Protocol B7981019

A PHASE 2B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF PF-06651600 WITH A PARTIALLY BLINDED EXTENSION PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF PF-06651600 AND PF-06700841 IN SUBJECTS WITH ACTIVE NON-SEGMENTAL VITILIGO

Statistical Analysis Plan
(SAP)

Version: 6

Date: 25-Feb-2021

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7981019 is based on the Protocol Amendment 5 dated 26 June 2020.

Table 1. Rationale of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	• In Section 6.2 "Analyses and Summaries During Extension Period", removed special instruction for placebo subjects from German sites.	To clarify that placebo subjects who achieve VASI 100 in Germany will be treated the same as other countries.
3	• Add Vitiligo Noticeability Scale (VNS) in Section 2.1, 2.2, 3.3, 6.1.3 and 6.2.2.	Vitiligo Noticeability Scale (VNS) was added in Protocol amendment 4 as a Patient Report Outcome Measure.
	• Add Change of extent of depigmentation in target lesion(s) in Section 2.1, 3.3, and 6.1.3.	Change of extent of depigmentation in target lesion(s) was in protocol as an exploratory endpoint.
4	• Add Missing data rule for missing due to COVID-19 in Section 5.3.3, 6.1.1.1. • Add sensitivity analyses for primary endpoint excluding TeleHealth data in Section 6.1.1.2. • In Section 6.1.3, add analyses for PGIS-V, PGIC-V, and VNS; Modify analyses for EQ-5D and HADS. • Provide more details for Section 6.1.4.1. • Update Appendix 1 of analysis models and Appendix 2 of visit windows.	Predefine analyses to address COVID-19 impacts. Update analyses methods for some PRO endpoints. Visit windows are updated for analysis visit mapping.

SAP Version	Change	Rationale
5	• Updated endpoints in dose-ranging and extension period to align with protocol amendment 5. • Section 3.1: Added formula for central read facial-VASI and shifted formula for site assessment facial-VASI to appendix. • Section 3.2. & 3.3: Added subsection for new key secondary endpoint, and moved other endpoints in secondary and tertiary endpoints as appropriate to align with new study endpoints. • Section 5.1: Updated Hochberg test to reflect the 3 statistical tests being completed (instead of 5). • Section 5.2.2: Added description of ANCOVA analysis for continuous data. • Section 5.3.1.1: Added text for the missing data approach for models using ANCOVA. • Section 6.1: The analysis for the primary endpoint is now an ANCOVA model instead of MMRM. The MMRM analysis for the primary endpoint was shifted to a sensitivity analysis, and additional sensitivity analyses were added and separated into their own section. Supportive analysis for the primary endpoint was also added in the form of a Bayesian Emax model. Clarifying language added throughout section and additional subheaders added to describe the role of each analysis (primary analysis, supportive, exploratory, or sensitivity). • Section 6.1.2: Secondary analyses updated for site assessment facial-VASI and VASI. Both	Updated as appropriate to align with new study endpoints. Clarified the differences in central read and site assessment facial-VASI and their accompanying analyses. Three statistical tests (instead of 5) will be used to save alpha for most critical comparisons. ANCOVA analyses will now be used for local read and site assessment facial-VASI and VASI, so updated text throughout to reflect new analyses. Clarified the role of each type of analysis completed in support of the primary endpoint analysis. Clarified potential analyses to be done if central-read facial-VASI is performed during the extension period. Added ANCOVA analyses to parallel analyses completed in the dose ranging period.

SAP Version	Change	Rationale
	now use ANCOVA instead of MMRM. The key secondary endpoint analyses were also added. • Section 6.2: Added text to emphasize that these analyses are for site assessment facial-VASI and that if central facial-VASI is assessed during the extension period, mirror analyses will be performed. • Section 6.2.2.2: Updated analyses for change from baseline and percent change from baseline VASI and site assessment facial-VASI to ANCOVA to mirror analyses from the dose-ranging period. • Section 6.2.2: Eliminated some analyses; will be moved to ad-hoc analyses. • Section 9.1.1: Updated summary of analyses to reflect new analyses being performed. • Section 9.5: Updated VitiQoL scoring algorithm and provided additional details.	Provided clarity for VitiQoL computation.
6	• Section 3.3: Clarified that all lesion data used in the target lesion analyses is centrally read. Defined formula for percent change from baseline in target lesion depigmentation. • Section 4.3: Defined additional analysis sets for the extension period. • Section 5.2.1: Clarified that GLMM results will only be reported if the model converges. • Section 5.3.1.1: Updated missing data language for ANCOVA from "complete case" to "observed cases".	Clarified analyses and removed unnecessary figures and analyses. Defined depigmentation formula and central read lesion analyses. Added extension group analyses for long term efficacy (Extension group 3 from baseline to Week 48) and nbUVB addon therapy effect (Extension group 2 vs. 3).

SAP Version	Change	Rationale
	• Section 5.3.3, Section 6.1.1.2.1: removed TeleHealth sensitivity analyses for primary endpoint. Added listing of summary of protocol deviations related to COVID-19. • Section 6.1.1.1: Added spaghetti panel plots for central read facial-VASI, removed percent change from baseline. • Section 6.1.2.1: Clarified reporting strategy. • Section 6.1.2.1, 6.1.2.1.1, 6.1.2.2: Model output will only be provided if GLMM converges. • Section 6.1.2.7: Removed figure for sIGA • Section 6.1.3.8: Updated PHQ-8 summary. • Section 6.1.3.12, 6.1.3.16: Added ANCOVA analysis for percent change from baseline in depigmentation rate of centrally read target lesions, updated other lesion analyses. [redacted] • Section 6.1.4.1: Added baseline summary tables for subjects meeting and not meeting central read facial-VASI75 at Week 24 of the dose ranging and extension periods. Also added baseline summary of central read facial BSA. • Section 6.1.4.3: Added listings for prior medications and nondrug treatments for dose-ranging and extension period. Also added listing for dosing compliance during dose-ranging and extension periods. • Section 6.2: Added baseline definition for Cystatin C and Cystatin C-based eGFR in	

SAP Version	Change	Rationale
	Extension group 1. Added extension analysis set terminology throughout 6.2. • Section 6.2.2: Added two categories of subgroup analyses to be completed during the extension period. Added Extension Group 1 analyses. • Section 6.2.2.1.1: Added separate extension group analysis section for PF-06700841. • Section 9.1.2: Updated analysis sets. • Section 9.6: Updated analysis method for categorical PGIS-V improvement to Fisher's exact test	

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7981019. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives and Endpoints During Dose Ranging Period

Table 2. Study Objectives and Endpoints During Treatment Period

Primary Objective:	Primary Endpoint:
• To evaluate the efficacy of PF-06651600 dose/dosing regimens at Week 24 in adult subjects with active non-segmental vitiligo.	• Percent change from baseline in central read facial vitiligo area scoring index (facial-VASI) at Week 24.
• To evaluate the safety and tolerability of PF-06651600 over time in adult subjects with active non-segmental vitiligo.	• Incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs) up to Week 24. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and liver function tests (LFTs) up to Week 24.

Secondary Objectives:	**Secondary Endpoints:**
Key Secondary Objective: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by facial-VASI at Week 24 in adult subjects with active non-segmental vitiligo.	Key Secondary Endpoint: • Proportion of subjects achieving central read facial-VASI75 (defined as at least 75% improvement in central read facial-VASI from baseline) at Week 24.
Other Secondary Objectives: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by other clinical assessments over time in adult subjects with active non-segmental vitiligo.	Other Secondary Endpoints: • Proportion of subjects achieving VASI50 (defined as at least 50% improvement in VASI from baseline) at Week 24. • Percent change from baseline in VASI, central read and site assessment facial-VASI, self assessment vitiligo extent score (SA-VES), and absolute change from baseline in VASI at designated time points (except for Week 24 for central read facial-VASI). • Proportion of subjects achieving VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in VASI from baseline) and central read and site assessment of the facial-VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in facial-VASI from baseline at designated time points (except for Week 24 in VASI50 and central read facial-VASI75). • Change from baseline in vitiligo specific quality of life (VitiQoL) at designated time points. • Proportion of subjects achieving a static investigator global assessment (sIGA) 0 or 1 and 2-point or greater improvement at Week 24.

Tertiary/Exploratory Objective(s):	Tertiary/Exploratory Endpoint(s):
• To evaluate the efficacy of PF-06651600 compared to placebo by other efficacy markers in adult subjects with active non-segmental vitiligo.	• Absolute change from baseline in central read and site assessment facial-VASI and VES at designated time points. • Percent change from baseline in vitiligo extent score (VES) at designated time points. • Proportion of subjects achieving VES50/75/90/100 (defined as at least 50%/75%/90%/100% improvement in VES from baseline) at designated time points. • Change from baseline in dermatology life quality index (DLQI)/EuroQol 5 dimension 5 level (EQ-5D-5L)/healthcare resource utilization (HCRU) at designated time points as specified in the protocol SoA. • Facial target lesion improvement (by planimetry) of ≥50% from baseline at Week 24 (if data allow). • Proportion of subjects achieving "very much improved" or "much improved" on patient global impression of change in vitiligo (PGIC-V). • Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) on Vitiligo Noticeability Scale (VNS). • Change of extent of depigmentation in target lesion(s).
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• To evaluate the effect of PF-06651600 on psychological assessments over time in adult subjects with active non-segmental vitiligo.	• Change from baseline in Columbia Suicide Severity Rating Scale (C-SSRS) and hospital anxiety and depression scale (HADS) as specified in the protocol SoA.
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2.2. Study Objectives and Endpoints During Extension Period

Table 3. Study Objectives and Endpoints During Extension Period

Primary Objective:	Primary Endpoint:
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in adult subjects with active non-segmental vitiligo.	• Incidence of treatment-emergent AEs and SAEs during the Extension Period. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and

