NOTE TO FILE

Project: Pelle-926-203 (NCT04155190) Statistical Analysis Plan

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

Date: 18 Jun 2026

Author: Sol-Gel Technologies Ltd.

Objective: Participant-level data for participant flow, study outcome measures, all-cause mortality, and adverse events were not collected by treatment arm (Patidegib and Vehicle) as described in the Statistical Analysis Plan. This Note to File has been authored to document how the data were collected and the analysis conducted.

Considerations: PellePharm Inc. was the Sponsor of this study until 29 January 2023. While they were Sponsor of this study, they made the decision to prematurely terminate the study (decision as of 15 June 2021).

Sol-Gel Technologies Ltd. (Sol-Gel) became responsible for Patidegib from PellePharm, Inc. as of 30 January 2023. The study's Statistical Analysis Plan was finalized on 25 August 2023. The data presented in this results posting reflect information collected prior to study termination by the previous responsible party, PellePharm Inc., and are being reported by the current responsible party, Sol-Gel Technologies Ltd.

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The study was originally planned as a 2-arm study. However, participant-level data were collected and reported only in aggregate for the overall study, rather than by treatment arm for the participant flow, study outcome measures, all-cause mortality, and adverse event data. Additionally, Sol-Gel was not provided data to indicate if any of the BCC events met the protocol-specified criteria to determine the event as a surgically eligible basal cell carcinoma (nSEB). Therefore, no data are available to be reported for the primary outcome measure for this study. In lieu of amending the study protocol and Statistical Analysis Plan, Sol-Gel has prepared this Note to File to document how the data were collected.

Outcome: Sol-Gel will not amend the finalized Statistical Analysis Plan for this terminated study with limited data available.

Signatures

PPD	18 Jun 2026
PPD *PPD*	**Date**

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NCT04155190

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

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

Sponsor Study Code: Pelle-926-203

[redacted]

Sponsor	Sol-Gel Technologies Ltd
Product/Compound/Device	Patidegib
Phase of the study	II
EudraCT number	2018-001462-42
Author	[redacted]
Company	TFS Trial Form Support
Address	[redacted]
Telephone number	[redacted]
Version:	Original: 25-AUG-2023

