Protocol B7931005

PHASE 2A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF PF-06651600 AND PF-06700841 IN SUBJECTS WITH MODERATE TO SEVERE ALOPECIA AREATA WITH A SINGLE-BLIND EXTENSION PERIOD AND A CROSS-OVER OPEN LABEL EXTENSION PERIOD

Statistical Analysis Plan (SAP)

Version: 4 (Amendment 3)

Date: 12-JUN-2018

[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7931005 is based on the Protocol Amendment 4 dated 6 June 2018.

Table 1. Rationale of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	• Updated study design. • Added details of the analyses required during the extension phase.	This SAP amendment is to support Protocol Amendment 3.
3	• In Section 3.2 "Secondary Efficacy Endpoint(s)", added that SALT 90 may be analyzed. • In Section 5.2.1 "Analyses for Binary Data", removed multiple imputation for binary data. Additionally, clarified that the exact method used for binary data would be based on Non-Responder imputation. • In Section 5.2.2 "Analyses for Continuous Data", added texts "**for the primary endpoint**" in the sentence "Sensitivity analyses **for the primary endpoint** will be completed using multiple imputation methods as described in Section 5.3."; added a second sensitivity analysis for primary endpoint, which is to fit a linear mixed effect model for longitudinal data using visit as continuous variable. • Removed Section 5.2.3 "Analyses	• To support the understanding of binary variables defined based on SALT score since it is believed by investigators that SALT 90 is regarded as achieving remission. • To be clear that binary data will be analyzed using GLMM method on observed data and exact test method on NRI data. • To be clear that multiple imputation will be used for primary endpoint as a sensitivity analysis. The addition of a second sensitivity analysis is to help investigate if time on treatment has linear effect on the primary endpoint. • To clarify the analysis

	for Categorical Data", and added texts regarding analysis method for ordinal categorical data in Section 5.2.1, which says ordinal data, like CCI [redacted] will be transformed to binary data for statistical analysis and be summarized with proportions by each category.	method for ordinal data.
	• In Section 5.3 "Methods to Manage Missing Data", deleted stepwise selection for selecting covariates to be used in multiple imputation and clarified that treatment, visit, baseline SALT score, and possibly duration since onset of current episode would be used as imputation covariates based on regression method (instead of propensity method); in addition, deleted multiple imputation for binary data including SALT 30, SALT 50, SALT 75, SALT 100.	• To clarify the covariates, method, and endpoints to be used with multiple imputation.
	• In Section 6 "Analyses and Summaries', clarified the "95% confidence interval" to be "95% 2-sided confidence interval" for primary endpoint, and clarified the "90% 2-sided confidence interval" for secondary and other endpoints.	• To clarify the level of confidence levels for different endpoints.
	CCI [redacted]	• To support the understanding of itchy scalp.
	• In Section 6.1.7.1 "Safety Summaries and Analyses" during Treatment Period, added that summary tables of TEAE by system organ class and preferred	

	to be generated separately for induction phase and maintenance phase. • In Section 6.2 "Analyses and Summaries During Extension Period", clarified that efficacy endpoints will be presented by visit and the treatment routes. The possible treatment routes subjects may go through in the Extension Period were listed based on the study design. • In Sections 6.2.2.1 and 6.2.2.2, updated that the active vs. placebo comparisons in both the Treatment Period and the Extension Period will be presented in the same figure, and the x-axis for presenting visits in Extension Period will be shifted to align with Treatment Period, ie, Week 2/ Week 30, Week 30 / AT Week 2 …etc. • In Section 6.2.2.4, added analysis of change from baseline in SALT for subjects who are treated with Placebo in Extension Period. • Updated Appendix 1 "Summary of Efficacy Analyses" according to above edits and added a table for efficacy analyses during Extension Period in Appendix 1.2. • Updated Appendix 4 "Criteria for Treatment Assignment during the Extension Period" by adding sections 3 and 4 based on the latest Communication Plan .	• To clarify the treatment groups in efficacy analyses in the Extension Period. • To compare the efficacy in Treatment Period and Extension Period. • To support understand the change in the hair volume after subjects stopped active treatment.
4	• Updated study title, and study objectives in Section 2.3 and 2.4 based on the update in the	• To be consistent with the protocol amendment 4.

	protocol amendment 4. • Updated "Extension Period" to be "Single-Blind Extension Period" according to the name change in the protocol amendment 4 for the first Extension Period. C C I [redacted] • Added Section 6.3 for the analyses during the cross-over open label extension period. • Added Section 6.4 about interim clinical study report.	• To reflect the addition of this period in the protocol amendment 4. • To specify that an interim clinical study report is planned after the 24-week Treatment Period is completed.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7931005. 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 Treatment Period

Primary Objective:	**Primary Endpoint:**
• To evaluate the efficacy of PF-06651600 and PF-06700841 compared to placebo at Week 24 in adult subjects with moderate to severe alopecia areata.	• Change from baseline of Severity of Alopecia Tool (SALT) score at Week 24.
Secondary Objectives:	**Secondary Endpoints:**
Key Secondary Efficacy Objective: • To evaluate the effect of PF-06651600 and PF-06700841 on SALT 30 at Week 24 in adult subjects with moderate to severe alopecia areata.	**Key Secondary Efficacy Endpoint:** • Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at Week 24.

Other Secondary Efficacy Objectives: • To evaluate the effect of PF-06651600 and PF-06700841 on additional efficacy endpoints over time in adult subjects with moderate to severe alopecia areata in the Treatment Period.	**Other Secondary Efficacy Endpoints:** • Change from baseline in Investigator Global Assessment (IGA) at all time points up to Week 24 as specified in the Schedule of Activities (SoA). • Change from baseline in SALT at intermediate time points up to Week 24 as specified in the SoA. • Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at intermediate time points up to Week 24 as specified in the SoA except for Week 24. • Proportion of subjects achieving a 50%, 75% and 100% improvement in SALT (SALT 50, SALT 75, and SALT 100) at all time points up to Week 24 as specified in the SoA. • Percentage change in SALT from baseline to Week 24 at intermediate time points as specified in the SoA.
Safety Objectives: • To evaluate the safety and tolerability of PF-06651600 and PF-06700841 over time in adult subjects with moderate to severe alopecia areata in the Treatment Period.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (AEs) 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.