	liver function tests during the Extension Period.
Exploratory Objectives:	**Exploratory Endpoints:**
• To evaluate the long term efficacy of PF-06651600, efficacy of PF-06651600 and add-on nbUVB, in adult subjects with active non-segmental vitiligo. • To evaluate the efficacy of PF-06700841 in a subset of adult subjects with active non-segmental vitiligo.	• Percent change from baseline in VASI during the Extension Period. • Proportion of subjects achieving VASI50/75/90/100 and central read* and site assessment facial-VASI50/75/90/100 during the Extension Period. • Percent change from baseline in VASI, central read[a] and site assessment facial-VASI, VES, and SA-VES and absolute change from baseline in VASI, facial-VASI and VES during the Extension period. • Change from baseline in VitiQoL during the Extension Period. • Proportion of subjects achieving a sIGA 0 or 1 and ≥2-point improvement during the Extension Period. • Change from baseline in DLQI/EQ-5D-5L/HCRU in Extension Period. • Change from baseline in C-SSRS and HADS at designated time in the Extension Period as specified in the protocol SoA. • Proportion of subjects achieving "very much improved" or "much improved" on patient global impression of change in vitiligo (PGIC-V). • Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) on Vitiligo Noticeability Scale (VNS).
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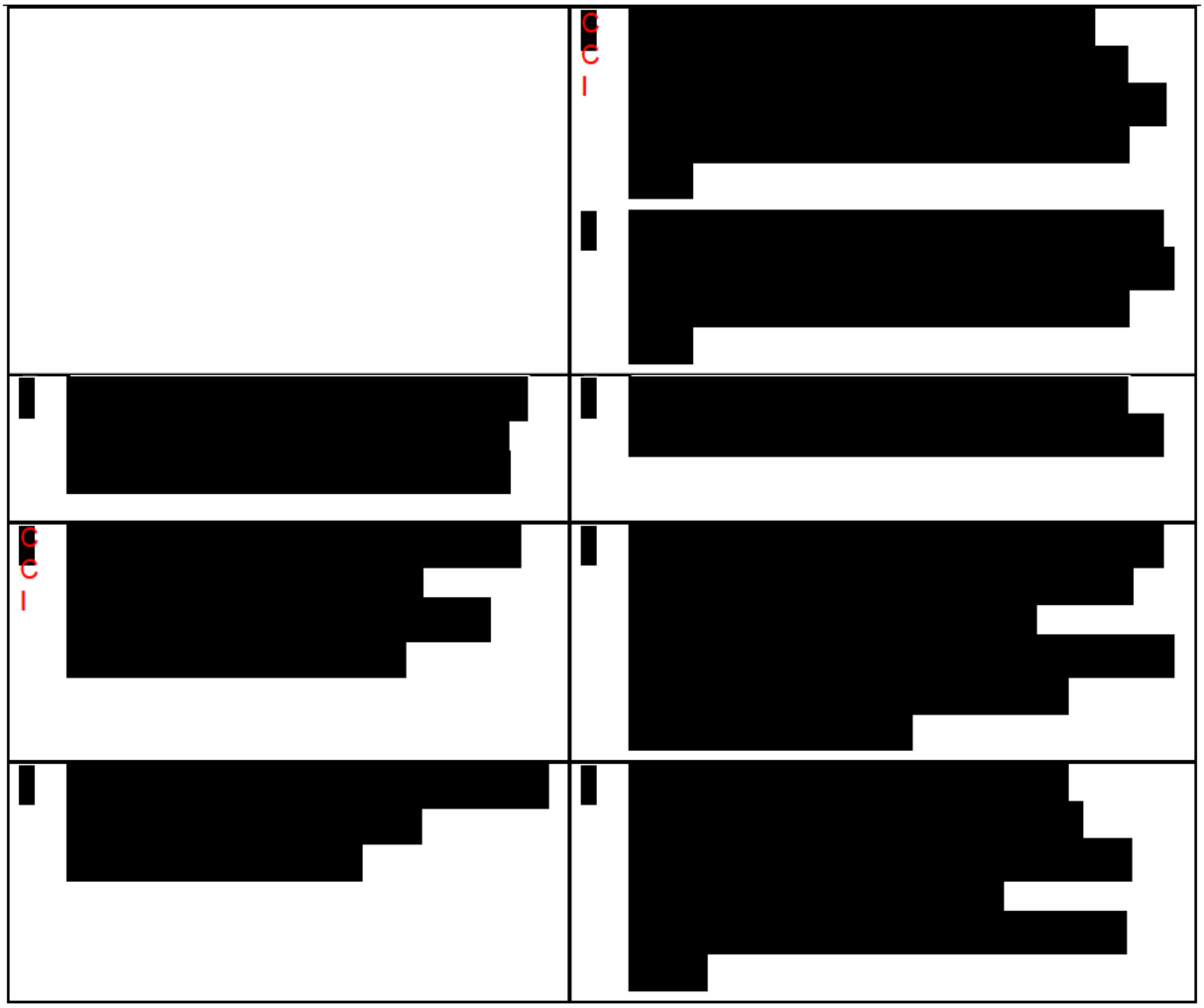


a. Central read facial-VASI may be performed and analyzed in the Extension Period as an exploratory endpoint.

2.3. Study Design

Study B7981019 will investigate different dose/dose regimens of PF-06651600 in active non-segmental vitiligo. This is a Phase 2b, randomized, double-blind, parallel group, multicenter, dose ranging study with a partially blinded extension period. The study will have a maximum duration of approximately 60 weeks. This includes an up to 4-week Screening Period, a 24-week Dose Ranging Period, an up to 24-week Extension Period, and an 8-week Follow-up Period. The study will enroll a total of approximately 330 subjects (expected to provide approximately 260 completers with central read facial-VASI data at Week 24 of the dose-ranging period). The study will be conducted globally at approximately 50 study sites.

Figure 1. Study Design Schema for Screening Period and Dose Ranging Period

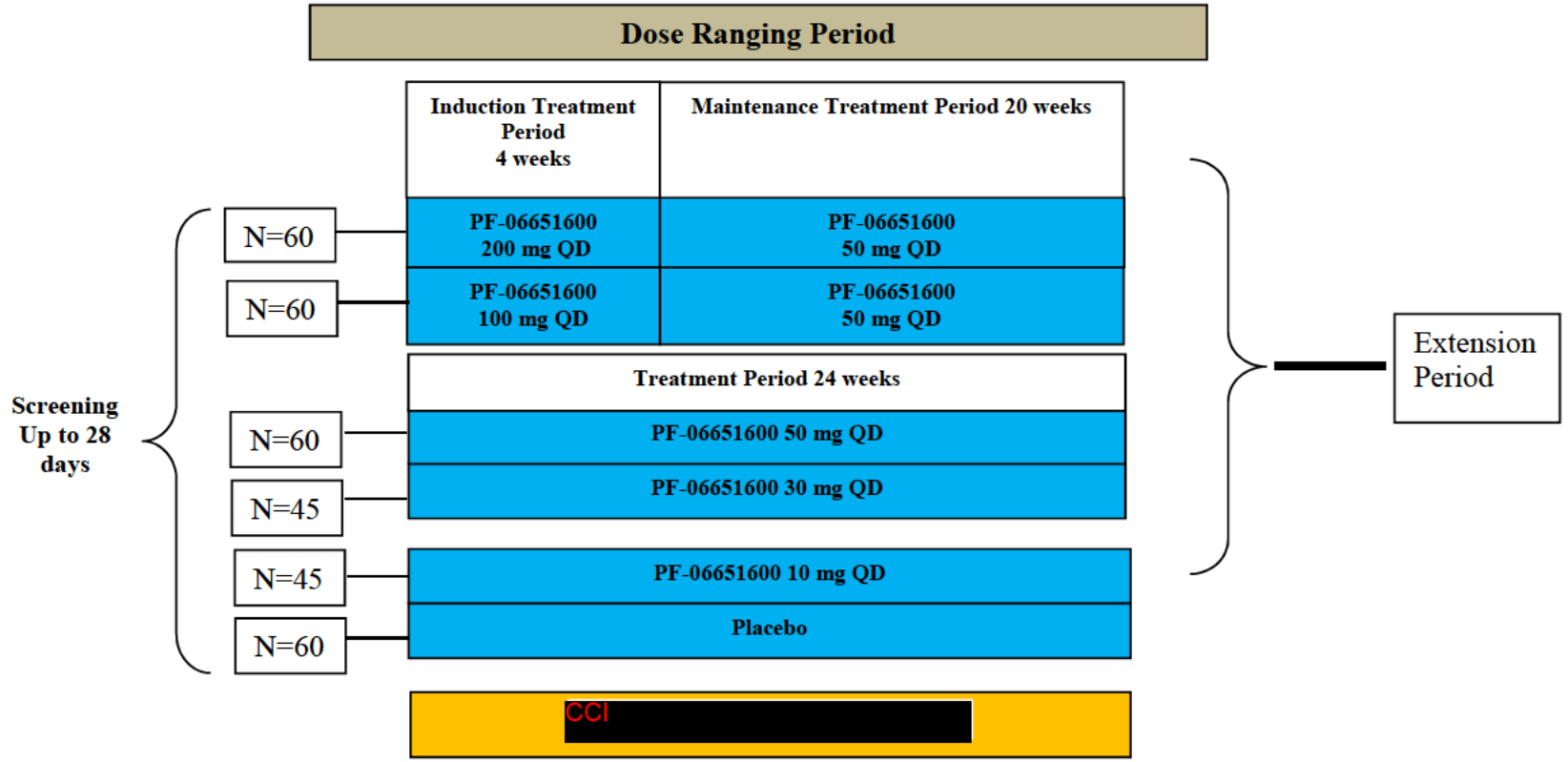
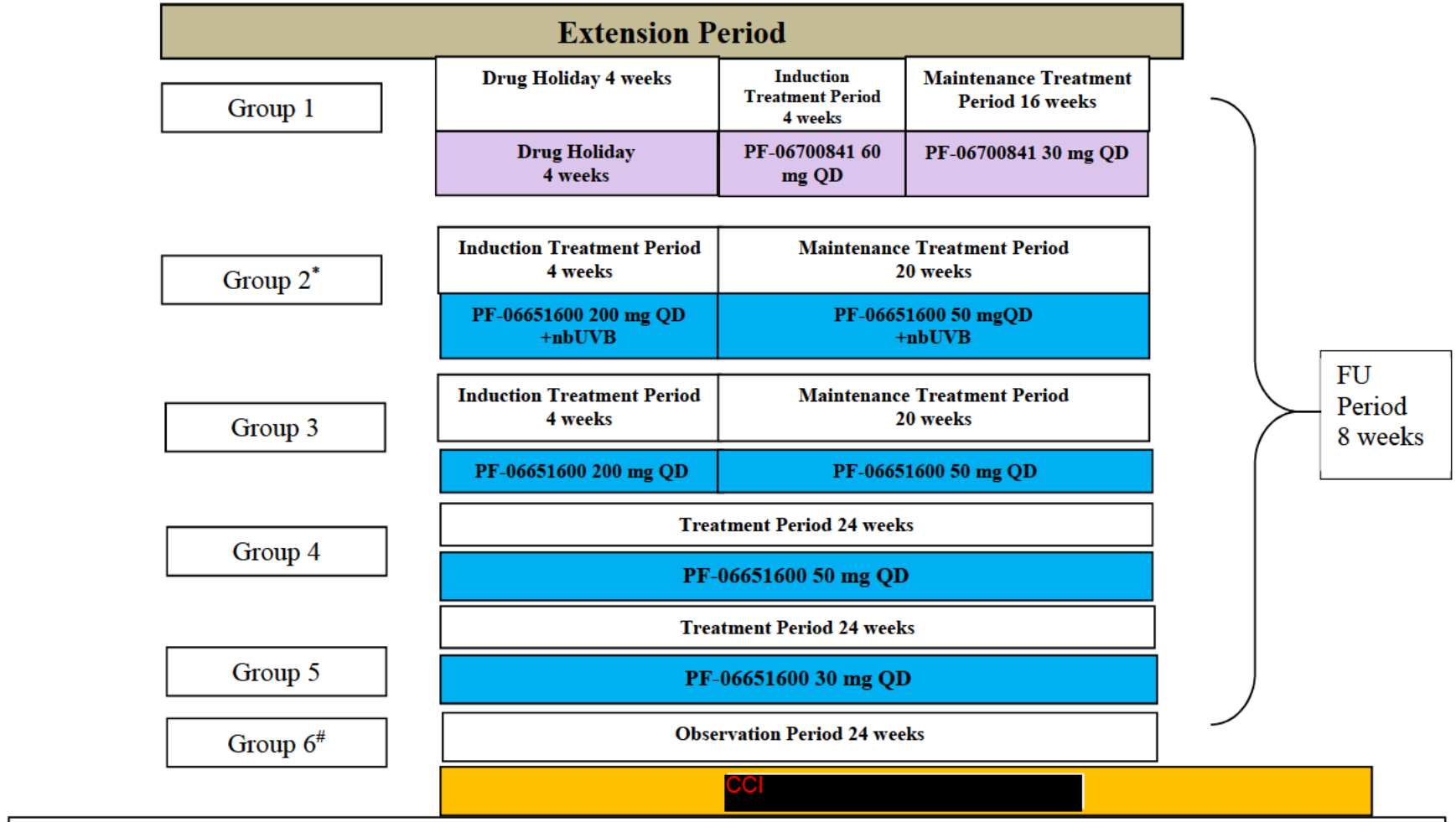


Figure 2. Study Design Schema for Extension Period and Follow up Period



* Subjects who have <10% improvement in percent change in VASI at Extension Week 12 from the baseline value at Dose Ranging Period Week 24 will be discontinued from the treatment and enter Follow-up Period.
# Visits will be conducted every 4 weeks until EOS or until 30% or greater depigmentation from baseline VASI occurs, whichever is shorter. No follow-up visits will be performed for subjects in Group 6.