SIGNATURES

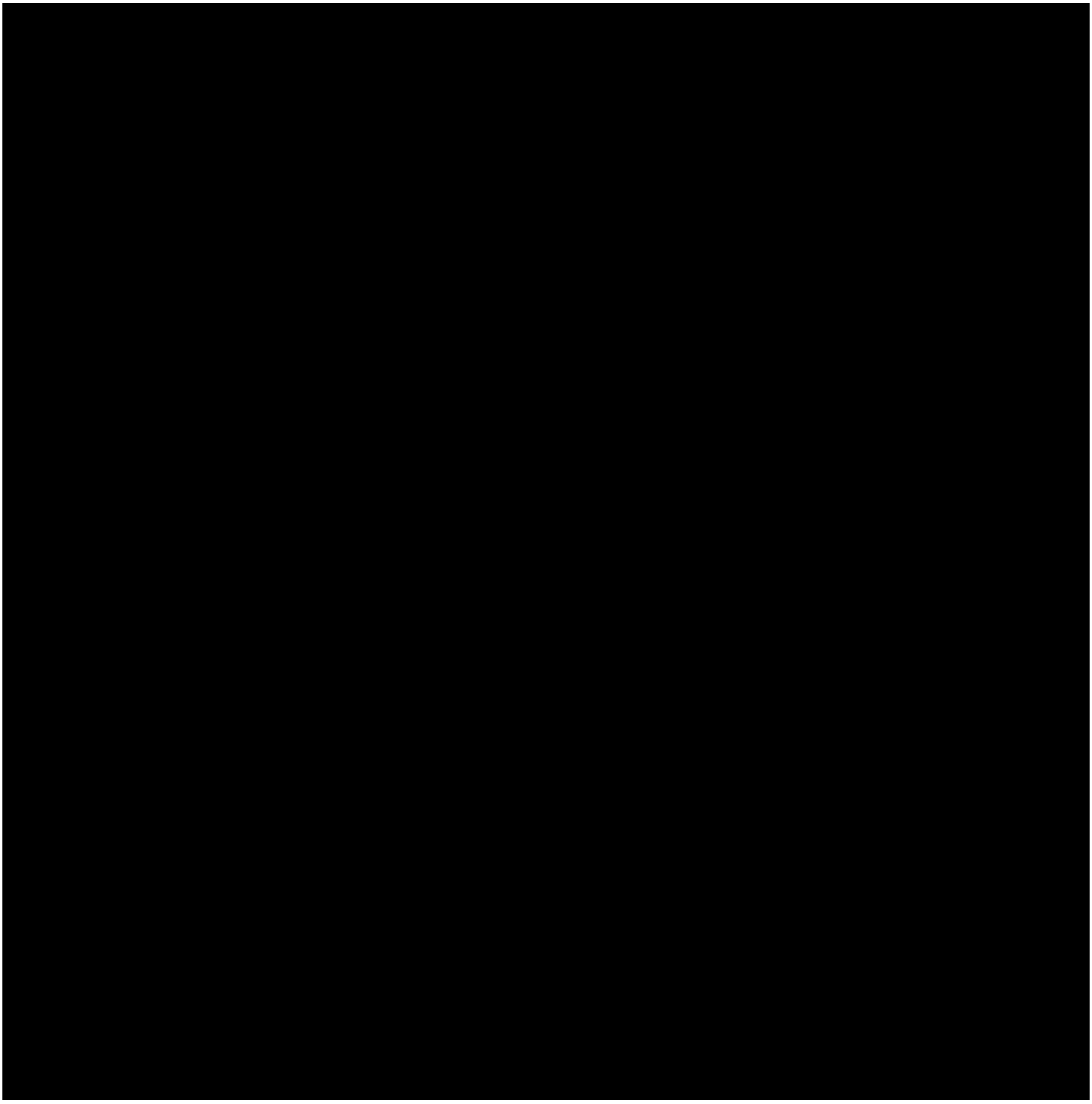


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ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse Event
ANCOVA	Analysis of Covariance
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
CI	Confidence Interval
CRF/eCRF	Case Report Form/electronic Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
[redacted]	[redacted]
[redacted]	[redacted]
EOT	End Of Treatment
EOS	End of Study
FCS	Fully Conditional Specification
GCP	Good Clinical Practice
HF-BCC	High Frequency Basal Cell Carcinoma
ICF	Informed Consent Form
ITT/mITT	Intention-To-Treat/modified Intention-To-Treat
IP	Investigational Product
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
nSEBs	New Surgical Eligible BCCs
ND	Not detected
NA	Not applicable
OC	Observed Case
PP	Per Protocol
PRO/ePRO	Patient Reported Outcome/electronic Patient Reported Outcome
PT	Preferred Term
PTCH1	Patched Protein 1
Q1	First Quartile

Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEB	Surgically Eligible Basal Cell Carcinoma
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, figures, and listings

1. VERSION HISTORY

Table 1. Summary of Major Changes in SAP

Version	Date	Summary of Changes
Initial version - Final	25-AUG-2023	Not applicable – Initial approved version

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analysis and detailed methodology for the Clinical Study Report (CSR) of study Pelle-926-203.

This SAP is based on Clinical Study Protocol (CSP) Final Version dated August 28, 2019. This analysis plan overrides any statistical plans outlined in the protocol.

The earlier study sponsor, PellePharm Inc., terminated study Pelle-926-203 due to low blinded event rate. The study termination was not related to safety of the drug Patidegib Topical Gel, 2%. Sol-Gel Technologies Ltd., the present sponsor, became responsible of the study from 30 Jan 2023 and decided to produce an abbreviated CSR centered on safety evaluations. By the time the study was halted, a version of the SAP had been drafted and reviewed. Instead of discarding the unnecessary analyses for the abbreviated CSR, an index of the agreed tables, figures, and listings (TFLs) is presented in Appendix 4 of this report. The analytical approach for the TFLs in the abbreviated CSR will adhere to the guidelines laid out in this SAP. All other analyses will remain unchanged from their state at the time the study was terminated.