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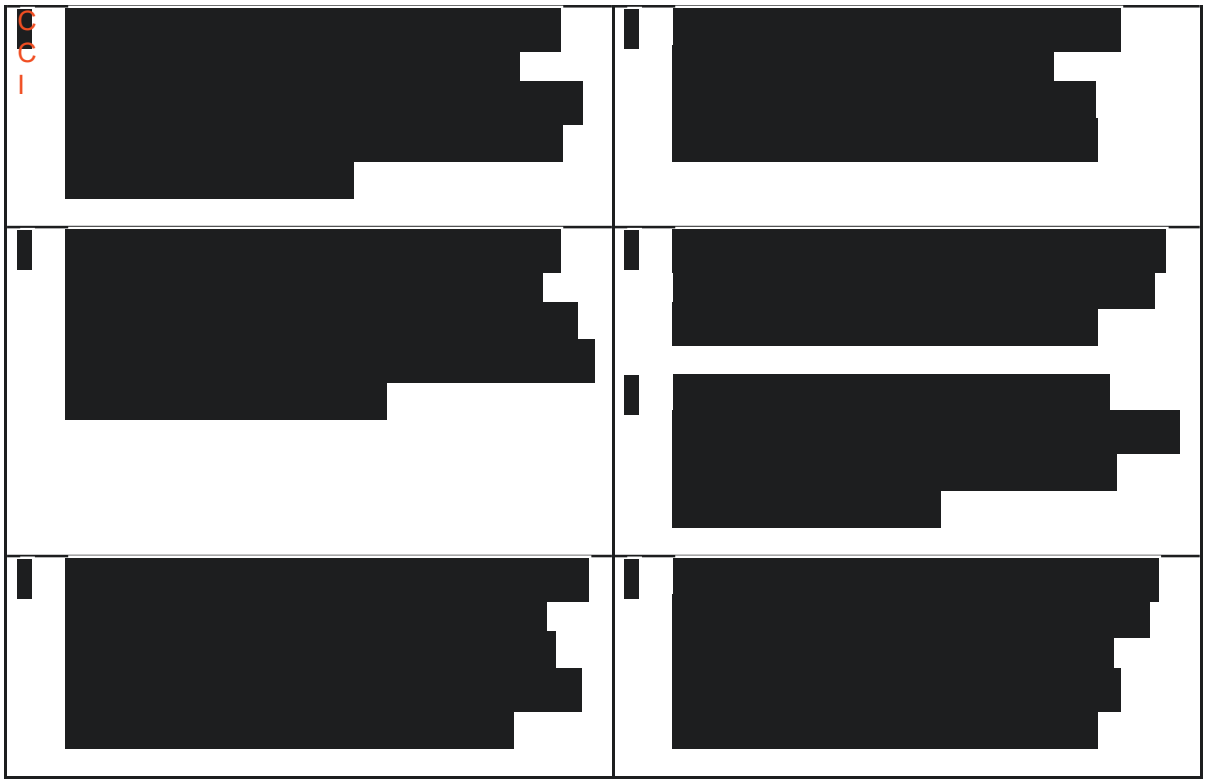

2.2. Study Objectives and Endpoints During Single-Blind Extension Period

Primary Objective:	Primary Endpoint:
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 over time in adult subjects with moderate to severe alopecia areata during the Single-Blind Extension Period.	• Incidence of treatment-emergent adverse events (AEs) during the Single-Blind 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 (LFTs) during the Single-Blind Extension Period.
CCI	
	• Change from baseline in SALT during the Single-Blind Extension Period at all time points as specified in the SoA. • Proportion of subjects achieving SALT 30 during the Single-Blind Extension Period at all time points as

	specified in the SoA. • Proportion of subjects achieving SALT 50, SALT 75, SALT 100 during the Single-Blind Extension Period at all time points as specified in the SoA. CCI [redacted] • Time to achieve the retreatment criteria during the Withdrawal/Retreatment part of the Extension Period among subjects who achieved primary endpoint at Week 24.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.3. Study Objectives and Endpoints during Cross-Over Open Label Extension Period

Primary Objective:	Primary Endpoint:
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 over time in subjects who are non-responders to PF-06700841 and PF-06651600, respectively, during the Cross-Over Open Label Extension period.	• Incidence of treatment-emergent adverse events (AEs) during the Cross-Over Open Label 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 (LFTs) during the Cross-Over Open Label Extension Period.