Subjects who have active non-segmental vitiligo (as defined in Protocol inclusion criterion #5) present and have met all other inclusion/exclusion criteria at the Screening Visit and Baseline Visit will be included in the study. Photographs will be taken to verify eligibility (Protocol inclusion criterion #5c). Investigators, subjects, and the sponsor study team will be blinded to treatment group during the study.

Subjects will be screened within 28 days prior to the first dose of Investigational product (IP) to confirm that they meet the subject selection criteria for the study. Subjects will be randomized for the 24-week Dose Ranging Period to 1 of 5 active treatment groups, or placebo, in the ratio of 4:4:4:3:3:4.

- An induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60);
- An induction dose of 100 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60);
- A dose of 50 mg QD of PF-06651600 for 24 weeks (n=60);
- A dose of 30 mg QD of PF-06651600 for 24 weeks (n=45);
- A dose of 10 mg QD of PF-06651600 for 24 weeks (n=45);
- Matching placebo for 24 weeks (n=60).

A biopsy sub-study will be performed at selected sites. Details will be described in the lab manual.

All subjects who complete the initial 24-week Dose Ranging Period may enter the Extension Period and will be allocated into one of 6 groups by pre-specified criteria.

- Group 1: Induction dose of 60 mg QD of PF-06700841 for 4 weeks followed by a 4-week drug holiday (no IP), then maintenance dosing of 30 mg QD of PF-06700841 for 16 weeks. This arm is open label.
- Group 2: Induction dose of 200 mg QD of PF-06651600 plus standardized narrow band UVB (nbUVB) add-on therapy for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 plus standardized nbUVB add-on therapy for 20 weeks. Subjects must provide nbUVB consent. Subjects who have <10% improvement in percent change in VASI at Extension Week 12 from the baseline value at Dose Ranging Period Week 24 will be discontinued from the treatment and enter Follow-up Period. This arm is open label.
- Group 3: Induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks. This arm is double blinded.
- Group 4: 50 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.

- Group 5: 30 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.
- Group 6: No IP will be administered. Observation Period for 24 weeks. Visits will be conducted every 4 weeks until EOS or until 30% or greater depigmentation from baseline VASI occurs, whichever is shorter. No Follow-up Period required. This arm is open.

Subjects in Group 1 and 2 who provide consent for the biopsy sub-study will participate in the biopsy sub-study at selected sites during the Extension Period. An optional biopsy will be performed at Follow-up Visit 1 only for subjects who provide biopsy consent.

Subjects who complete the Extension Period (except for Group 6) or withdraw early from treatment will enter the Follow-up Period. Subjects who discontinue during the initial Dose Ranging period will enter the 8-week Follow-up Period and will not be eligible for the Extension Period.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint for this study is percent change from baseline in central read facial-VASI score at Week 24. Baseline is defined as the last measurement prior to randomization (Day 1). Percent change from baseline is defined as the value at a specific visit minus the baseline value, divided by baseline value and multiplied by 100%, ie,

$$\%\ \text{change from BL central read facial VASI} = \frac{\text{post BL central read facial VASI} - \text{BL central read VASI}}{\text{BL central read VASI}} \times 100$$

A negative percent change from baseline in central read facial-VASI signifies an improvement.

The central read facial-VASI is calculated using a formula that includes contribution of affected facial surface areas showing all six (6) different depigmentation rates (0.1, 0.25, 0.5, 0.75, 0.9 and 1) with a modified method described by Hamzavi, et al:[3]

$$\text{Facial VASI (central read)} = \sum_{\text{Six (6) Different Depigmentation Rates}} [\text{Affected Facial Surface Area}] \times 4 \times [\text{Depigmentation Rates}]$$

The calculation of % affected total body surface area (BSA) is shown below:

Affected facial surface area × 4 = % Affected total body surface area

As an exploratory analysis for central read facial-VASI, the above formula will be modified to use 3 instead of 4 (Section 6.1.1.3). Face is defined as the area from the hairline on top of the forehead to the jawline at the bottom of the cheeks. Facial VASI (central read) will range from 0.000 to 4.000 by defining the affected Facial Surface Area (expressed as a value between 0.0 to 1.0) being 4% of total Body Surface Area.

The extent of depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%.

- 100% depigmentation: no pigment is present;
- 90% depigmentation: specks of pigment are present;
- 75% depigmentation: the depigmented exceeds the pigmented area;
- 50% depigmentation: the depigmented and pigmented areas are equal;
- 25% depigmentation: the pigmented area exceeds the depigmented area; and
- 10% depigmentation: only specks of depigmentation are present.

Scalp, neck, eyebrows, eyelashes, and vermilion will be excluded from this calculation, although the total VASI assessment includes all of these regions.

3.2. Secondary Endpoint(s)

3.2.1. Key Secondary Endpoint

The key secondary endpoint is the proportion of subjects achieving at least 75% improvement from baseline in central read facial-VASI (central read facial-VASI75: central read facial-VASI75 = 1 if percent change from baseline ≥75; central read facial-VASI75 = 0 if percent change from baseline <75) at Week 24 of the Dose-Ranging Period.

3.2.2. Other Secondary Endpoints(s)

A secondary endpoint for this study is percent change from baseline in VASI score at Week 24. Baseline is defined as the last measurement prior to Randomization (Day 1). Percent change from baseline is defined as the value at a specific visit minus the baseline value, then divided by baseline value and multiply by 100%, ie,

$$\% \text{ CFB VASI} = ((\text{post Baseline VASI} - \text{Baseline VASI})/\text{Baseline VASI}) \times 100$$

Negative percent change from baseline in VASI signifies an improvement.

The total body VASI will be calculated using a formula that includes contribution from 6 different body regions (possible range, 0-100):

$$\text{VASI} = \sum_{\text{Six (6) Body Sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and is used as a guide to estimate the baseline percentage of vitiligo involvement of each body region.

The body will be divided into 6 separate and mutually exclusive regions: head/neck, hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary regions are included with the upper extremities, while the buttocks and inguinal regions are included with the lower extremities. Genital area is included in trunk. Face and neck lesions will be measured in this study. The extent of residual depigmentation percentages are the same as described in Section 3.1.

Another secondary endpoint is the proportion of subjects achieving at least 50% improvement in VASI (VASI50: VASI50 = 1 if percent change from baseline ≥50, VASI50 = 0 if percent change from Baseline <50) at Week 24. In addition to calculating the proportion of subjects achieving VASI50 at Week 24, VASI50 will be calculated at all intermediate time points in the Dose-Ranging Period.

The proportion of subjects achieving VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in VASI from baseline) and central read and site assessment of the facial-VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in central read and site assessment facial VASI from baseline) at designated time points (except for Week 24 in VASI50 and central read facial-VASI75) will be calculated in a similar manner to VASI50. Measurement of site assessment facial-VASI is described in Appendix 5 (Section 9.5).

In addition to the percent change from baseline in central read facial-VASI at Week 24, as described in the primary analysis, percent change from baseline in VASI, central read and site assessment facial-VASI, SA-VES, and absolute change from baseline in VASI at designated time points (except for percent change from baseline in central read facial-VASI at Week 24) will be used as secondary endpoints.

The clinical evaluator of vitiligo will perform an assessment of the overall improvement of vitiligo and assign a static investigator global assessment (sIGA) score of 0 - 4. The proportion of subjects achieving a static investigator global assessment (sIGA) 0 or 1, and ≥2-point improvement at Week 24 is a secondary endpoint.

The change from baseline in vitiligo specific quality of life (VitiQoL) at designated time points is another secondary endpoint.

3.3. Exploratory Endpoint(s)

Exploratory endpoints are the absolute change from baseline in central read and site assessment facial-VASI and VES, percent change from baseline in vitiligo extent score (VES), and proportion of subjects achieving VES50/75/90/100 (defined as at least 50%/75%/90%/100% improvement in VES from baseline) at designated time points as specified in the SoA.

Other exploratory endpoints include the change from baseline in dermatology life quality index (DLQI), EQ-5D-5L, and HCRU at designated time points as specified in SoA. They will be analyzed with all patients in the full analysis set (FAS). Baseline for all exploratory endpoints will be the last measurement prior to randomization.

Facial target lesion improvement (by planimetry) of ≥50% from baseline at Week 24 will be calculated if data permit.

Proportion of subjects achieving "very much improved" or "much improved" on patient global impression of change in vitiligo (PGIC-V) will be reported.

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The C-SSRS is a validated tool to evaluate suicidal ideation and behavior. At the Screening Visit and Baseline Visit, if there are "yes" answers on items 4 or 5, or on any suicidal behavioral question of the C-SSRS, the subject will not be included in the study.

At any post-baseline visits, if there are "yes" answers on items 4 or 5, or on any behavioral question of the C-SSRS, the subject will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment. If the subject cannot be seen by a mental health professional within 24 hours, then the subject should be sent to a local emergency room for psychiatric assessment.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes (Appendix 4, Section 9.4).

Change from baseline on the anxiety and depression sub-scales on the Hospital Anxiety and Depression Scale (HADS) will be collected and include both the anxiety and depression subscores.

Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) in Vitiligo Noticeability Scale (VNS) will be reported by treatment arm at Week 24. Percent depigmentation in target lesion(s) will be collected at designated time points as specified in SoA. It will be analyzed with all patients in the FAS. Note that all target lesion data used in the analyses will be central read target lesion data. The change in extent of depigmentation in target lesion(s) from baseline will be calculated by taking current depigmentation level minus the depigmentation level at baseline (eg, 50% depigmentation at Week 12 – 75% depigmentation at Baseline = -25% improvement in depigmentation). The percent change from baseline in target lesion depigmentation rate will be computed as follows:

% CFB lesion depigmentation = ((post Baseline lesion depigmentation – Baseline lesion depigmentation)/Baseline lesion depigmentation) X 100

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3.5. Baseline Variables

Demographic will be collected at screening and medical history will be collected at screening and baseline. Complete vitiligo disease history includes collection of details of vitiligo at Screening: background, vitiligo history, vitiligo diagnosis, the use of topical treatments, systemic treatments, and other treatments for vitiligo. In addition, medical history, including history of drug, alcohol, tobacco use, auditory, skin rash, skin infection, and any dermal abnormalities that may predispose to infection will be collected at Screening and Baseline (if applicable). Smoking status and average weekly alcohol consumption (units/week) will be collected.