In addition, Pharmacokinetic endpoints stated in the protocol are not described in this document since the analyses will not be performed by TFS.

2.1. Study Objectives

Primary Objective

- To assess the number of new surgically eligible Basal Cell Carcinomas (nSEBs) in patients treated with Patidegib Topical Gel 2% or Vehicle when applied twice daily to the face of subjects with non-Gorlin High Frequency Basal Cell Carcinoma (HF-BCC).

Secondary Objectives

- To assess the safety and tolerability of Patidegib Topical Gel, 2%, in subjects treated twice daily on the face.

2.2. Study Design

This is a multicenter, randomized, double-blind, stratified, vehicle-controlled study of the efficacy and safety of Patidegib Topical Gel, 2%, applied topically twice daily to the face of

adult subjects with HF-BCC. Subjects will be required to apply the Investigational Product (IP) or vehicle for 9 months. The primary endpoint is the number of nSEBs that develop on the face over the 9-month period. Basal Cell Carcinomas (BCCs) will be imaged and tracked consistently throughout the study in order to accurately identify nSEBs.

Study duration is approximately 10.5 months: up to 14-day screening period, 9 months of active treatment, and a 30-day safety follow up.

3. STUDY PROCEDURES AND ASSESSMENTS

3.1. Background and Demography

- Inclusion and exclusion criteria
- Demographic data (date of birth, gender at birth, race and ethnicity)
- Medical history
- Prior and concomitant medication (separately for BCC and other indications)

3.2. Safety Assessments

- Adverse Events (AEs) as characterized by type, severity, timing, seriousness, and relationship to study treatments
- Laboratory abnormalities as characterized by type, severity and timing
- Physical Examination, Pregnancy Tests and Vital Signs
- Dermal Safety and Tolerability Events

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

Table 2 Dermal Safety and Tolerability Scales

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

3.3. Efficacy Assessments and Patient Reported Outcomes

- Digital imaging (unmarked and marked) and BCC measurement

  Digital imaging of the BCCs in digital facial images will be uploaded to the imaging vendor portal for further review. All BCCs will be unmarked or marked, respectively, and the measurement of the longest diameter of each BCC recorded.

- SEB biopsy/excision

  The biopsy will be reviewed and reported by a licensed physician with appropriate experience. The biopsy diagnosis will be captured in the electronic Case Report Form (eCRF).

- [redacted]

4. ANALYSIS POPULATIONS

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 and classifications will be documented per TFS's standard operating procedures (SOP).

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

Table 4 summarizes the use of the analysis sets for efficacy, safety, baseline characteristics and exposure.

Table 3. Statistical Analyses by Analysis Population

Endpoints	Intent-to-treat population	Modified Intent-to-treat population	Per Protocol population	Safety population
Baseline Characteristics	✓			
Prior and Concomitant Therapies	✓			
Exposure				✓
Efficacy: Primary		✓	✓	
Efficacy: Secondary		✓		
Efficacy: Exploratory		✓		
Safety				✓

4.1. Intent-to-Treat Population

The Intent-to-treat population (ITT) will include all randomized patients. Patients will be classified according to the study treatment assigned at randomization.

4.2. Modified Intent-to-Treat Population

The modified ITT (mITT) population will comprise all patients in the ITT population, excluding those who tested positive for pathogenic variants in the Patched Protein 1 (PTCH1) gene. The mITT population will be the primary efficacy analysis population.

4.3. Safety Population

The safety analysis set will include all patients who receive at least one IP application. Patients will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period. Patient who received both Patidegib and Vehicle will be classified in the Patidegib treatment arm.

4.4. Per-protocol Population

Per protocol (PP) Population will include all randomized patients who do not meet any of the following criteria that could impact the key objectives of the study. Patients will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period. Patient who received both Patidegib and Vehicle will be classified in the Patidegib treatment arm. Patients who meet any of the following criteria will be excluded from the PP analysis set.