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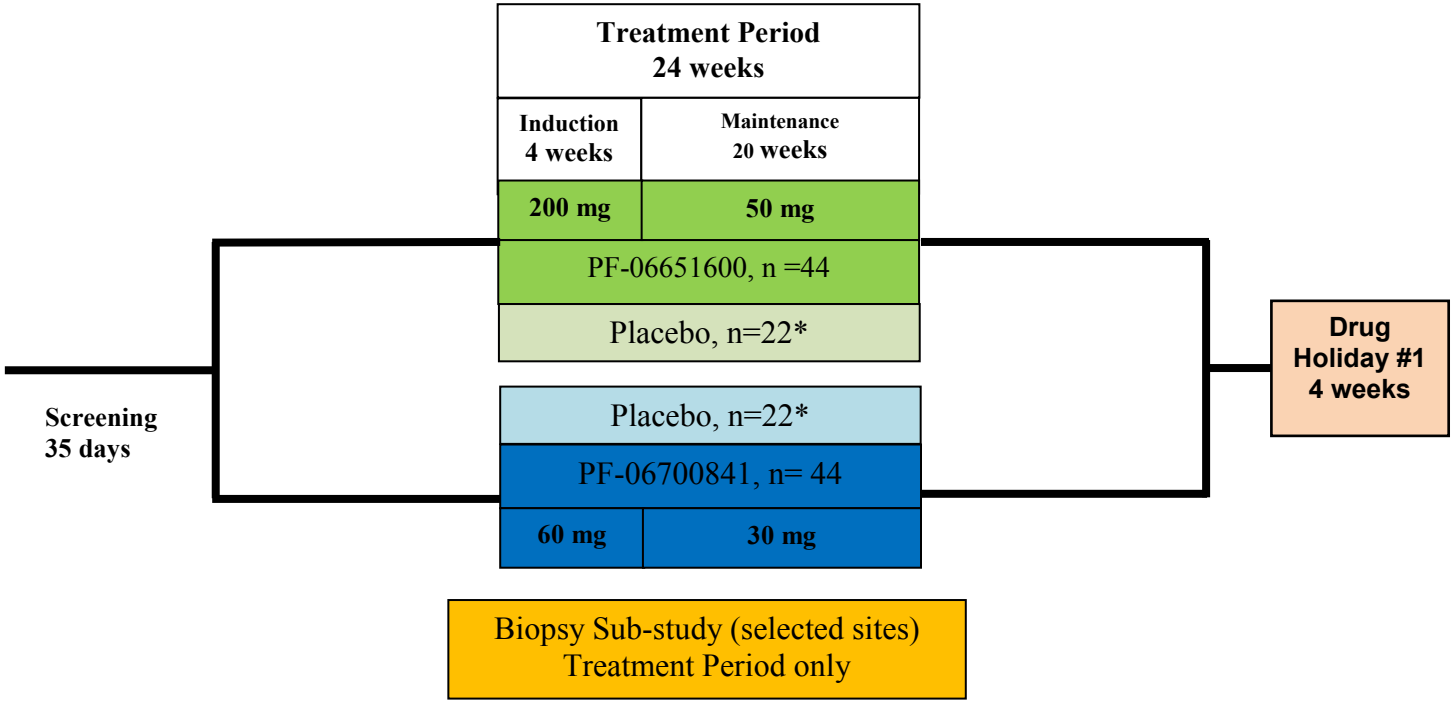
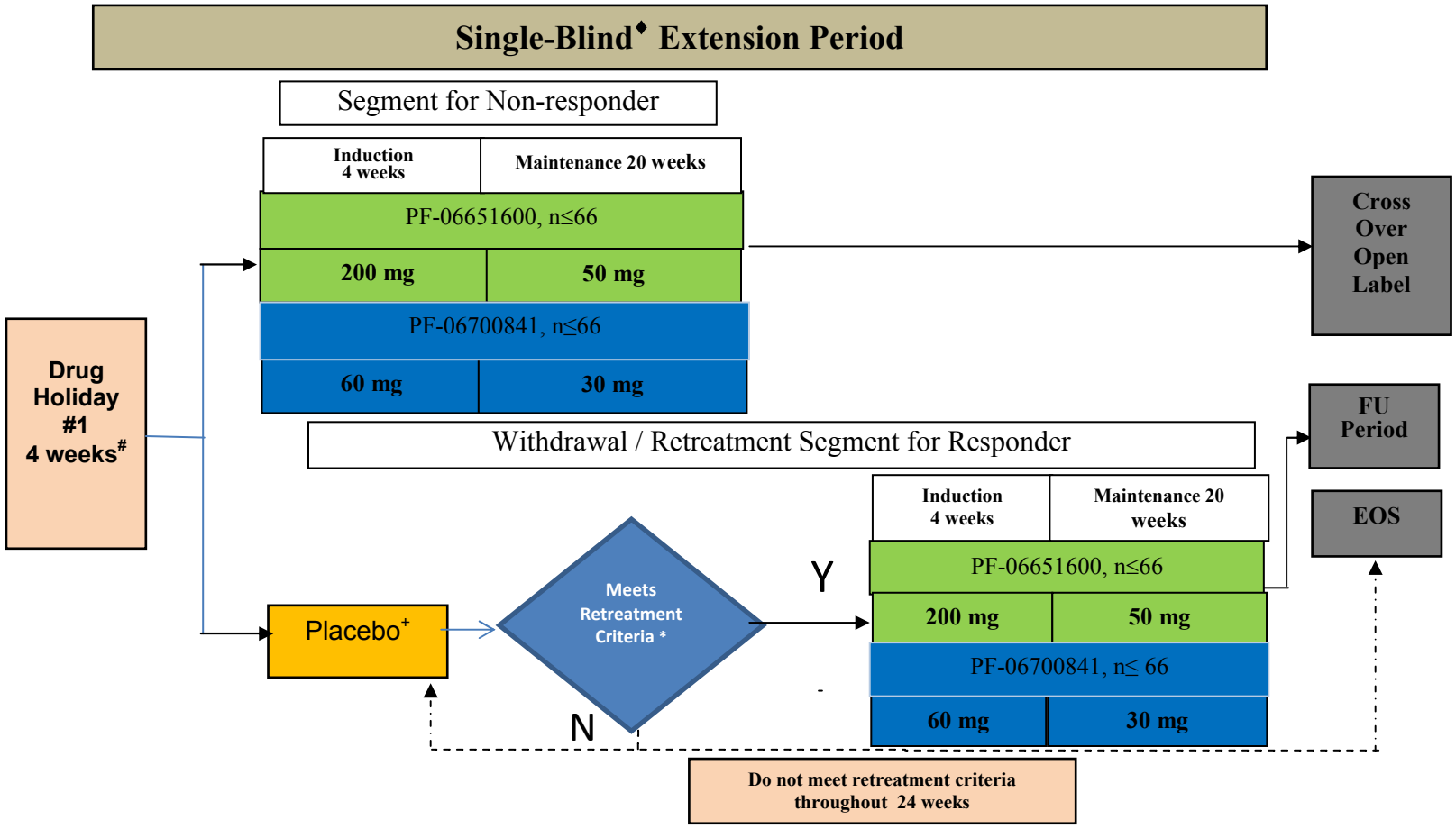
2.4. Study Design

Study B7931005 will investigate the JAK3 inhibitor PF-06651600 and TYK2/JAK1 inhibitor PF-06700841 in alopecia areata (AA). This is a Phase 2a, randomized, double-blind, parallel group, multicenter study with two Extension Periods. The study will have a maximum duration of approximately 113 weeks. This includes an up-to-5-week screening period, a 24-week Treatment Period, a 4-week Drug Holiday #1, an up-to-12-month Single-Blind (sponsor open, investigator open and subject blind) Extension Period, a 4-week Drug Holiday #2, a 6-month Cross-Over Open Label Extension Period and a 4-week Follow-up Period. The study will enroll a total of approximately 132 subjects. The study will be conducted at approximately 30 to 40 sites.