Baseline is defined as pre-dose on Day 1. Data from the screening period may be used if Day 1 data are missing. If multiple data points are available, we will use the last observation before Day 1 dosing.

3.6. Safety Endpoints

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, and clinical laboratory results in all subjects who receive at least one dose of IP. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns.

3.6.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

For each subject the time period for actively collecting AEs and SAEs begins from the time the subject provides informed consent through and including a minimum of 28 calendar days after the last administration of the IP.

3.6.2. Laboratory Data

The laboratory tests will be performed at time points identified in the SoA. Unscheduled clinical labs may be obtained at any time during the study, at the investigator's discretion, to assess any perceived safety concerns.

3.6.3. Vital Signs

Vital signs (BP, pulse, respiratory rate, and temperature) will be measured after 5 minutes of rest as indicated in the SoA.

3.6.4. Electrocardiograms

Single 12-lead ECGs should be collected at times specified in the SoA. Each subject's Baseline ECG value will be the last measurement prior to receiving study treatment on Day 1.

Only categorical summaries of the ECG data will be provided.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

4.1. FAS

The FAS consists of all subjects who receive at least one dose of randomized study medication and have a baseline and at least one post-baseline measurement (after taking randomization study medication). The FAS is the primary patient population for the efficacy endpoints.

4.2. Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of IP. Subjects will be classified according to actual study treatment received. The safety analysis set is the primary population for treatment administration/compliance and safety. A randomized but not treated subject will be excluded from the safety analyses. A treated but not randomized subject will be reported under the treatment actually received.

4.3. Other Analysis Sets

The extension analysis set includes all subjects who received at least one dose of planned IP in the extension period. Several subsets of the extension analysis set are defined based on extension group assignment. These include extension analysis set Group 1, extension analysis set Group 2/3, and extension analysis set Group 3. CCI [redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS

An interim analysis may be performed when approximately 50% of subjects have completed or had the chance to complete the Week 24 visit during the Dose Ranging Period. The interim analysis, if any, will be based on a total of approximately 165 randomized subjects.

After the initial Dose Ranging Period (Week 0-24) or the primary objective is completed for all the subjects, some members of the study team who are otherwise not responsible for study conduct until the database is locked will be unblinded so that a report for the corresponding data may be generated. The subjects, investigators, site personnel, and remaining study team members will remain blinded to randomized study treatments throughout the remainder (including the Extension Period) of the study. The database will be officially released after last subject last visit occurs. The final analysis will be then conducted and the CSR will be issued. The decision rules for the final analyses are also described in the next section.

Per Section 9.1 of the Protocol, all sample size calculations are based on a conservative estimate of 260 participants completing the study. This conservative approach protects the study's power against missing data in the primary endpoint analysis (see Section 5.3.1.1).

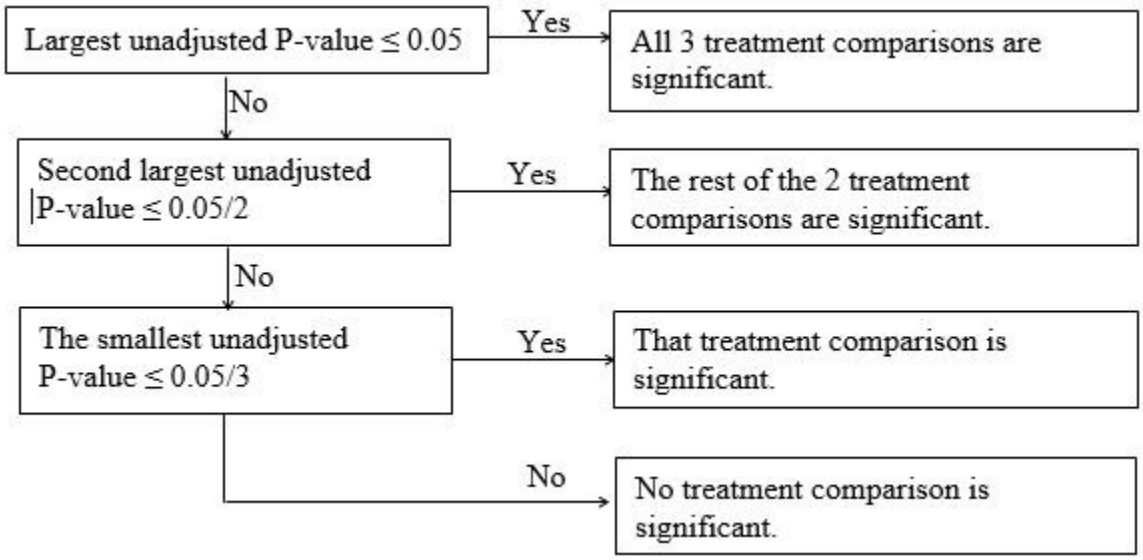
5.1. Hypotheses and Decision Rules

The hypotheses to be tested are that at least one of the following active treatment groups (200 mg QD/50 mg QD, 100 mg QD/50 mg QD, 50 mg QD/50 mg QD) is superior to placebo as measured by the percent change from baseline in central read facial-VASI at Week 24.

Multiple comparisons among these 3 dose groups vs placebo will be conducted, applying Hochberg's step-up procedure using observed p-values. The familywise Type 1 error rate will be controlled at one-sided 0.05. The 30 mg and 10 mg groups are part of the dose-response assessment for the facial-VASI.

The Hochberg procedure will be applied as described below.

Figure 3 Hochberg Procedure



Adjustments for multiple comparisons will only be made for the primary endpoint at the Week 24 time point. Statistical tests for 30 mg QD vs placebo and 10 mg QD vs placebo at Week 24 will also occur but these p-values will be considered descriptive. The 30 mg QD and 10 mg QD arms will help characterize the dose response curve.

5.2. General Methods

5.2.1. Analyses for Binary Data

The frequency and percentages for all binary data will be presented. The binary data will be analyzed by first treating the non-COVID-19-related missing data as non-responders and then applying Chan and Zhang's exact CI method. Binary data that is missing due to COVID-19 will be treated as described in Section 5.3.3.

Additionally, supportive analyses will performed for the VASI50 and central read facial-VASI75 endpoints using a generalized linear mixed model (GLMM). For all GLMM analyses, results will only be reported if the model converges. This GLMM will include fixed factors of treatment, visit, treatment by visit interaction, baseline VASI or central read facial-VASI score, baseline VASI or central read facial-VASI score by time (if possible), Fitzpatrick skin type, and a random subject effect. P-values and inference for relative risks between treatments will be provided based on the link function of logit. The delta method may be used to derive point estimates and confidence intervals of relative risks, which is described in Appendix 3 (Section 9.3).

5.2.2. Analyses for Continuous Data

An ANCOVA model will be used to analyze the Week 24 data for the site assessment and central read facial-VASI and VASI. The ANCOVA model will include treatment, baseline efficacy score, and Fitzpatrick skin type as covariates.

As one of the sensitivity analyses, a linear mixed-effect repeated measures models with fixed effects for treatment, time (visit), treatment by time, baseline efficacy score, baseline efficacy score by time, and a random effect for subject will be used to analyze the percent change from baseline in site assessment and central read facial-VASI and VASI. This model will also include Fitzpatrick skin type as a baseline covariate. Due to the unknown nature of the longitudinal data, different covariance structures among repeated measures will be examined based on model diagnostics starting with the unstructured variance-covariance model. Using this model, 95% upper confidence-bound (ie, 90% two-sided CI) comparing the mean percent change from baseline for PF-06651600 dose regimens vs placebo will be computed.

Other continuous data will be analyzed as described in Section 6.

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5.3. Methods to Manage Missing Data

5.3.1. Efficacy Data

5.3.1.1. Continuous efficacy data

The following strategies apply only to missing data that is not missing due to COVID-19. For analyses involving ANCOVA models, observed case analysis will be used (eg, for the ANCOVA analysis at Week 24, the subject will be included if they have baseline and Week 24 efficacy data). For MMRM analyses, no missing data will be imputed.

5.3.1.2. Binary Efficacy Data

The following strategy applies only to missing data that is not missing due to COVID-19. For binary endpoints VASI 50/75/90/100 and Facial-VASI 50/75/90/100, the non-COVID-19 related missing data will be treated as non-responders (except for the GLMM analysis). For the GLMM analyses, no missing data will be imputed.

5.3.3. Missing data due to COVID-19

For continuous endpoint data missing due to COVID-19 in the ANCOVA models, the missing data strategy is the same as described in Section 5.3.1.1. Namely, visits missing due to COVID-19 will be removed from the ANCOVA model and observed data will be used. For continuous endpoint data missing due to COVID-19 in the MMRM, only the visits missing due to COVID-19 will be removed from the analysis (the participant will not be removed). Similarly, for missing binary endpoints, only the visits missing due to COVID-19 will be removed from the analysis (eg, the missing visits will not contribute to the denominator in the calculation of the proportion).

A summary of protocol deviations related to COVID-19 during the dose-ranging period and the extension period will be included as a listing.

6. ANALYSES AND SUMMARIES

6.1. Analyses and Summaries During Dose Ranging Period

Data will be cleaned, a snapshot of the database will be created, and efficacy and safety data from the 24-week Treatment Period will be summarized once the last subject last visit occurs for the initial 24-week Treatment Period. The following section provides details during the Dose Ranging Period.

6.1.1. Primary Endpoint

6.1.1.1. Primary Analysis - Percent Change From Baseline in Central Read Facial-VASI Score at Week 24

Endpoint: Percent change from baseline in central read facial-VASI

- Analysis time points**:** Week 24.
- Analysis population**:** FAS.
- Analysis methodology**:** Percent change from baseline will be analyzed using an ANCOVA model (specified in Section 5.2.2). This model will include treatment, baseline efficacy score, and the Fitzpatrick skin type as covariates.

Reporting results:

- Descriptive data: n, mean, SD, median, min, and max at baseline and post-baseline visits will be presented for each treatment arm.
- Percentage change from baseline: n, mean, SD, median, min, and max will be presented for each treatment arm. The LS means, 90% 2-sided CI for the LS means, difference between the LS means for each pair of PF-06651600 and placebo group and the corresponding 90% 2-sided CI will be presented.
- Listing by individual patient data for each of the 6 depigmentation rates used for the calculation of the central read facial-VASI for each treatment arm.

Figures:

- LS mean percent change from baseline by visit and by treatment.
- LS means and 90% 2-sided CI at Week 24.
- Spaghetti panel plots of individual subject's facial-VASI score by study day in dose ranging period.

6.1.1.2. Sensitivity/Robustness Analyses for Primary Endpoint

To support the interpretation of the primary analysis, the following analyses will be performed:

6.1.1.2.1. Sensitivity Analyses for Primary Endpoint using ANCOVA

One sensitivity analysis involving the ANCOVA model of Section 6.1.1.1 will be implemented.

- Percent change from baseline in central read facial-VASI using the following additional covariates in the ANCOVA model: total BSA (≤10% pigmentation vs. >10% pigmentation), geographic latitude (high vs. low, as data permits).