- Patient tested positive for pathogenic variants in the PTCH1 gene
- Patient did not complete 9 months of treatment [redacted] treatment compliance
- Patient with any major protocol violations in regard to inclusion/exclusion criteria

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Sample Size Determination

The study is not powered for statistical significance. The study will enroll approximately [redacted] subjects (ITT population). It is expected that [redacted] of these subjects will have pathogenic variants in the PTCH1 gene. There will be approximately [redacted] subjects in the mITT population. With [redacted] randomized subjects, the estimated effects will have the following precision (Standard Error): Number of new SEBs: It is assumed that in the active group, there will be [redacted] new SEBs per-subject, with a standard deviation (SD) of [redacted]. The SE of the estimate will be [redacted]. The vehicle group will have [redacted] new SEBs per-subject, with an SD of [redacted] The SE of the estimate will be [redacted] These estimates are based on Gorlin patients in the phase 2 study, Pelle- 926-201. If the distribution of new SEBs is Poisson, then the actual SE may be smaller than estimated here.

5.2. General Methods

Endpoints will be summarized based on the analysis sets described in Table 4 by treatment arm, unless otherwise specified.

5.2.1. Patient Listings

Patient listings of raw data will be listed in agreement with the standardized structure of C-DISC SDTM, meaning listed as mapped in the various SDTM domains, respectively. Listings of raw data will include study day of visit/assessment/start and end dates, as applicable and as defined in paragraph 5.2.5. Listings may be split and/or combined as deemed appropriate.

Derived data used for analyses will be listed separately as described further in each section, where applicable.

5.2.2. Study Treatment

In this study, '**study drug**' refers to Patidegib Topical Gel, 2% (w/w), or Vehicle and '**study treatment**' (or '**treatment arm**') refers to one of the following:

- Arm A = Patidegib
- Arm B = Vehicle

Start date 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.

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

5.2.3. Pooling of Centers

Approximately 10 centers are planned in this study to enable a sufficient number of subjects to be enrolled. In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients randomized at each center. Descriptive summary statistics will not be presented by center.

5.2.4. 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, 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 with non-missing data at that visit, unless otherwise specified.

5.2.5. Definition of Baseline

In this study, the baseline measurement will be defined as the measurement taken at the Baseline visit or, if the measurement at the Baseline visit is missing and that of the Screening visit is present, the Screening visit.

5.2.6. Definition of Study Day

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 start of study treatment will be negative and calculated as:

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

In this way, there will be no Day 0. Day 1 is the same day as the randomization date, and Day -1 is the day before. Study day will only be calculated if the dates are complete.

5.2.7. 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 through 30 days + last IP application of study treatment.

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

5.2.8. 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.

5.2.9. Unscheduled Visits

Data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, vital signs will include only data from scheduled visits.

5.3. Methods to Manage Missing Data

5.3.1. Missing Data

For the primary analysis, the Multiple Imputation (MI) method will be the primary method for dealing with missing data. Last Obsevation Carried Forward (LOCF) and Observed Case (OC) analyses will be done as sensitivity analyses. For the count secondary endpoints, MI will be used; for the dichotomous secondary endpoints and the [redacted] endpoint, LOCF will be used.

For the MI model, 100 imputations will be generated using PROC MI of SAS. Fully conditional specification (FCS) model using the regression method will be used with the number of SEBs at prior post-baseline visits, treatment group, number of SEBs at baseline, and gender as covariate to impute the data. The ROUND and MINIMUM options will be utilized to ensure imputed values are non-negative integers. The seed to be used is 20180330. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

For the primary and secondary efficacy endpoints related to number of nSEBs, a nSEB that was first reported at or prior to Month 9 will be counted in the endpoint. The biopsy may occur later, but the lesion will still be considered a nSEB.

Patient data listings of the primary endpoint will include imputed values and these will be flagged.

Missing statistics, e.g., when they cannot be calculated, will be presented as ‘Not detected (ND)’ or ‘Not applicable (NA)’.