Figure 1. Design Schematic



*** During the data analysis, the placebo groups will be combined in Treatment Period**

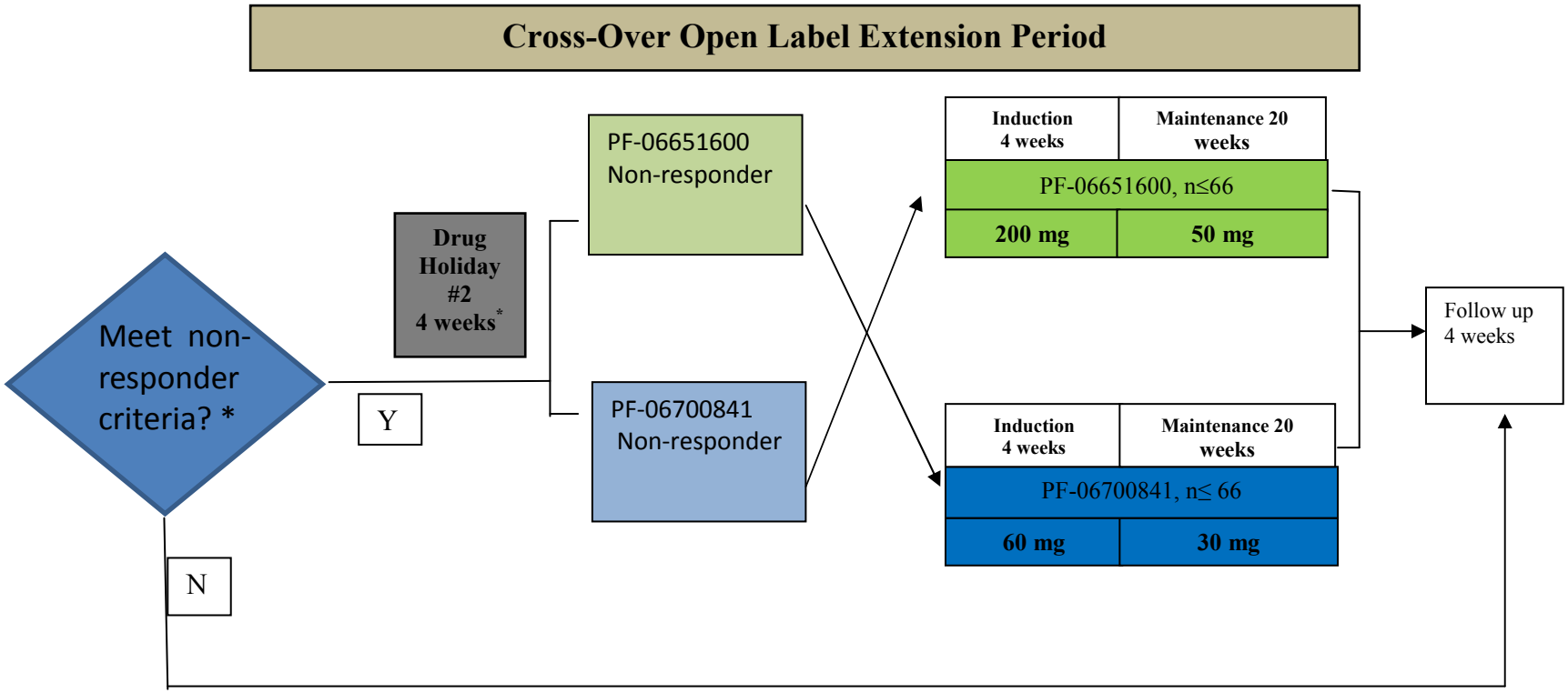


♦ Sponsor open, investigator open, subject blind.

All subjects who complete the initial 24-week Treatment Period will be evaluated for potential entry into the Single-Blind Extension Period during the Drug Holiday #1. Subjects will enter the Single-Blind Extension Period providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's entrance in the Single-Blind Extension Period. Subjects will be assigned by the study designee(s) to receive either active treatment (PF-06651600 or PF-06700841) to start the segment of non-responders or placebo at Week 28 (after the 4-week Drug Holiday #1) to start the Withdrawal/Retreatment segment for responders.

+ Subjects who are assigned to the placebo group will receive placebo for up to 24 weeks until they meet the retreatment criteria described in the SAP. Subjects who meet the criteria will receive the same respective active compound (PF-06651600 or PF-06700841), dose, and treatment duration as the original treatment which consists of a 4-week induction period and a 20-week maintenance period, providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's participation (audiogram result available within 8 weeks is acceptable). Subjects who do not meet the retreatment criteria throughout the 24 weeks will go directly to the EOS visit. Subjects who complete the Withdrawal/Retreatment segment will go directly to the Follow-up and will not participate in the Cross-Over Open Label Extension Period.

* Retreatment criteria will be described in the SAP. The study designee(s), who are independent of the study team, will inform the site if the subject meets the criteria to start active treatment, providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's participation (audiogram result available within 8 weeks is acceptable).



* All subjects who are assigned to receive active treatment (PF-06651600 or PF-06700841) directly and complete the segment for non-responder in Single-Blind Extension Period may be evaluated for potential entry into the Cross-Over Open Label Extension Period during the Drug Holiday #2. Subjects will enter the Cross-Over Open Label Extension Period providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's entrance in the Cross-Over Open Label Extension Period as well as the non-responder criteria is met at Week 52.

Subjects who have moderate to severe alopecia areata (≥50% hair loss of the scalp [SALT score ≥50] without evidence of hair regrowth within the previous 6 months; current episode of fixed hair loss ≤7 years) present at the screening and baseline visits will be included in the study. Photographs will be taken at the Screening Visit to verify eligibility (≥50% hair loss of the scalp). Subjects will be randomized to PF-06651600 or matching placebo in a 2:1 ratio or to PF-06700841 or matching placebo in a 2:1 ratio. During the data analysis for the initial Treatment Period, placebo groups will be combined to yield final investigational product: placebo ratios of 1:1:1 for each investigational product. Investigators, subjects, and the sponsor study team will be blinded as to treatment group. 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 in the interim CSR and published once the last subject last visit occurs for the initial 24-week Treatment Period. The interim study report may be shared with the principal investigator (PI) when it is available.

Subjects will be screened within 35 days prior to the first dose of study drug to confirm that they meet the subject selection criteria for the study. The initial 24-week treatment consists of a **4-week induction** treatment period and a **20-week maintenance** treatment period.

An induction dose of 200 mg QD for 4 weeks followed by maintenance dosing of 50 mg QD for 20 weeks of PF-06651600, an induction dose of 60 mg QD for 4 weeks followed by maintenance dosing of 30 mg QD for 20 weeks of PF-06700841, and matching placebo will be investigated.

A biopsy sub-study will be performed at selected sites only during the initial 24 weeks of the study. Approximately 42 subjects will be randomized (expected to provide approximately 30 completers). Subjects will be randomized to PF-06651600 or matching placebo in a 2:1 ratio or PF-06700841 or matching placebo in a 2:1 ratio. During the data analysis for the biopsy sub-study, placebo groups will be combined to yield final investigational product: placebo ratios of 1:1:1 for each investigational product.