Analysis time points: Week 24

Analysis population: FAS

Reporting results:

- Percent change from baseline: n, LS means, 2-sided 90% CI for the LS means, difference between the LS means for each pair of treatment groups and the corresponding 2-sided 90% CI will be presented.

Figures:

- LS mean percent change from baseline by treatment at Week 24.
- LS means and 90% 2-sided CI at Week 24.

6.1.1.2.2. Sensitivity Analyses for Primary Endpoint using MMRM

Endpoint: Percent change from baseline in central read facial-VASI

- Analysis time points**:** Week 24 (primary).
- Analysis population**:** FAS.
- Analysis methodology**:** Percent change from baseline will be analyzed using a linear mixed-effect repeated measures model (as specified in Section 5.2.2) with fixed effects for treatment, time (visit), treatment by time, baseline efficacy score, baseline efficacy score by time, and a random effect for subject. This model will also include Fitzpatrick skin type as a baseline covariate.

Reporting results:

- Descriptive data: n, mean, SD, median, min, and max at baseline and post-baseline visits will be presented for each treatment arm.

- Percentage change from baseline: n, mean, SD, median, min, and max will be presented for each treatment arm. The LS means, 90% 2-sided CI for the LS means, difference between the LS means for each pair of PF-06651600 and placebo group and the corresponding 90% 2-sided CI will be presented.

Figures:

- LS mean percent change from baseline by visit and by treatment.
- LS means and 90% 2-sided CI at Week 24 and all other intermediate time points.
- A forest plot will be produced to present the primary endpoint at Week 24 and all the supporting and exploratory analyses (except the dose response analysis).

6.1.1.3. Exploratory Analysis for the Primary Endpoint Involving Facial-VASI Definition

An exploratory analysis that uses a facial surface area of 3% instead of 4% in the facial-VASI computation will also be performed. The formula for the central read facial-VASI, defined in Section 3.1, will use a multiplier of 3 instead of 4. The analysis method and reporting for these rescaled central read facial-VASI values will be the same as Section 6.1.1.1.

6.1.1.4. Supportive Analysis for the Primary Endpoint

To characterize the dose response for central read facial-VASI, a Bayesian 4-parameter maximum effect attributable to the drug (E_{max}) dose-response model will be used. The response function will be the percent change from baseline in central facial-VASI. To account for missing data, the MMRM output for the percent change from baseline in facial-VASI (estimates for each dose group and their standard errors) will be used for the response in the model. There will be two dose response models: (1) using the average dose across the 24 week treatment period and (2) using an indicator function for the loading dose. For (1) the average doses in the model will be 75 mg (for 200/50 mg PF-06651600), 58 mg (for 100/50 mg PF-06651600), 50 mg, 30 mg, 10 mg and 0 mg. For (2) the doses in the model will be 50 mg, 30 mg, 10 mg, 0 mg with an indicator variable of 1 for 200/50 mg and 100/50 mg arms.

In modeling the dose response, diffusive prior distributions will be specified for placebo or e0, e_{max} and dose yielding half of e_{max} (ed_{50}). Using these prior distributions for the true dose response function, we intend to present a Bayesian fit to the data. The fitted curve will be graphically displayed with 95% credible band. Model-based estimation of treatment effect for each dose compared to placebo will be presented with 95% credible interval. The dose response analysis will be done using the R package clinDR.

6.1.2. Secondary Endpoint(s)

6.1.2.1. Key Secondary Endpoint: Central Read Facial-VASI75

Endpoint: Central read facial-VASI75

- Analysis time points**:** Week 24.
- Analysis population**:** FAS.
- Analysis methodology**:** binary data of subjects achieving at least 75% improvement in central read facial-VASI from baseline will be analyzed using Chan and Zhang's exact CI method after applying the non-responder imputation discussed in Section 5.3.1.2.

Reporting results:

- Descriptive data: The number and percentage of subjects meeting central read facial-VASI75 will be presented by visit (using observed data and non-responder imputation).
- The RD from placebo and the 90% 2-sided CI will be presented.

Figures:

- Plot of the proportion of subjects meeting central read facial-VASI75 with 2-sided 90% CI over time by treatment.
- Forest plot will be produced for all the facial-VASI binary endpoints using the Chang and Zhang method.

6.1.2.1.1. Sensitivity Analysis for Key Secondary Endpoint

Endpoint: Central read facial-VASI75

- Analysis time points**:** Week 24.
- Analysis population**:** FAS.
- Analysis methodology**:** Longitudinal central read facial-VASI75 may be analyzed by GLMM, with fixed factors of treatment, visit, treatment by visit, baseline central read facial-VASI score, baseline central read facial-VASI score by time (if possible), and a random subject effect. This model will also include Fitzpatrick skin type as a baseline covariate. This model will only be reported if the GLMM converges.

Reporting results:

- P-values and inference for risk differences between active and placebo will be provided based on the link function of logit.

Figures:

- Plot of the proportion of subjects meeting central read facial-VASI75 with 2-sided 90% CI over time by treatment.

6.1.2.2. Secondary Endpoint: VASI50

Endpoint: VASI50.

- The analysis method, analysis population, and reporting results for VASI50 will match the analysis used for the key secondary endpoint and include reporting of the exact CI (Section 6.1.2.1) and GLMM if the model converges (Section 6.1.2.1.1).

6.1.2.3. Secondary Endpoints: Percent Change From Baseline in Central Read Facial-VASI (Except Week 24), Site Assessment Facial-VASI, VASI, SA-VES, and Absolute Change From Baseline in VASI

The analysis method, analysis population, and reporting results for percent change from baseline in central read facial-VASI (except Week 24) and SA-VES will be the same as the analysis used for MMRM sensitivity analysis for the primary endpoint (see Section 6.1.1.2.2).

The analysis method, analysis population, and reporting results for percent change from baseline in site assessment facial-VASI and VASI will be the same as the ANCOVA analysis for the primary endpoint (see Section 6.1.1.1).

The analysis method for the absolute change from baseline in VASI will be the same as the ANCOVA analysis for the primary endpoint (see Section 6.1.1.1).

6.1.2.4. Secondary Endpoints: VASI 75, VASI 90 and VASI 100

The analysis method, analysis population, and reporting results for these endpoints will be identical to the analysis used for central read facial-VASI75 (Section 6.1.2.1).

6.1.2.5. Secondary Endpoints: Central Read and Site Assessment Facial-VASI 50/75/90/100 (Except Central Read Facial-VASI75)

The analysis method, analysis population, and reporting results for these endpoints will be identical to the analysis used for central read facial-VASI75 (Section 6.1.2.1).

6.1.2.6. Secondary Endpoint: Change From Baseline in VitiQoL

The change from baseline in total VitiQoL score and VitiQoL domain scores will be analyzed using the MMRM analysis as specified in Section 6.1.1.2.2. Details of the scoring algorithm are provided in Appendix 6.

6.1.2.7. Secondary Endpoint: Proportion of Subjects achieving a Static Investigator Global Assessment score of 0 or 1, and at least 2-point Improvement at Week 24

Endpoint: sIGA.

- Analysis time points**:** Scheduled time points in the SoA.
- Analysis population**:** FAS.
- Analysis methodology**:** the number and percentage of subjects in each category will be presented (see Section 5.2.1). Additionally, the number and percentage in each category will be analyzed using Chan and Zhang's exact CI method after applying the non-responder imputation discussed in Section 5.3.1.2.

Reporting results:

- The number and percentage of the proportion of subjects achieving sIGA 0/1 and sIGA ≥2-point improvement will be presented by visit and treatment. The RD from placebo and the 90% 2-sided CI will also be presented.

6.1.3. Tertiary Endpoint(s)

6.1.3.1. Tertiary Endpoints: Percent Change From Baseline in VES

The analysis method will be the same as the analysis used for MMRM sensitivity analysis for the primary endpoint (see Section 6.1.1.2.2). Analysis time points will be Week 24 and all intermediate time points.

6.1.3.2. Tertiary Endpoints: VES 50/75/90/100

The analyses for each endpoint will be identical to the analysis used for central read facial-VASI75 (Section 6.1.2.1).

6.1.3.3. Tertiary Endpoints: Absolute Change From Baseline in Central Read and Site Assessment Facial-VASI and VES

For absolute change from baseline in VES, the analysis method will be the same as the analysis used for MMRM sensitivity analysis for the primary endpoint (see Section 6.1.1.2.2). Analysis time points will be Week 24 and all intermediate time points.

For absolute change from baseline in central read and site assessment facial-VASI, the analysis method will be the same as the analysis used for primary analysis (see Section 6.1.1.1). The analysis time point will be Week 24.

6.1.3.4. Tertiary Endpoints: VASI/Central Read Facial-VASI vs PGIS-V at Week 24

Endpoint: VASI/central read facial-VASI vs PGIS-V at Week 24; Change from baseline VASI/central read facial-VASI vs PGIS-V improvement categories (worsening (>0); no change, 1-point improvement, ≥2-point improvement) at Week 24.

- Analysis time point: Week 24.

- Analysis population: FAS.
- Analysis methodology: Descriptive summary.

Reporting results:

- A summary table of descriptive statistics will be provided.

Figures:

- Box and whisker plots of VASI/central read facial-VASI vs PGIS-V will be presented.

6.1.3.5. Tertiary Endpoint: Change from Baseline in DLQI

The DLQI is calculated by summing the score of all questions. The maximum score is 30 and the minimum is 0. The analysis method will be the same as the analysis used for MMRM sensitivity analysis for the primary endpoint (see Section 6.1.1.2.2).

6.1.3.6. Tertiary Endpoint: Change from Baseline EQ-5D-5L

The number and percentage of subjects in 5 levels of 5 dimensions will be summarized by visit and by treatment. Summary statistics (n, mean, SD, median, min, and max) for mean EQ-5D-5L utility score and EQ-5D-VAS score will be provided by visit and treatment.

The EQ-5D-5L scoring manual will be provided separately. US-based weights will be used across all study sites.

6.1.3.7. Tertiary Endpoint: Change from Baseline HCRU

The number and percent of subjects with at least one HCRU questionnaire event will be summarized by visit and treatment. Descriptive statistics of change from baseline of HCRU by each question will be provided by visit and treatment.

6.1.3.8. Tertiary Endpoint: PHQ-8

PHQ-8 is collected only at screening. Descriptive statistics of PHQ-8 score categories will be summarized by treatment group.

6.1.3.9. Tertiary Endpoint: Facial Target Lesion Improvement (by Planimetry) ≥50% From Baseline at Week 24

If data permit, the proportion of subjects achieving ≥50% improvement from baseline at Week 24 will be summarized using descriptive statistics.

6.1.3.10. Tertiary Endpoint: Proportion of "Much Improved" and "Very Much Improved" on PGIC-V

Endpoint: PGIC-V; Change from baseline VASI / central read facial-VASI vs PGIC-V at Week 24.

- Analysis time point: Week 24.

- Analysis population: FAS.
- Analysis methodology: PGIC-V will be summarized with frequency counts by each category at Week 24. The proportion of subjects in 'Much Improved' and 'Very Much Improved' will be compared to placebo using RD and CIs using the Chan and Zhang exact method.