5.3.2. Handling of Incomplete Dates

5.3.2.1. Adverse Events

Incomplete AE-related dates will not be imputed, but interpreted as follows:

- If the AE onset date is completely missing, the AE will be assumed to be treatment emergent.
- If the AE onset date is partially missing, the available information will be used to assess treatment emergence. This means that if the AE stop date is after start of study treatment and 1. 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 will be assumed to be treatment emergent and 2. 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 AE will be assumed to be treatment emergent.

5.3.2.2. Prior and Concomitant Medications

Incomplete prior/concomitant medication dates will not be imputed, but interpreted as follows:

- If the medication starts and end dates are completely missing, the medication will be assumed to be concomitant.
- If the medication start date is partially missing, the available information will be used to assess concomitance. This means that if the medication end date is after start of study treatment and 1. only the day part of the medication date is missing, but the month and year are equal to the start of study treatment, then the medication will be assumed to be concomitant and 2. both the day and month of the medication date are missing but the onset year is equal to the start of study treatment, then the medication will be assumed to be concomitant.

5.3.2.3. Exposure

If last date of study drug is completely or partially missing the End of Study (EOS) date will be used to impute the missing day, month and/or year, as applicable and rational, for derivation of compliance.

6. ANALYSES AND SUMMARIES

Given the early termination of the study and the transition to the current client, who specified for essential outputs in the abbreviated CSR, only certain safety analyses and pertinent demographic or background characteristics of patients will be summarized. A comprehensive list of contents to be included in the CSR are shown in Appendix 4.

6.1. Primary Endpoints

6.1.1. Number of nSEBs per Subject by Month Nine.

The primary endpoint is the number of nSEBs per subject by month nine.

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

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

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

6.1.1.1. Primary Analysis

The following analyses will be based on the mITT using the strata assigned at randomization.

This endpoint will be analyzed using a Poisson regression to compare treatment groups, with number of BCCs that are not SEBs at Baseline, and gender strata, as a covariate. PROC GENMOD of SAS will be used with distribution=Poisson.

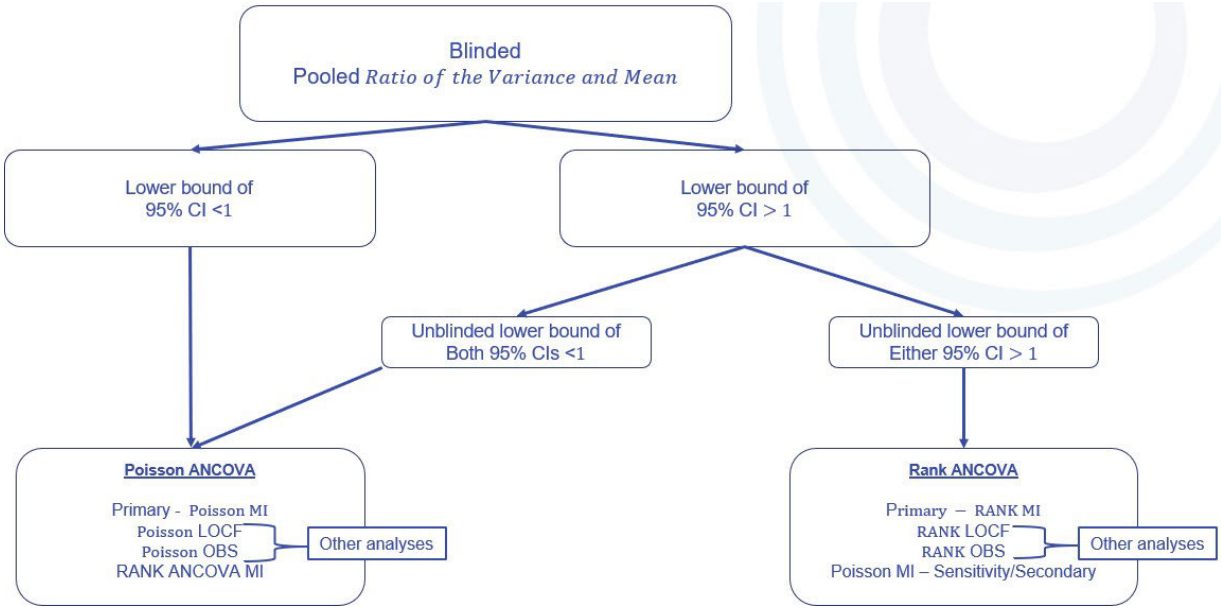
The primary feature of the Poisson assumption, the equality of the variance to the mean, will be investigated by testing that the ratio of the variances in the 2 treatment groups equals the ratio of the means. A 95% confidence interval (CI) will be calculated for the ratio of the variance to the mean. The 95% CI will be calculated by inverting the following test statistic from Wang et al.:

