efficacy assessments will be summarized descriptively by visit, depending on the nature of the variable. Changes from Baseline will also be displayed.

6.2.3. Exploratory Endpoints

The exploratory endpoints will investigate PROs:

1. Change in aBCCdex Worry About Future Lesions scale score from Baseline to Month 12.
2. Change in aBCCdex Mental Health scale score from Baseline to Month 12.
3. Change in aBCCdex Social/Relationships scale score from Baseline to Month 12.
4. Change in aBCCdex Life Impact scale score from Baseline to Month 12.
5. Change in Dermatology Life Quality Index (DLQI) total score from Baseline to Month 12
6. Shift in EuroQol (Quality of Life) using 5 levels (EQ-5D-5L) from baseline to Month 12
7. Change in EQ-5D-5L Visual Analog Scale (VAS) from Baseline to Month 12

A shift table will be presented for changes from baseline of the EQ-5D-5L dimension scores. Additionally, the VAS Scores will be summarized descriptively by visit.

6.2.4. Pharmacokinetic endpoints

Not applicable

6.3. Baseline and Other Summaries and Analyses

6.3.1. Baseline summaries

The following analyses will be based on the Safety population.

6.3.1.1. Demographic characteristics

Demographic characteristics and physical measurements will be summarized using the following information from screening visit in the 'Demographics' eCRF page.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown
  - Ethnicity: Hispanic/Latino (Yes/No)

  - Age (years): summary statistics
  - Geographic Region:
    - United States + Canada
    - United Kingdom + European Union

- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)
- Method of contraception
- Fertility

Demograhic characteristics and physical measurements will be summarized by descriptive statistics. All demographics data will be listed for the safety set.

6.3.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables ordered by primary SOC and PT in alphabetical order.

6.3.1.3. Prior and concomitant medications/therapies

Prior and concomitant medications/therapies 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.

6.3.2. Study conduct and patient disposition

The following analyses will be performed based on the Safety population.

6.3.2.1. Patient disposition

The percentages below will be calculated based on the number of patients in the Safety population.

- Total number of patients enrolled
- Number and percentage of enrolled patients in each of the analysis populations defined in Section 4
- Number of enrolled patients who discontinued from the study and the main reason for discontinuation
- Number and percentage of enrolled patients who discontinued study treatment overall and by the main reason for discontinuation of study treatment

Additionally, Time to Treatment Discontinuation will be graphically displayed using Kaplan-Meier curves.

6.3.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of a study and/or its evaluation will be reported. These include:

- Patients who are treated on the study despite not satisfying the inclusion criteria
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn
- Patients who receive an excluded concomitant medication
- Patient not completing 12 months of treatment within 80% - 120% treatment compliance (See section 6.3.3)
- Deviations from GCP

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.3.3. Study treatment compliance and exposure

The following analyses will be based on the Safety population.

Compliance will be calculated using subject's diary by dividing doses taken by doses planned.

Compliance will be summarized by visit and will also be a factor in defining the PP population as noted in Section 4.3.1.

Listings of baseline study drug application, study drug accountability, compliance, and study drug interruption will be created.

6.4. Safety Summaries and Analyses

The Safety Population will be the primary population for safety evaluations. All summaries of AEs and other safety parameters will be based on the safety population.

6.4.1. Dermal Safety and Tolerability

Dermal 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.

Shift tables of the frequency of dermal safety and tolerability assessments including pain/burning, pruritus, erythema, edema, and crusting will be summarized using counts and percentages by visit compared to baseline.

A listing of all dermal safety and tolerability assessments will be also provided.

6.4.2. Adverse Events

AEs will be graded by the investigator and coded using most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event is during the on-treatment period.

All analyses described **Error! Reference source not found.** will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Possibly / Probably / Definitely) reported by the investigator and those of unknown relationship (i.e., no answer to the question ‘Relationship with study treatment’). Related AEs are those related to any study treatment.
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).

- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal).

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by primary SOC and PT in decreasing frequency based on the frequencies observed.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.4.2.1. All adverse events

Adverse events will be summarized by worst severity per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing severity, the maximum of the non-missing severity will be displayed. No imputation of missing severity will be performed.

AEs will be split between “prior to treatment” and “treatment emergent”. The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following:
  - TEAEs
  - TEAEs related to IP
  - TEAEs leading to treatment discontinuation
  - TEAEs related to IP leading to treatment discontinuation
  - Paralesional TEAEs
  - Serious TEAEs
  - Serious TEAEs related to IP
  - TEAEs leading to death
  - TEAEs related to IP leading to death
- TEAEs by SOC and PT and maximum severity
- TEAEs by closest relationship to study drug

6.4.2.2. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients TEAEs leading to discontinuation of Patidegib will be tabulated by SOC and PT.

A listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.4.2.3. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died will be tabulated based on information from the 'End of Treatment', 'End of Study' and 'Adverse Event Log' eCRF pages.

6.4.2.4. Serious Adverse Events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.4.3. Laboratory data

Pregnancy test results will be the only laboratory data in this study. Results will be listed for the Safety analysis.

6.4.4. Vital signs

Vital sign summaries will include all vital sign assessments from the on-treatment period:

- Body temperature (ºF)
- Respiration (breaths per minute)
- Heart Rate (beats per minute)
- Blood Pressure (systolic and diastolic, in mmHg)

All vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each visit over time. All vital signs data will be listed as well.

7. REFERENCES

1. Mathias, S.D., Chren, M.M., Crosby, R.D., et al. Reliability and validity of the Advanced Basal Cell Carcinoma Index (aBCCdex). British Journal of Dermatology. 2015;173:713-719.

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8. APPENDICES

Appendix 1. aBCCdex Scoring

Appendix 2. DLQI Scoring

Appendix 3. EQ-5D-5L Scoring