Reporting results:

- A table of RD for subjects achieving 'Much Improved' and 'Very Much Improved' in active treatment arms vs placebo will be provided.
- A summary table of descriptive statistics will be provided.

Figures:

- Box and whisker plots of change from baseline VASI/central read facial-VASI vs PGIC-V will be presented.

6.1.3.11. Tertiary Endpoint: Proportion of "A lot less noticeable" or "No longer noticeable" on VNS

The proportion of subjects in each category of VNS will be summarized by treatment groups. Subjects who achieve VNS = 4 or 5 will be considered as a treatment success, ie, responders. The number and proportion of subjects achieving VNS = 4 or 5 at Week 24 will be provided by treatment group.

If data permits, Chan and Zhang's exact CI will be computed for the RD to compare the proportion of treatment success between PF-06651600 vs placebo at Week 24.

Box and whisker plots of change from baseline VASI/central read facial-VASI vs VNS at Week 24 will be presented.

6.1.3.12. Tertiary Endpoint: Change of Extent of Depigmentation in Target Lesion(s)

Endpoint: Percent change from baseline in depigmentation rate of target lesions.

- Analysis time points**:** Week 24.
- Analysis population**:** FAS.
- Analysis methodology**:** Percent change from baseline will be analyzed using an ANCOVA model (specified in Section 5.2.2). This model will include treatment, baseline score, location (if data available) and the Fitzpatrick skin type as covariates.

Reporting results:

- Desciptive data: n, mean, SD, median, min, and max at baseline and post-baseline visits will be presented for each treatment arm. The LS means and 90% 2-sided CI for the LS means will be presented.
- If data permits, Chan and Zhang's exact CI method may be used to compare the proportion of depigmentation level improvement of 25% or more between PF-06651600 and placebo.

Figures:

- LS mean percent change from baseline by visit and by treatment.

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6.1.3.14. Tertiary Endpoint: C-SSRS

Endpoint: Change from baseline in C-SSRS.

- Analysis time points**:** Scheduled time points in the SoA.
- Analysis population**:** FAS.
- Analysis methodology**:** Number and percentage of subjects in each category at each visit using the C-CASA categories.

Reporting results:

- Descriptive data: The number and percentage of subjects in each category at baseline and post-baseline visits will be presented for each treatment arm. For subjects who have the wrong version of C-SSRS at the baseline assessment, C-SSRS at screening will be used as baseline.

Figure:

- Frequency plot for C-SSRS mapped to C-CASA.

6.1.3.15. Tertiary Endpoint: Hospital Anxiety and Depression Scale

Endpoint: Change from baseline in HADS.

- Analysis time points**:** Scheduled time points in the SoA.
- Analysis population**:** FAS.

- Analysis methodology: Descriptive scores at each time point for anxiety sub-scale and depression subscale by treatment arms. The number and percentage of subjects with anxiety and depression sub scales score 0 to <8 (normal); 8 to <11 (mild); ≥11 to <15 (moderate); ≥15 (severe) at each time point by treatment arms.

Reporting results:

- A summary table of descriptive statistics will be provided.

The HADS scoring manual will be provided separately.

6.1.3.16. Tertiary Endpoint: Target Lesion Assessments for Stable Vitiligo and for Segmental Vitiligo, if any

Endpoint: Depigmentation rate of targeted lesions.

- Analysis time points**:** Baseline and Week 24.
- Analysis population**:** FAS.
- Analysis methodology**:** Number and percentage of lesions in each depigmentation category by active, stable and/or segmental vitiligo lesion status.

Reporting results:

- Descriptive data: The number and percentage of lesions in each depigmentation category at baseline and post-baseline visits will be presented for each treatment arm and by stable vitiligo lesion and/or segmental vitiligo lesion status.
- Number and percent of lesions by lesion type (active, stable, or segmental) at baseline.

6.1.3.17. Tertiary Endpoint: Dermoscopy

Endpoint: Number of lesions with less than 30% of white hair in the depigmented lesion.

- Analysis time points**:** Scheduled time points in the SoA.
- Analysis population**:** FAS.
- Analysis methodology**:** Mean and standard deviation of number of fields with less than 30% of white hair.

Reporting results:

- Descriptive data: The number and percentage of subjects in each category at baseline and post-baseline visits will be presented for each treatment arm.

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6.1.4. Baseline and Other Summaries and Analyses

6.1.4.1. Baseline and Other Summaries

Demographics and vitiligo medical history variables as defined in Section 3.5 will be summarized by treatment group. This will include: age, gender, race, Fitzpatrick Skin Type, geographic location zone (zone A and zone B based on latitude 38), vitiligo duration since onset (years), baseline total BSA ≤10% and >10%, baseline total BSA (continuous variable), baseline VASI ≤10% and >10%, baseline VASI (continuous variable), baseline central read and site assessment facial-VASI, baseline central read facial BSA, baseline sIGA, baseline VitiQoL, and PGIS-V (item 16 of VitiQoL).

In addition, sun exposure complier status will be summarized by treatment group if data permit. Compliers are defined as subjects who have >50% of days with approximate 15 minutes daily sun exposure without sunscreen and non-compliers are defined as subjects who have <50% of days with approximate 15 minutes daily sun exposure without sunscreen.

The above baseline summaries will also be completed for subjects meeting and not meeting central read facial-VASI75 at Week 24 of the dose-ranging period and at Week 24 of the extension period.

6.1.4.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed in the FAS, and as well as for safety. Frequency counts will be supplied for subject discontinuations by treatment.

Data will be reported in accordance with reporting standards.

6.1.4.3. Concomitant Medications, Non-Drug Treatments, and Dosing Compliance

All concomitant medication(s) as well as non-drug treatment(s) prior to the start of the study, during the dose-ranging period, and during the extension period will be provided in the listings. In addition, a listing of dosing compliance during the dose-ranging period and the extension period will be provided.

6.1.5. Safety Summaries and Analyses

6.1.5.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification.

The TEAEs by system organ class and preferred term will be generated for the Induction Phase, Maintenance Phase, and Dose Ranging Period for both all-causality and treatment-related AEs. The SAEs (both all causality and treatment-related) by system organ class and preferred term may also be generated for Induction Phase, Maintenance Phase, and Dose Ranging Period as needed.

6.1.5.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.6.2. In addition the incidence of specific clinical laboratory abnormalities including, but not limited to, anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and LFTs.

The following laboratory abnormalities require re-testing within 1 week until resolution or agreement with sponsor.

Table 4. Laboratory Re-Testing Criteria

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<2000/mm^3 (2.0 x 10^9/L)
Hemoglobin	<9.0 g/dL
Platelet count	<100,000/mm^3 (100 x 10^9/L)
Lymphocytes	<600/mm^3 (< 0.6 x 10^9/L)
Chemistry	
CK	>3x ULN (This also triggers urine myoglobin.)

Laboratory values meeting the following criteria will be summarized by number and percent.

Table 5. Laboratory Abnormality Criteria

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<1000/mm^3 (<1.0 x 10^9/L)
Hemoglobin	<8.0 g/dL (<4.96 mmol/L; <80 g/L)
Platelet count	<75,000/mm^3 (<75.0 x 10^9/L)
Lymphocytes	<500/mm^3 (<0.5 x 10^9/L)
Chemistry	
AST	>2.5x ULN
ALT	>2.5x ULN
Total bilirubin	>1.5x ULN
CK	>10x ULN

6.1.5.3. Vital Signs

Absolute values and change from baseline in systolic and diastolic BP, respiratory rate, pulse rate and temperature will be summarized by treatment and time post-dose, according to sponsor reporting standards.

6.1.5.4. Electrocardiogram

Categorical summary tables will be summarized by treatment and time post-dose using sponsor reporting standards. A listing of ECG comments on findings and normal/abnormal results will be provided.

6.1.5.5. Physical Examination

All physical exam data will be provided in the listings.

6.2. Analyses and Summaries During Extension Period

At Week 16 of the Dose Ranging Period, subjects will be evaluated for eligibility to enter the Extension Period and be assigned to one of the treatment groups at Week 24. If due to COVID-19, the Week 16 visit of Dose Ranging Period is missing, the Week 12 or Week 20 Visit value will be used for Extension Period mapping.

An unblinded programmer and unblinded study manager, independent from the blinded study team, will perform the response status calculation and group mapping for the Extension Period. The subjects, investigators, and individuals from the sponsor (or designee) who interact with the investigators and monitor safety will continue to be blinded to individual study treatments throughout the Extension Period of the study.

Figure 4 lists the routes subjects may experience.

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The percent change from baseline VASI score at Week 16 Visit of the Dose Ranging Period will be used to decide whether the subject is a Responder (defined as subjects who achieve 50% or more improvement in VASI from baseline) or Non-responder (defined as subjects who achieve less than 50% improvement in VASI from baseline). Treatment regimen by group for the Extension Period are described in Figure 2.

- Responders from the 200-50 mg, 100-50 mg, 50 mg, or Placebo arm will be allocated to Group 4.
- Responders from the 30 mg, or 10 mg arm will be allocated to Group 5.
- Responders from the 10 mg or Placebo arm who achieve VASI100 (absolute VASI of 0; 100% improvement in VASI from baseline) at Week 16 will enter Group 6 (no treatment).
- Responders who achieve VASI100 from the 200-50 mg, 100-50 mg, and 50 mg arms will be allocated to Group 4.
- Responders who achieve VASI100 from the 30 mg arm will be allocated to Group 5.

Non-responders from 200-50 mg, 100-50 mg, or 50 mg arm in Dose Ranging period who:

- Agree with nbUVB consent and agree with additional contraception methods -- will be allocated to Group 1. After Group 1 caps, they will be allocated to Group 2; after Group 2 caps, they will be allocated to Group 3.
- Agree with nbUVB consent and do not agree with additional contraception methods -- will be allocated to Group 2; after Group 2 caps, they will be allocated to Group 3.
- Do not agree with nbUVB consent and agree with additional contraception methods -- will be allocated to Group 1. After Group 1 caps, they will be allocated to Group 3.
- Do not with nbUVB consent and do not agree with additional contraception methods -- will be allocated to Group 3.

Non-Responders from 30 mg arm in Dose Ranging period who:

- Agree with additional contraception methods -- will be allocated to Group 1. After Group 1 caps, they will be allocated to Group 3.
- Do not agree with additional contraception methods -- will be allocated to Group 3.

Non-Responders from 10 mg or Placebo arm who:

- Agree with nbUVB consent -- will be allocated to Group 2. After Group 2 caps, then subjects will be allocated to Group 3.
- Do not agree with nbUVB consent -- will be allocated to Group 3.

Group 1 and Group 2 will be capped at 60 subjects each.

In general, for efficacy endpoints, analyses and summaries will be presented by visit and group.

For safety endpoints and pharmacodynamics endpoints, analyses and summaries will be presented by visit and treatment. For safety endpoints, Baseline will be the same as the baseline in Dose Ranging Period. For pharmacodynamics endpoints, Baseline will be Week 24 of Dose Ranging Period (or the previous non missing visit if Week 24 visit is missing).

The only exception where the baseline definition differs from above are for Cystatin C and Cystatin C-based eGRF in Extension Group 1, which use the last measurement prior to first dose of PF-06700841 for baseline.