$$T_1 = \sqrt{\frac{n}{2}}\left(\frac{S_n^2}{\bar{X}} - 1\right)$$

To obtain the 95% CI

$$\left(\frac{s^2}{\bar{X}} - Z_{\frac{\alpha}{2}}\sqrt{\frac{2}{n}},\ \frac{s^2}{\bar{X}} + Z_{\frac{\alpha}{2}}\sqrt{\frac{2}{n}}\right)$$

The CIs (blinded and unblinded) will determine the primary analysis method in the following manner:



If the lower bound of the blinded pooled CI of the ratio between the variance to the mean is less than 1 or lower bound of the unblinded CI is less than 1, then it will be concluded that the underlying distribution is not Poisson. In that case, a non-parametric rank analysis of covariance (ANCOVA, Stokes et al), will be used as the primary analysis with number of BCCs that are not SEBs at Baseline, and gender strata, as covariates. Both analyses will be presented regardless of the result of the test of the Poisson underlying assumption.

1. When the distribution of nSEBs follows Poisson with low or high intensity parameter, both a Poisson regression and the non-parametric rank ANCOVA are valid (type-1 error is controlled) and give very similar results.
2. When the distribution is not Poisson (and unknown to sufficiently allow a different parametric regression model), then the non-parametric ANCOVA gives type-1 error close to the nominal level, but the Poisson regression can substantially exceed the nominal type-1 error.

	mITT		**PP**	
Analysis	**Poisson**	**Rank**	**Poisson**	**Rank**
MI	x; s	x; s		
LOCF	x	x		
OC	x	x	x; s	x; s
Derived	Listing Only			

Note: 'x' denotes that the full population will be used, and 's' denotes that subgroup analyses will be provided in the given population and analysis type.

The primary method for dealing with missing data will be the MI method discussed in detail in section 5.3.1. An analysis in the PP Population using the OC method will be provided as a sensitivity analysis. A box plot of the mean number of nSEBs per subject over time will be

presented. Additionally, a stacked histogram showing the proportion of subjects with [redacted], and [redacted] nSEBs will be presented over time.
LOCF and observed case analyses using both the Poisson and Rank ANCOVA models will be done as sensitivity analyses.
The derived number of nSEBs, determined using the actual measurements provided instead of relying on the answer to the question "Lesion has a longest diameter [redacted] mm and has grown by at least [redacted] in longest diameter from Baseline:", will be presented in the listings.
Listings of derived efficacy endpoints, BCC measurements, facial BCC procedures, and digital imaging of BCCs will be created.

6.2. Secondary Endpoint(s)

6.2.1. Safety Endpoints

See Section 6.4.

6.2.2. Efficacy Endpoints

The secondary efficacy endpoints are:
1. The number of new BCCs that develop from Baseline to Month 9.
2. The proportion of subjects developing [redacted] facial nSEB(s) by Month 9.
3. The proportion of subjects developing [redacted] facial nSEB(s) by Month 9.
4. The number of BCC surgeries from Baseline to Month 9.
5. The number of qualifying nSEBs per subject at Month 6.
6. [redacted] from Baseline to Month 9.

Secondary endpoints that are based on number of lesions will be analyzed similar to the primary endpoint.

The proportion of subjects with at least [redacted] nSEB lesions and the proportion of subjects with at least [redacted] nSEB lesion will be analyzed using a logistical regression to compare treatment groups with gender as a covariate.