Single-Blind Extension Period

Alopecia Areata is a disease with high unmet medical need. Currently there are no approved medications for treatment of AA. A Single-Blind Extension Period has been added to this study to evaluate additional safety and tolerability of PF-06651600 and PF-06700841. The Extension Period will become Single-Blind (investigator open, sponsor open and subject blind) upon approval of amendment 4.

The Single-Blind Extension Period will provide an opportunity for subjects to receive additional active study treatment. It will start after a 4-week Drug Holiday #1. The duration of the Single-Blind Extension Period can be up to 12 months. Only subjects who complete Week 24 of the initial Treatment Period may be considered for eligibility to enter the Single-Blind Extension Period. Subjects who discontinue during the initial Treatment Period will enter the 4-week Follow up Period and will not be eligible for the Single-Blind Extension Period.

All subjects who complete the initial 24-week Treatment Period will be evaluated during the Drug Holiday #1 for potential entry into the Single-Blind Extension Period. After the 4-week Drug Holiday #1, subjects will enter the Single-Blind Extension Period providing none of the Exclusion criteria #9, #10, and #26 (see Appendix 4) are met and the audiogram result does not preclude patient's entrance in the Single-Blind Extension Period. Subjects who meet Exclusion criteria #9, #10, or #26 will be discontinued and enter the Follow-up Period.At Week 28 (after the 4-week Drug Holiday #1 that follows completion of Week 24), subjects will be assigned by the study designee(s) to receive either active treatment (PF-06651600 or PF-06700841) to start the segment for non-responder or placebo to start the Withdrawal/Retreatment segment for responder. The detailed criteria for treatment assignment is described in Appendix 4. The study designee(s), who are independent of the study team, will provide the site with a treatment assignment when IP is being supplied via the IRT system post Week 24. A detailed communication plan will be provided to the site. The probability to receive active treatment in the Single-Blind Extension Period is approximately 33% to 100%. All patients in the placebo group during the Treatment Period who are eligible for the Extension Period will be assigned to active treatment. During the Single-Blind Extension Period, all the subjects assigned to placebo at Week 28 will have a probability of 100% to receive active treatment if they meet the retreatment criteria outlined in Appendix 4.

During the Single-Blind Extension Period, subjects who are assigned to the active treatment (PF-06651600 or PF-06700841) at Week 28 to start the segment for non-responder will receive the same respective active compound (PF-06651600 or PF-06700841), dose, and treatment duration (a 4-week Induction Period and a 20-week Maintenance Period) as the original Treatment Period.

Subjects who are assigned to the placebo group at Week 28 to start the Withdrawal/Retreatment segment will receive placebo for up to 24 weeks until they meet the retreatment criteria described in Appendix 4. These subjects will be assessed every 2 weeks during the first 8 weeks and then every 4 weeks up to 24 weeks by the study designee(s). The study designee(s), who are independent of the study team, will inform the site if the subject meets the criteria to start active treatment. Subjects who meet the criteria will receive the same respective active compound (PF-06651600 or PF-06700841), dose, and treatment duration as the original treatment which consists of a 4-week induction period and a 20-week maintenance period, providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's participation (audiogram result available within 8 weeks is acceptable). Subjects who meet Exclusion criterion #9, #10, or #26 will be discontinued from the Single-Blind Extension Period and will go directly to the EOS visit. Subjects who do not meet the retreatment criteria for initiation of active treatment throughout the 24-week period (Week 28 to Week 52) will go directly to the EOS visit. Subjects who complete the Withdrawal/Retreatment segment will go directly to the Follow-up Period and will not participate in the Cross-Over Open Label Extension Period.

Any subject that has completed the initial 24 weeks of the Protocol B7931005 prior to the Protocol Amendment 3 availability is eligible for evaluation for potential enrollment into the Single-Blind Extension Period. Subjects are to be discussed with the sponsor for possible enrollment for the Single-Blind Extension Period.

Cross-Over Open Label Extension Period

A 24 week Cross-Over Open Label Extension Period has been added to this study to evaluate safety and efficacy of PF-06651600 and PF-06700841 in subjects who complete the segment for non-responder in Single-Blind Extension Period and did not respond to the initial active treatment. More specifically, subjects who are PF-06651600 non-responder at Week 52 will receive PF-06700841 in the Cross-Over Open Label Extension Period. Subjects who are PF-06700841 non-responder at Week 52 will receive PF-06651600 in the Cross-Over Open Label Extension Period. The subjects who were responders at Week 52 will enter the Follow-up Period directly. Non-responders are defined as subjects who have not achieved 30% improvement in SALT relative to the baseline of the Treatment Period at Week 52.

All subjects who complete the segment for non-responder in Single-Blind Extension Period and are non-responders will be evaluated during the Drug Holiday #2 for potential entry into the Cross-Over Open Label Extension Period. After the 4-week Drug Holiday #2, subjects will enter the Cross-Over Open Label Extension Period providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's entrance in the Cross-Over Open Label Extension Period as well as the non-responder criteria is met at Week 52. Audiogram result available within 8 weeks is acceptable. Subjects who meet Exclusion criteria #9, #10, or #26 will enter the Follow-up Period directly. Subjects who do not meet the non-responder criteria at Week 52 will be informed by the study designee(s) during the Drug Holiday #2 and go directly to the Follow-up Period. Subjects who discontinue during the Single-Blind Extension Period will enter the 4-week Follow-up Period and will not be eligible for the Cross-Over Open Label Extension Period.

At Cross-Over Open Label Day 1 (after the 4-week Drug Holiday #2 that follows completion of Single-Blind Extension Period), non-responders will be assigned to receive either PF-06651600 or PF-06700841(the opposite of the assigned treatment in the initial 24 weeks and Single-Blind Extension Period).

During the Cross-Over Open Label Extension Period, subjects will receive an induction dose of 200 mg QD for 4 weeks followed by maintenance dosing of 50 mg QD for 20 weeks of PF-06651600 or an induction dose of 60 mg QD for 4 weeks followed by maintenance dosing of 30 mg QD for 20 weeks of PF-06700841.

Any subject who has completed the segment for non-responder in Single-Blind Extension Period prior to protocol Amendment 4 initiation at the investigator site is eligible for evaluation for potential enrollment into the Cross-Over Open Label Extension Period. These subjects are to be discussed with the sponsor prior to any possible enrollment into the Cross-Over Open Label Extension Period.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint for this study is change from baseline of SALT score at Week 24. SALT is collected at all study visits. Baseline is defined as the last measurement prior to randomization (Day 1). Change from baseline is defined as the baseline value minus the value at a specific visit. Positive change from baseline signifies an improvement.