6.2.1. Primary Endpoints (Safety)

Safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of the study medication. All clinical AEs, SAEs, TEAEs, as well as discontinuations due to AEs, will be summarized with frequency and percentage. Continuous outcomes (eg, vitals, safety lab parameters, etc.) will be summarized using n, mean, median, SD, etc.

Baseline will be the same as the baseline in Dose Ranging Period. Percent change from baseline on selected safety endpoints such as hemoglobin, absolute neutrophil count, platelet count, lymphocytes, creatine phosphokinase, lipid profile, and LFTs may be summarized. Subject listings may also be produced for these safety endpoints. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Detailed methodologies of these analyses are the same as those described in Section 6.1.5 for the analysis during Dose Ranging Period.

6.2.2. Exploratory Efficacy Analysis

Central read facial-VASI assessments performed in the Extension Period will be analyzed in the same manner as the site assessment facial-VASI analyses described below for continuous and binary endpoints.

Two categories of analyses will be performed as part of the exploratory efficacy analyses for the continuous and binary endpoints in the extension period:

1. The first set of analyses will assess the long term effect of PF-06651600 for subjects enrolled in Extension Group 3. These analyses include all subjects in Extension Group 3 who received at least one dose of PF-06651660 during the extension period (ie, extension analysis set group 3). Baseline will be Day 1 of the dose-ranging period, and all post-baseline visits up to Week 24 of the extension period will be included.

2. The second set of analyses will assess the effect of the add-on nbUVB therapy with PF-06651660 (ie, compare extension Groups 2 and 3). These analyses include all subjects in Extension Group 2 or 3 who received at least one dose of PF-06651660 during the extension period (ie, extension analysis set Group 2/3). Baseline will be Day 1 of the extension period (or the previous non-missing visit), and all post-baseline visits up to Week 24 of the extension period will be included.

6.2.2.1. Continuous Endpoints

For all extension groups, Baseline will be Week 24 of Dose Ranging Period (or the previous non missing visit if Week 24 visit is missing) or Day 1 of the dose ranging period as explained in Section 6.2.2 for the two sets of analyses.

Endpoints:

- Percent change from baseline in VASI, site assessment facial-VASI, VES, and SA-VES.

- Change from baseline in VASI, site assessment facial-VASI, and VES.
- Change from baseline in VitiQoL, DLQI, EQ-5D-5L, HCRU, C-SSRS, and HADS.

Analysis time points: Scheduled time points in the SoA.

Analysis population: Extension analysis set.

Analysis methodology:

- Summary statistics may be provided by treatment group and time point in the Extension Period.
- The following four endpoints will be analyzed at Extension Week 24 using the same ANCOVA model as in the primary analysis (Section 6.1.1.1): Percent change from baseline VASI, percent change from baseline site assessment facial-VASI, change from baseline VASI, change from baseline site assessment facial-VASI.
- The following two endpoints may additionally be analyzed using the same MMRM model as described in the sensitivity analysis for the primary endpoint (Section 6.1.1.2.2): Percent change from baseline VASI, percent change from baseline site assessment facial-VASI.
- The following seven endpoints may be analyzed using a MMRM model (Section 5.2.2): change from baseline in VES, VitiQoL, DLQI, EQ-5D-5L, HCRU, C-SSRS, and HADS.

Reporting results:

- Descriptive data: n, mean, SD, median, min, and max at baseline and post-baseline visits will be presented.
- Percent change from baseline: n, mean, SD, median, min and max will be presented. The LS means, 2-sided 90% CI for the LS means, difference between the LS means for each treatment by visit and the corresponding 2-sided 90% CI will also be presented.

Figures:

- LS mean change from baseline and corresponding 2-sided 90% CI by visit and by treatment reporting group.

6.2.2.1.1. Extension Group 1 endpoints

An ANCOVA model will be performed for Extension Group 1. Baseline will be Week 24 of Dose Ranging Period (or the previous non missing visit if Week 24 visit is missing).

Endpoints:

- Percent change from baseline in central read facial-VASI.

Analysis time points: Scheduled time points in the SoA.

Analysis population: Extension group 1 analysis set.

Analysis methodology:

- Summary statistics may be provided by treatment group and visit in the Extension Period.
- The following endpoint will be analyzed at Extension Week 24 and intervening visits during the extension period using the same ANCOVA model as in the primary analysis (Section 6.1.1.1): Percent change from baseline central read facial-VASI.

Reporting results:

- Descriptive data: n, mean, SD, median, min, and max at baseline and post-baseline visits will be presented.
- Percent change from baseline: n, mean, SD, median, min and max will be presented, as well as the LS means and 2-sided 90% CI for the LS means.

6.2.2.2. Binary Endpoints

For all extension groups, Baseline will be Week 24 of Dose Ranging Period (or the previous non missing visit if Week 24 visit is missing) or Day 1 of the dose ranging period as explained in Section 6.2.2 for the two sets of analyses.

Endpoints:

- VASI 50/75/90/100 and site assessment facial-VASI 50/75/90/100.
- Proportion of subjects achieving sIGA 0 or 1 and ≥2-point improvement.
- Proportion of subjects achieving "much improved" or "very much improved" in PGIC-V.
- Proportion of subjects achieving "a lot less noticeable" or "no longer noticeable" on VNS.

The following descriptions use VASI50 as an example. The analyses for all binary endpoints except for VNS are identical.

Analysis time points: Scheduled time points in the SoA.

Analysis population: Extension analysis set.

Analysis methodology:

- The number and percentage of subjects achieving a 50% improvement in VASI will be provided.
- For the Extension Period, the proportion of subjects achieving a 50% improvement in VASI may be analyzed using exact method (Section 5.2.1).

Reporting results:

- Descriptive data: The number and percentage of subjects meeting VASI 50 will be presented;

Figures:

- Plot of the proportion of subjects meeting VASI 50 in the Extension Period by visit and by reporting group.

Proportion of subjects in each category of VNS will be summarized by treatment groups.

Subjects who achieve VNS = 4 or 5 will be considered as a treatment success, ie, responders. The number and proportion of subjects achieving VNS = 4 or 5 at Week 48 will be provided by treatment group from the two stages of the study, eg, PF-06651600 200 mg/50 mg DR/ExtGroup1, Placebo DR/ExtGroup3, etc.

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7. INTERIM ANALYSES

7.1. Introduction

A separate interim analysis plan (IAP) for this protocol may include an interim analysis using percent change from baseline VASI score for all active treatments. Details regarding the analysis procedures to be used for the interim analysis will be provided in the IAP. The interim analysis, if any, will be performed when approximately 50% of subjects have completed or had the chance to complete the Week 24 visit in Dose Ranging Period.

7.2. Interim Analyses and Summaries

The objective of the interim analysis is to determine if there is evidence of lack of differentiation ("futility") for the active treatments compared to placebo. The interim analysis, if any, will be based on predicted power conducted on a total of approximately 50% of subjects (~165) who have completed the Week 24 visit or discontinued from the study in Dose Ranging Period.

The interim analysis results will be used to facilitate internal decision-making. The results will only be distributed to a select list of individuals involved in the internal decision-making process to protect the integrity of the study. This list of individuals will be provided in the IAP. The results of the interim analysis will not enable individuals directly involved in running the study (such as investigators) to identify treatment assignments for individual subjects still in the study. There are no prospective plans to stop the study early for success as a result of the interim analyses.

During the interim analysis, some members of the study team may be unblinded and replaced with blinded colleagues. The subjects, investigators, and individuals from the sponsor (or designee) who interact with the investigators and monitor safety will continue to be blinded to individual study treatments throughout the follow up period of the study.

8. REFERENCES

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9. APPENDICES

9.1. APPENDIX 1. Summary of Efficacy Analyses

9.1.1. APPENDIX 1.1. Brief Summary of Key Efficacy and PRO Analyses in the Dose Ranging Period

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Percent change from baseline in central read facial-VASI at Week 24	FAS	ANCOVA	Treatment, baseline efficacy score, skin type	None	Primary
Percent change from baseline in central read facial-VASI at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment*Visit, baseline central read facial-VASI, baseline central read facial-VASI*treatment, skin type	None	Sensitivity for Primary (Week 24) and Secondary (intermediate time points)
Percent change from baseline in central read facial-VASI at Week 24	FAS	ANCOVA	Treatment, baseline efficacy score, skin type, BSA, geographic region	None	Sensitivity for Primary
Percent change from baseline in central read facial-VASI at Week 24 (with central read facial-VASI as 3% BSA instead of 4%)	FAS	ANCOVA	Treatment, baseline efficacy score, skin type	None	Exploratory for Primary
Change from baseline in central read facial-VASI at Week 24	FAS	4-parameter Bayesian Emax model	See Section 6.1.1.4	None	Supportive for Primary
Central read and site assessment facial-VASI 50/75/90/100 at Week 24 and at intermediate time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Key secondary (central read facial-VASI75 at Week 24) and Secondary (all others)

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Percent change from baseline in VASI at Week 24	FAS	ANCOVA	Treatment, baseline efficacy score, skin type	None	Secondary
Change from baseline SA-VES at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline SA-VES, baseline SA-VES*treatment, skin type	None	Secondary
VASI 50/75/90/100 at Week 24 and at intermediate time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
Change from baseline in VitiQoL total score at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline VitiQoL, baseline VitiQoL*treatment, skin type	None	Secondary
sIGA 0 or 1 and 2-point or greater improvement	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
Change from baseline central read and site assessment facial-VASI at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline central read and site assessment facial-VASI, baseline central read and site assessment facial-VASI*treatment, skin type	None	Exploratory
Change from baseline VES at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline VES, baseline VES*treatment, skin type	None	Exploratory

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Change from baseline in DLQI score	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline DLQI, baseline DLQI*treatment, skin type	None	Exploratory

9.1.2. APPENDIX 1.2. Brief Summary of Key Exploratory Efficacy and PRO Analyses in the Extension Period

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Percent change from baseline in VASI at ExWeek 24 and at intermediate time points	Extension analysis set	ANCOVA	Treatment, baseline efficacy score, skin type	None	Exploratory
Percent change from baseline in site assessment facial-VASI* at ExWeek 24	Extension analysis set	ANCOVA	Treatment, baseline efficacy score, skin type	None	Exploratory
Percent change from baseline in VES at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline VES, baseline VES*treatment, skin type	None	Exploratory
Percent change from baseline in SA-VES at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline SA-VES, baseline SA-VES* treatment, skin type	None	Exploratory

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Change from baseline in VASI at ExWeek 24	Extension analysis set	ANCOVA	Treatment, baseline efficacy score, skin type	None	Exploratory
Change from baseline in site assessment facial-VASI at ExWeek 24	Extension analysis set	ANCOVA	Treatment, baseline efficacy score, skin type	None	Exploratory
Change from baseline in VASI at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment*Visit, baseline VASI, baseline VASI*treatment, skin type	None	Exploratory
Change from baseline in site assessment facial-VASI at ExWeek 24	Extension analysis set	MMRM	Treatment, Visit, Treatment*Visit, baseline site assessment facial-VASI, baseline site assessment facial-VASI*treatment, skin type	None	Exploratory
Change from baseline in VES at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline VES, baseline VES*treatment, skin type	None	Exploratory
Change from baseline in VitiQoL at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline VitiQoL, baseline VitiQoL *treatment, skin type	None	Exploratory

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Change from baseline in DLQI score at ExWeek 24 and at intermediate time points	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline DLQI, baseline DLQI*treatment, skin type	None	Exploratory
Change from baseline HADS score	Extension analysis set	MMRM	Treatment, Visit, Treatment* Visit, baseline HADS, baseline HADS*treatment, skin type	None	Exploratory
VASI 50/75/90/100 at ExWeek 24 and at intermediate time points	Extension analysis set	Chan and Zhang's exact test	None	None	Exploratory
Site assessment facial-VASI 50/75/90/100 at ExWeek 24 and at intermediate time points*	Extension analysis set	Chan and Zhang's exact test	None	None	Exploratory
sIGA 0 or 1 and 2-point or greater improvement	Extension analysis set	Chan and Zhang's exact test	None	None	Exploratory

* If central read facial-VASI is completed in the extension period, analyses may also be repeated using central read facial-VASI values.