The number of BCC surgeries will be analyzed in the same manner as the primary endpoint.

All efficacy assessments (secondary and exploratory endpoints) will be summarized descriptively by treatment group and visit.

6.2.3. Exploratory Endpoints

The exploratory endpoints are:

1. Time to first new SEB
2. The proportion of SEBs that undergo clinical resolution by Month 9.
3. Change in [redacted] from Baseline to Month 9.
4. Change in [redacted] from Baseline to Month 9.

5. Change in [redacted] from Baseline to Month 9.
6. Change in [redacted] Baseline to Month 9.
7. Change in [redacted]) total score from Baseline to Month 9
8. Shift in [redacted] from baseline to Month 9
9. Change in [redacted]) from Baseline to Month 9

The exploratory endpoints will be summarized using descriptive statistics, including a shift table for changes from baseline of the [redacted] dimension scores.

6.3. Baseline and Other Summaries and Analyses

6.3.1. Baseline Summaries

The following analyses will be based on the ITT population overall and separately by treatment arm.

6.3.1.1. Demographic Characteristics

Demographic characteristics and physical measurements will be summarized by treatment arm using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Sex: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Unknown
  - Ethnic origin: Hispanic/Latino (Yes/No)
  - Age (years): summary statistics
  - Age categories:
    - [redacted]
- Physical measurements
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2)

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment arm, age, sex, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2).

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.

6.3.2. Study Conduct and Patient Disposition

The following analyses will be performed based on the ITT population overall and separately by treatment arm.

6.3.2.1. Patient Disposition

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

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to randomization overall and by the main reason for discontinuation
- Number and percentage of randomized patients in each of the analysis populations defined in Section 4
- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation

The results of the randomization algorithm (according to Interactive Response Technology [IRT]) will be summarized as follows:

- Number and percentage of randomized patients by center
- Number and percentage of randomized patients by randomization strata (IRT)

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
- Deviations from Good Clinical Practice (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 by treatment arm.

At each visit when study drug is returned by the subject, returned tubes will be weighed. Compliance with study drug application will be calculated from the previous dispensation of study drug. Compliance will be calculated using the following formula:



Where DW represents the dispensed weights and RW represents the returned weights of each kit. If a tube is not returned, then it will be assumed that the subject used all of it, i.e., the returned weight is 0.

Total dose received, duration of treatment, and compliance will be compared between the 2 treatment groups using summary statistics. Compliance will also be a factor in defining the PP population as noted in Section 4.4.1.

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 by treatment arm.

6.4.1. Dermal Safety and Tolerability

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 treatment group and visits of the most severe post baseline assessment and end of treatment from baseline.

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

6.4.2. Adverse Events

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 as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Definitely, Possibly and Probably) 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 drug (i.e., at least one of the study drugs).

- **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 treatment arm, primary SOC and PT in decreasing frequency based on the frequencies observed for the Patidegib treatment arm.

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.

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 by treatment arm:
  - TEAEs
  - TEAEs, by severity
  - Related TEAEs
  - Related TEAEs, by severity
  - TEAEs leading to permanent treatment discontinuation
  - Related TEAEs leading to permanent treatment discontinuation
  - Serious TEAEs
  - Related Serious TEAEs
  - TEAEs leading to death
  - Related TEAEs leading to death
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- SAEs by SOC and PT

6.4.2.2. Adverse Events Leading to Discontinuation of Study Treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment arm:

- TEAEs leading to discontinuation of Patidegib by SOC and PT
- Related TEAEs leading to discontinuation of Patidegib by SOC and PT
- TEAEs leading to discontinuation of Vehicle by SOC and PT
- Related TEAEs leading to discontinuation of Vehicle by SOC and PT

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

6.4.3. 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”, “End of follow-up” and “Adverse Event Log” eCRF pages.

6.4.4. Serious Adverse Events

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

- 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.

6.4.5. Laboratory Data

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

the Safety analysis

6.4.6. Vital Signs

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

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. End of Treatment visit will be summarized separately. The changes computed will be the differences from baseline.

6.4.7. Physical Examination

Number and percentage of patients with abnormal findings in physical examination will be summarized by body system.