SALT is a quantitative assessment of AA severity based on scalp hair loss. A visual aid showing the division of the scalp hair into four quadrants, back, top of scalp, and both sides, with each of the four quadrants given an accurate determination of the % of scalp surface area covered, representing 24%, 40%, 18%, and 18% of the total scalp surface area. Score parameters are detailed in Appendix 5. For any male subject, the male pattern alopecia should be permitted to score SALT equal to 0 at the end of trial.

3.2. Secondary Efficacy Endpoint(s)

The percent change from baseline will be calculated as baseline value – value at a specific visit divided by baseline and multiplied by 100, ie, it is determined by the following formula: (baseline SALT – post-baseline SALT)/baseline SALT x 100% = % change from baseline. Positive percentage change from baseline will denote improvement. For example: 75% hair loss at baseline (SALT score = 75), 50% hair loss at a post-baseline visit (SALT score = 50), the percent change from baseline = (75 - 50) / 75 x 100% = 33% regrowth.

The key secondary endpoint for this study is the proportion of subjects achieving a 30% improvement in SALT (SALT 30) at Week 24. A subject with a 30% improvement in SALT is one whose percent change from baseline is greater than or equal to 30 (SALT 30 = 1 if percent change from baseline ≥30, SALT 30 = 0 otherwise). In addition to calculating SALT 30 at Week 24, SALT 30 will be calculated at all intermediate time points as well.

The proportion of subjects achieving a 50%, 75%, and 100% improvement in SALT (SALT 50, SALT 75, and SALT 100) at all time points will be calculated in a similar manner to SALT 30. For example, a subject will meet the SALT 50 definition if the percent change from baseline is greater than or equal to 50 (SALT 50 = 1 if percent change from baseline ≥50, SALT 50=0 otherwise).

In addition to the change from baseline in SALT as described in the primary analysis, all intermediate timepoints will be used as secondary endpoints.

Furthermore, it is believed by investigators that 90% improvement (SALT 90) is the same as achieving remission, and therefore, SALT 90 at all timepoints may be summarized.

The clinical evaluator of AA will perform an assessment of the overall improvement of AA and assign an IGA score and category as described in the table below. This takes into account extent and density of regrowth by the SALT scoring system.

For determination IGA, the percent change from baseline in SALT score would be determined at each follow-up visit.

The IGA should be permitted to score 0 (no change or further loss) at baseline.

The IGA scores are defined as below.

Table 2. IGA Score

Score	Description
0	No change or further loss
1	1-24% regrowth
2	25-49% regrowth
3	50-74% regrowth
4	75-99% regrowth
5	100% regrowth

3.3. Exploratory Efficacy Endpoint(s)

The eyelash assessment scale ranges from 0 (none) to 3 (normal) and corresponds to frontal and superior eyelash views. This assessment will be done at all study visits. Proportion of responders achieving at least 1 grade improvement in eyelash assessment scale at the scheduled timepoints in the study will be assessed for patients with eyelash involvement at baseline. The analysis will also be conducted with all patients in the full analysis set. Baseline will be the last measurement prior to randomization. The scores are as defined below.

The rating scale ranges from 0 (none) to 3 (normal) for eyelash assessment.

Table 3. Eyelash Assessment Scale

Score	Description
0	None
1	Minimal
2	Moderate
3	Normal

The eyebrow assessment scale ranges from 0 (none) to 3 (normal). The eyebrow assessment scale will be evaluated in all subjects. This assessment will be done at all study visits. Proportion of responders achieving at least 1 grade improvement in eyebrow assessment scale at the scheduled timepoints in the study will be assessed for patients with eyebrow involvement at baseline. The analysis will also be conducted with all patients in the full analysis set. Baseline will be the last measurement prior to randomization. The scores are as defined below. The rating scale ranges from 0 (none) to 3 (normal) for eyebrow assessment.

Table 4. Eyebrow Assessment Scale

Score	Description
0	None
1	Minimal
2	Moderate
3	Normal

[redacted]

CCI

CCI

[redacted]

3.5. Baseline Variables

Demographic and medical history will be collected at baseline. Complete AA disease history includes collection of details of AA at Screening: background, AA history, AA diagnosis, pattern of scalp hair loss, body hair loss, nail involvement, the use of topical treatments, systemic treatments and other treatments for AA. Medical history, in addition to AA history, including history of drug, alcohol, tobacco use, skin rash, skin infection, and any dermal abnormalities that may predispose to infection will be collected at Screening. Smoking status and average weekly alcohol consumption (units/week) will also be collected.

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 the investigational product. 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 treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 6.1.6.1).

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA PT is defined as a tier-2 event if there are at least 4 in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

3.6.2. Laboratory Data

The following laboratory tests (Table 5) will be performed at time points identified in the Schedule of Activities. Baseline will be the last measurement prior to receiving study treatment (Day 1). Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

Table 5. Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine	pH	HIV[a]
Hematocrit	Cystatin C[h]	Glucose (qual)	HBsAg[a]
RBC count		Protein (qual)	HBcAb[a]
Reticulocyte count	Creatine Phosphokinase	Blood (qual)	HepB reflex (HbsAB[a]), if
Platelet count	Glucose	Ketones	applicable
WBC count with differential	Na+, K+, Cl- ,Ca++	Nitrites	HCVAb[a]
Total neutrophils (%, Abs)	Total CO2 (Bicarbonate)	Leukocyte esterase	Serum pregnancy test [a, c]
Eosinophils (%, Abs)	AST, ALT	Microscopy and/or	Urine pregnancy test [c]
Monocytes (%, Abs)	Total Indirect & Direct Bilirubin	culture[d]	FSH[a, g]
Basophils (%, Abs)	Alkaline phosphatase		QFT-G or other IGRA, or
Lymphocytes (%, Abs)	Uric acid		PPD[a,e]
	Albumin		EBV, CMV, HSV1, HSV2,
	Total protein		VZV
	Fasting lipid Profile Panel [f]:		CCI
	Total cholesterol		
	LDL		
	HDL		
	Triglycerides		
			CCI
			Skin swab for herpetiform rash[i]
			Skin swab for potential drug-related rash[j]

[a] At Screening only.
[b] HepB reflex testing only if HBsAg negative but HBcAb positive at Screening.
[c] Pregnancy tests (serum/urine) for females of childbearing potential. Serum pregnancy test must be performed at Screening.
[d] Only if urine analysis is positive for blood, protein, nitrites, or leukocyte esterase.
[e] PPD results should be read within 48 to 72 hours.
[f] Fasting lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 8, Week 24, Week 28, and ET (if applicable), and will include total cholesterol, LDL, HDL, and triglycerides.
[g] Females of non-child bearing potential.
[h] Cystatin C will be measured at baseline and EOT as well as the reflex testing if the serum creatinine is elevated above the ULN as specified in Section 7.3.7.2 of the protocol.
[i] In case of a herpetiform rash (eg, suspected herpes zoster and herpes simplex) Section 7.3.7.1.1 of the protocol.
[j] In case of a potential drug-related rash as specified in Section 7.3.7.1.2 of the protocol.
[k] At Screening, Week 28, and in case of CK > 3x ULN.