9.2. APPENDIX 2. Data Derivation Details

9.2.1. Appendix 2.1. Definition and Use of Visit Windows for Analysis

The use of visit windows in reporting the Extension Period will be explained in detail in the programming plan for this study. The key is to ensure that the windowing algorithm accommodates the visits for the active patients in the Extension Period and the placebo patients when they enter the retreatment period.

Visit	Start Day	End Day
Visit 1 (Screening)	Day -28	Day -1
Visit 2 (Day 1, Week 0)	Day 1	Day 1
Visit 3 (Day 15, Week 2)	Day 9	Day 22
Visit 4 (Day 29, Week 4)	Day 23	Day 49
Visit 5 (Day 57, Week 8)	Day 50	Day 77
Visit 6 (Day 85, Week 12)	Day 78	Day 105
Visit 7 (Day 113, Week 16)	Day 106	Day 133
Visit 8 (Day 141, Week 20)	Day 134	Day 161
Visit 9 (Day 169, Week 24)	Day 162	Day 189
Visit 10 (Day 170, ExD1) Group 2 only	Day 162	Day 178
Visit 11 (Period Day 1, ExW4) Group 1 only	Period Day 1	Period Day 1
Visit 11 (Day 184, ExW2) Groups 2, 3, 4, and 5	Day 179	Day 192
Visit 12 (Period Day 15, ExW6) Group 1 only	Period Day 2	Period Day 21
Visit 12 (Day 198, ExW4) Groups 2, 3, 4, and 5	Day 193	Day 218
Visit 13 (Period Day 29, ExW8) Group 1 only	Period Day 22	Period Day 49
Visit 13 (Day 226, ExW8) Groups 2, 3, 4, and 5	Day 219	Day 246
Visit 14 (Period Day 57, ExW12) Group 1 only	Period Day 50	Period Day 77
Visit 14 (Day 254, ExW12) Groups 2, 3, 4, and 5	Day 247	Day 274
Visit 15 (Period Day 85, ExW16) Group 1 only	Period Day 78	Period Day 105
Visit 15 (Day 282, ExW16) Groups 2, 3, 4, and 5	Day 275	Day 302
Visit 16 (Period Day 113, ExW20) Group 1 only	Period Day 106	Period Day 133
Visit 16 (Day 310, ExW20) Groups 2, 3, 4, and 5	Day 303	Day 330
Visit 17 (Period Day 141, ExW24) Group 1 only	Period Day 134	Period Day 161

Visit	Start Day	End Day
Visit 17 (Day 338, ExW24) Groups 2, 3, 4, and 5	Day 331	Day 358
Visit 18 (Day 366, Follow-Up Visit 1)	Day 359	Day 386
Visit 19 (Day 394, End of Study Visit)	Day 387	Day 414

9.3. APPENDIX 3. Statistical Methodology Details of Delta Method

It is known that the estimate and CI on the logit scale can be obtained using the SAS GLIMMIX procedure with dist=binary and link=logit; using ilink option in GLIMMIX will generate the estimate for proportions. The variance of RD (proportion difference) cannot be directly obtained by GLIMMIX procedure using link=logit. This appendix describes how to obtain the estimate and the CI for RD (proportion difference) by the delta method.

Suppose that p_1 and p_2 are the two proportions of interest. $l_1 = \log it(p_1) = \log(\frac{p_1}{1-p_1})$ and $l_2 = \log it(p_2) = \log(\frac{p_2}{1-p_2})$ are the logit for the two proportions. Note that the l_1, l_2, p_1 and p_2 can be obtained by GLIMMIX procedure, and so are the covariance matrix for l_1 and l_2.
Our interest is to derive the variance of $p_1 - p_2$.

Denote that $f(l_1, l_2) = \frac{e^{l_1}}{1+e^{l_1}} - \frac{e^{l_2}}{1+e^{l_2}} = p_1 - p_2$. A Taylor series expansion of $f(l_1, l_2)$ about the values (l_{10}, l_{20}) is given by:

$$f(l_1, l_2) = f(l_{10}, l_{20}) + \frac{\partial f(l_1, l_2)}{\partial l_1}|_{(l_{10}, l_{20})} (l_1 - l_{10}) + \frac{\partial f(l_1, l_2)}{\partial l_2}|_{(l_{10}, l_{20})} (l_2 - l_{20}) + (\text{2nd or higher order terms})$$

Therefore

$$Var(f(l_1, l_2)) \approx \left[\frac{\partial f(l_1, l_2)}{\partial l_1}|_{(l_{10}, l_{20})}\right]^2 Var(l_1) + \left[\frac{\partial f(l_1, l_2)}{\partial l_2}|_{(l_{10}, l_{20})}\right]^2 Var(l_2) + 2\left[\frac{\partial f(l_1, l_2)}{\partial l_1}|_{(l_{10}, l_{20})}\right]\left[\frac{\partial f(l_1, l_2)}{\partial l_2}|_{(l_{10}, l_{20})}\right] Cov(l_1, l_2) \quad \text{(A.6.1)}$$

Since

$$\frac{\partial f(l_1, l_2)}{\partial l_1} = \frac{e^{l_1}}{(1+e^{l_1})^2} \text{ and } \frac{\partial f(l_1, l_2)}{\partial l_2} = -\frac{e^{l_2}}{(1+e^{l_2})^2},$$

$$Var(f(l_1, l_2)) \approx \left[\frac{e^{l_1}}{(1+e^{l_1})^2}\right]^2 Var(l_1) + \left[\frac{e^{l_2}}{(1+e^{l_2})^2}\right]^2 Var(l_2) - 2\left[\frac{e^{l_1}}{(1+e^{l_1})^2}\right]\left[\frac{e^{l_2}}{(1+e^{l_2})^2}\right] Cov(l_1, l_2) \quad \text{(A.6.2)}$$

Now take $(l_{10}, l_{20}) = (\hat{l}_1, \hat{l}_2)$ where $(\hat{l}_1, \hat{l}_2)$ are the estimates of logits which are obtained by GLIMMIX procedure. Then by analogy with the above result, the corresponding estimated variance of the estimator is given by

$$\hat{Var}(f(\hat{l}_1,\hat{l}_2)) \approx \left[\frac{e^{\hat{l}_1}}{(1+e^{\hat{l}_1})^2}\right]^2 Var(\hat{l}_1) + \left[\frac{e^{\hat{l}_2}}{(1+e^{\hat{l}_2})^2}\right]^2 Var(\hat{l}_2)$$
$$-2\left[\frac{e^{\hat{l}_1}}{(1+e^{\hat{l}_1})^2}\right]\left[\frac{e^{\hat{l}_2}}{(1+e^{\hat{l}_2})^2}\right] Cov(\hat{l}_1,\hat{l}_2) \quad \text{(A.6.3)}$$

In conclusion, using GLIMMIX the estimates of logit, variance of the estimate and the corresponding CI for $p_1 - p_2$ can be written as

$$\hat{p}_1 - \hat{p}_2 = \frac{e^{\hat{l}_1}}{1+e^{\hat{l}_1}} - \frac{e^{\hat{l}_2}}{1+e^{\hat{l}_2}};$$
$$\hat{Var}(\hat{p}_1 - \hat{p}_2) = \hat{Var}(f(\hat{l}_1,\hat{l}_2)); \quad \text{(A.6.4)}$$
$$(1-\alpha)\%\text{CI}: \hat{p}_1 - \hat{p}_2 \pm z_{1-\alpha/2}\sqrt{\hat{Var}(\hat{p}_1 - \hat{p}_2)}.$$

Where $\hat{Var}(f(\hat{l}_1,\hat{l}_2))$ is given in (A.6.3).

9.4. APPENDIX 4. Details on C-SSRS Mapping

Table 1. C-CASA Suicidality Events and Codes

Event Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other, accident, psychiatric; mental
9	Not enough information, non fatal

* Note: Event Codes 5, 6, 8 and 9 are not applicable to prospectively collected data

Table 2. C-SSRS Mapped to C-CASA - Suicidality Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: • "Aborted attempt", or • "Interrupted attempt", or • "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: • "Wish to be dead", or • "Non-Specific Active Suicidal Thoughts", or • "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or • "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or • "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

9.5. APPENDIX 5. Facial Vitiligo Area Scoring index (facial-VASI) - Site Assessment

The facial VASI will be assessed by the Investigator. The local read facial VASI is calculated using a formula that is similar to facial-VASI central read. It includes contribution from face (possible range, 0.00 to 4.00). Scalp, neck, eyebrows, eyelashes, and vermilion will be excluded from this calculation, although total VASI assessment includes all of these regions.

Facial VASI = Digit Units × Depigmentation × 0.1

The volar surface of one digit (the subject's thumb) is approximately 0.1% of the total body surface area and is used as a guide to estimate the baseline percentage of vitiligo involvement of face.

The extent of depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%.

- 100% depigmentation: no pigment is present;
- 90% depigmentation: specks of pigment are present;
- 75% depigmentation: the depigmented exceeds the pigmented area;
- 50% depigmentation: the depigmented and pigmented areas are equal;
- 25% depigmentation: the pigmented area exceeds the depigmented area; and
- 10% depigmentation: only specks of depigmentation are present.

9.6. APPENDIX 6. Analysis of Change from Baseline VitiQoL scores

VitiQoL total score is calculated as sum of items 1-15 if no items are missing. If any items are missing, use the sum of the domain scores for the Total Score if all three domains have a computed score. The analysis method for the VitiQoL total score will be the same as the analysis used for MMRM sensitivity analysis for the primary endpoint (see Section 6.1.1.2.2). Three domain scores will be analyzed using the same method as for VitiQoL total score: Participation Limitation (sum of items 3, 4, 6, 9, 10, 11, 14), Stigma (sum of items 1, 2, 5, 7, 15), and Behaviors (sum of items 8, 12, 13). If any item is missing but at least ½ of the domain items are non-missing (no more than 3, 2, or 1, respectively, for Participation Limitation, Stigma, or Behaviors), use the average of the domain's non-missing as the missing item's raw score and add all 7, 5 or 3 domain items scores to make the respective Domain score.

VitiQoL item 16, PGIS-V, will be summarized with frequency counts by each category of PGIS-V (0-6) at baseline and at Week 24. The proportion of subjects achieving improvement in each treatment group will be compared using a Fisher's exact test for categories worsening (>0), no change, 1-point improvement, and ≥2-point improvement.