7. REFERENCES

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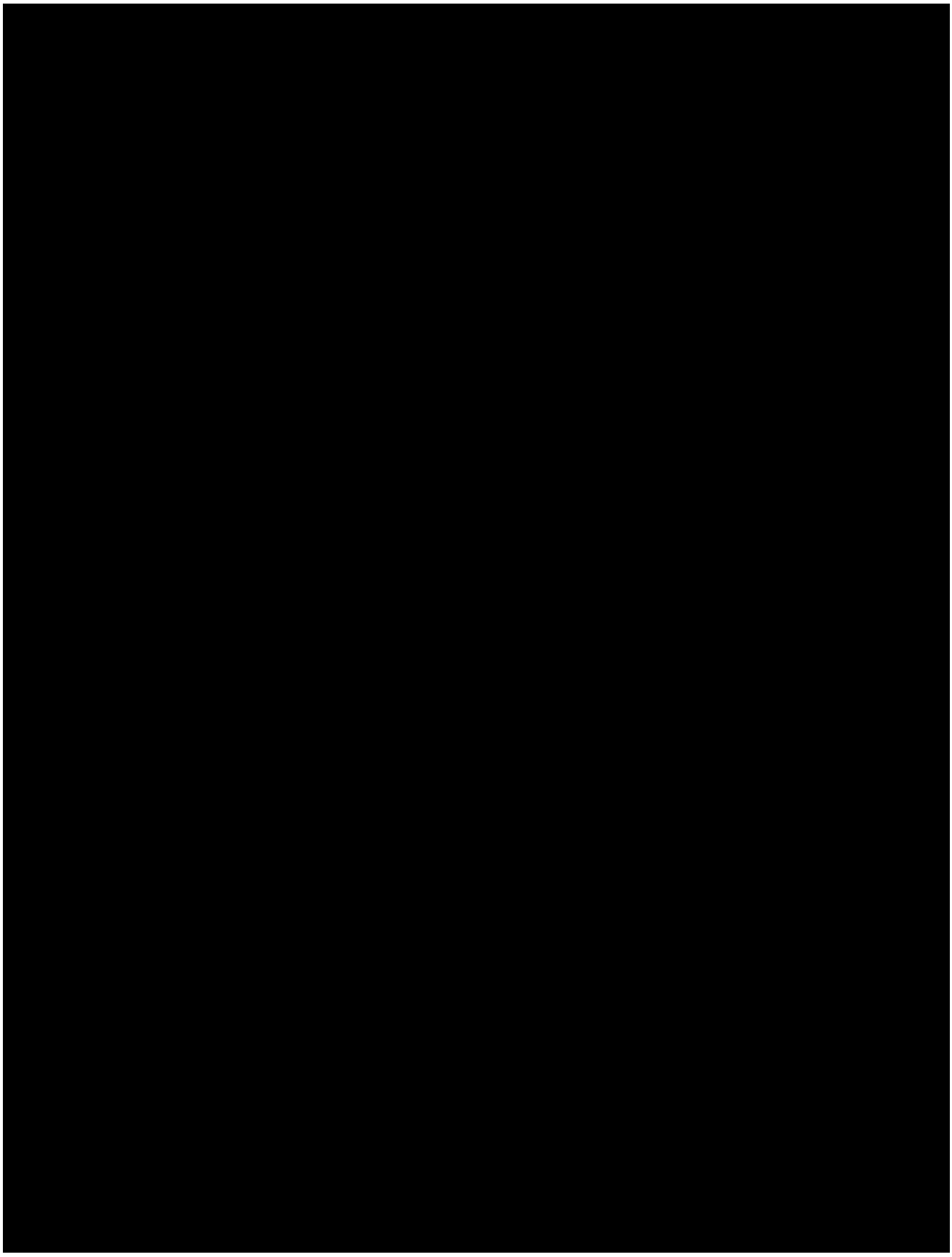
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8. APPENDICES











Appendix 4. Index of Tables, Figures and Listings for the abbreviated Clinical Study Report.

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