3.6.3. Vital Signs

Vital signs (blood pressure, pulse, respiratory rates and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities. Baseline will be the last measurement prior to receiving study treatment.

3.6.4. Electrocardiograms

Single 12-lead ECGs should be collected at times specified in the Schedule of Activities.

The baseline ECG values (collected on Day 1) will serve as each subject's baseline values. To ensure safety of the subjects, qualified medical personnel at the investigator site will make comparisons to baseline measurements. A paper or digital copy of the ECG should be filed in the subject's chart and must be available to the sponsor upon request. Any clinically significant changes will be recorded and evaluated further, as clinically warranted. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

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 and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

The full analysis set (FAS) consists of all randomized subjects, assigned to the randomized treatment regardless of what treatment, if any, was received. The full analysis set is the primary patient population for the primary endpoints. A randomized but not treated subject will be reported under their randomized treatment group for the full analysis set.

4.2. Safety Analysis Set

The safety analysis set consists of all subjects who receive at least one dose of study medication. Subjects are 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 PK concentration population is defined as all enrolled subjects who received at least one dose of PF-06651600 or PF-06700841 and in whom at least one concentration value is reported.

5. GENERAL METHODOLOGY AND CONVENTIONS

An interim analysis will be performed when Week 12 data has been accumulated for approximately 66 subjects initially randomized.

After the initial Treatment Period (Week 0-24) is finished 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 can be generated. The subjects, investigators, and site personnel will continue to be blinded to randomized study treatments throughout the remainder of the study until the protocol amendment 4 is implemented at which point the sponsor, investigators and site personnel will become unblinded to the study treatment (study subjects will be blinded for the duration of the Single-Blind Extension Period). The sponsor, investigators, site personnel, and study subjects will all be unblinded during the Cross-Over Open Label Extension Period.

After the protocol amendment 4 is implemented, an interim CSR will be developed to report the results of the initial 24-week Treatment Period.

The database will be officially released after last subject last visit occurs. The final analysis will be then conducted and the final CSR will be issued.

The decision rules for the primary analyses of the 24-week Treatment Period are described in the next section.

5.1. Hypotheses and Decision Rules

The null hypothesis to be tested is that the difference between PF-06700841 or PF-06651600 and placebo is less than or equal to 0 vs the alternative hypothesis of the difference between PF-06700841 or PF-06651600 and placebo is greater than 0. Using a between-group comparison at Week 24, for PF-06700841 vs placebo and PF-06651600 vs placebo, the treatment will be considered superior to placebo if the lower bound of the 97.5% (95% adjusted for two comparisons) one-sided confidence interval is greater than 0.

Because multiple comparisons are being made for the comparison between PF-06700841 and placebo and PF-06651600 and placebo, the Hochberg procedure will be used to adjust for multiple comparisons. To apply the test, the treatment with the larger unadjusted p-value will be tested first. If it is less than 0.05 then both treatment comparisons will be considered significant. If the larger p-value is greater than 0.05, the smaller p-value will still be considered to be significant if it is less than 0.025. Otherwise, neither value will be considered significant.

Adjustments for multiple comparisons will only be made for the primary endpoint at the Week 24 time point. All other p-values reported will be considered descriptive.

5.2. General Methods

5.2.1. Analyses for Binary Data

The frequency and percentages for all binary data will be presented. Longitudinal binary data will be analyzed by a generalized linear mixed model, with fixed factors of treatment, visit, treatment by visit, baseline SALT score, baseline SALT score by treatment (if possible), and a random subject effect. P-values and inference for relative risks between treatments will be provided based on the link function of logit. A delta method will be used to derive point estimates and confidence intervals of relative risks, which is described in

Appendix 3. If the GLMM model does not converge, the estimates using Chan and Zhang's exact method based on Non-Responder Imputation (NRI) will be presented.

Ordinal endpoints transformed as responder rates CCI [redacted] will be analyzed using the method aforementioned for binary data. Descriptive summaries for the ordinal endpoints will be presented with proportions of subjects in each category.

5.2.2. Analyses for Continuous Data

A linear mixed-effect repeated measures model with fixed effects for treatment, time (visit), treatment by time, baseline SALT score, baseline SALT score by treatment, and a random effect for subject, will be used to analyze the change from baseline. CCI [redacted] The estimation method used will be restricted maximum likelihood. 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, 97.5% upper confidence bound (ie. 95% two-sided confidence interval) comparing the mean change from baseline for PF-06700841 vs. placebo and PF-06651600 vs placebo will be computed (for the primary endpoint). Sensitivity analysis for the primary endpoint will be completed using multiple imputation (MI) methods as described in Section 5.3. Another sensitivity analysis for the primary endpoint will be a linear mixed effect model (for longitudinal data) regarding time as a continuous variable based on the observed data.

CCI [redacted]

[redacted]

[redacted]

5.3. Methods to Manage Missing Data

Multiple imputation (MI) will be used as a sensitivity analysis for the primary endpoint. The MI will impute the SALT score at least 100 times using the propensity score method for monotone missing pattern and the covariates of treatment, time, baseline SALT score, and duration since onset of current episode (if possible). Once the SALT score has been imputed, the analysis variable using the imputed SALT variable will be calculated.

Non-Responder Imputation (NRI) will be used for the binary endpoints when Chan and Zhang's exact method is performed, in which missing value will be imputed as Non-Responders.

6. ANALYSES AND SUMMARIES

The placebo group for PF-06651600 and the placebo group for PF-06700841 will be combined for all analyses unless otherwise noted.

6.1. Analyses and Summaries During the Treatment Period

6.1.1. Primary Endpoint(s)

6.1.1.1. Change from Baseline for SALT score

6.1.1.1.1. Primary Analysis

Endpoint: Change from baseline in SALT

- Analysis time points**:** Week 24 (primary) and all intermediate scheduled timepoints in the protocol.
- Analysis population**:** FAS.
- Analysis methodology**:** Change from baseline will be analyzed using a longitudinal model (specified in Section 5.2.2).

Reporting results:

- Raw data: n, mean, standard deviation, median, minimum and maximum at baseline and post-baseline visits will be presented for each treatment arm;
- Change from baseline: n, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 95% 2-sided confidence interval for the LS means, difference between the LS means for each pair of treatment groups and the corresponding 95% 2-sided confidence interval will be presented.

Figures:

- LS mean change from baseline by visit;
- Placebo adjusted LS means and 95% 2-sided confidence interval at Week 24;
- Placebo adjusted LS means and 90% 2-sided confidence interval will also be presented for all other intermediate time points to reflect trend over time.

6.1.1.1.2. Sensitivity/Robustness Analyses

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

Endpoints:

- Change from baseline in SALT using multiple imputation for missing data;
- Change from baseline in SALT without imputation.

Analysis time points: Week 24 and all intermediate scheduled timepoints in the protocol.

Analysis population: FAS.

Analysis methodology:

- Change from baseline based on multiple imputation will be analyzed using a longitudinal model (specified in Section 5.2.2) in which visit is regarded as categorical variable;
- Change from baseline without imputation will be analyzed as longitudinal data with visit regarded as a continuous variable to explore whether time on treatment has linear relationship with hair growth and consequently examine the treatment difference.

Reporting results:

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

Figures:

- LS mean change from baseline by visit;
- Placebo adjusted LS means and 90% 2-sided confidence interval at Week 24 and all intermediate scheduled time points in the protocol.

6.1.2. Secondary Endpoint(s)

6.1.2.1. SALT 30

Endpoint: SALT 30

- Analysis time points**:** Week 24 (primary) and all intermediate scheduled timepoints in the protocol;
- Analysis population**:** FAS;
- Analysis methodology**:** proportion of subjects achieving a 30% improvement in SALT will be analyzed using a repeated measures GLMM model. If the GLMM model does not converge the estimates using exact method will be presented. (see Section 5.2.1).

Reporting results:

- Raw data: The number and percentage of subjects meeting SALT 30 will be presented by visit;
- Risk differences: The risk differences from placebo and the 90% 2-sided confidence interval for risk difference will be presented.

Figures:

- Plot of the proportion of subjects meeting SALT 30 with 90% 2-sided CI over time;
- Plot of risk differences (compared to placebo) with 90% 2-sided CI by treatment group over time.

6.1.2.2. Change from Baseline in Investigator Global Assessment (IGA)

Endpoint: IGA

- Analysis time points**:** All post-baseline visits during Treatment Period;
- Analysis population**:** FAS;
- Analysis methodology**:** number and percentage of subjects in each category will be presented (see Section 5.2.1).

Reporting results:

- The number and percentage of subjects in each category will be presented by visit and by treatment.

Figures:

- Vertical bar chart of the percentage of subjects in each category will be presented by visit and by treatment.

6.1.2.3. SALT 50, SALT 75, SALT 90 and SALT 100

The analyses will be identical to the analysis used for SALT 30 (Section 6.1.2.1).

6.1.2.4. Percentage change in SALT

Endpoint: Percentage change from baseline in SALT

- Analysis time points**:** All visits during Treatment Period;
- Analysis population**:** FAS;
- Analysis methodology**:** Percentage change from baseline will be analyzed using a longitudinal model (specified in Section 5.2.2).

Reporting results:

- Raw data: n, mean, standard deviation, median, minimum and maximum at baseline and post-baseline visits will be presented for each treatment arm.

- Percentage change from baseline: n, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm. The LS means, 90% 2-sided confidence interval for the LS means, difference between the LS means for each pair of treatment groups and the corresponding 90% 2-sided confidence interval will be presented.

Figures:

- LS mean percentage change from baseline in SALT by visit;
- Placebo adjusted LS means and 90% 2-sided confidence interval at Week 24 and all intermediate scheduled timepoints in the protocol.

6.1.3. Other Endpoint(s)

CCI [redacted]

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

[redacted]

- [redacted]
- [redacted]

CCI [redacted]

- [redacted]
- [redacted]

CCI

CCI

CCI

CCI

CCI

[redacted]

6.1.4. Subset Analyses

Summary statistics and statistical analyses for the primary and secondary endpoints may be presented for AT/AU subjects.

6.1.5. Baseline and Other Summaries and Analyses

6.1.5.1. Baseline Summaries

Demographics and AA medical history variables as defined in Section 3.5 will be summarized by treatment group.

6.1.5.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed in the full analysis set, 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.

6.1.5.3. Study Treatment Exposure and Compliance

Compliance will be calculated for each subject using the formula:

Compliance = (# tablets actually administrated / # tablets planned) * 100.

A summary of compliance and the number of doses received as well as the median total dose by visit and treatment group will be provided. This will be done for both the induction and maintenance phases as well as overall. For these summaries, the placebo groups will be treated as separate groups since the dosing was different depending on which arm the subject was assigned to.

6.1.5.4. Concomitant Medications and Non-Drug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

6.1.6. Safety Summaries and Analyses

6.1.6.1. 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 adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. CCI [redacted]

CCI [redacted]

The Treatment emergent adverse events (TEAEs) by system organ class and preferred term will be generated for the induction phase, maintenance phase, and Treatment Period, respectively, for both all causality and treatment-related AEs. The Serious TEAEs (both all causality and treatment-related) by system organ class and preferred term may also be generated for induction phase, maintenance phase, and Treatment Period, respectively, as needed.

Nominal p-values (Tier 1 events only) and 90% confidence intervals (Tier 1 and Tier 2 events) will be provided for between treatment differences in the percentage of patients with events. Reporting p-values and confidence intervals will follow Pfizer standards.

6.1.6.2. 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 liver function tests (LFTs).

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

Table 6. Laboratory Re-Testing Criteria

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<2000/mm^3 (2.0 x10^9/L)
Hemoglobin	<9.0 g/dL
Platelet count	<100,000/mm^3 (100 x10^9/L)
Lymphocytes	<600/mm^3; <0.6x10^9/L
Chemistry	
CK	>3xULN (This also triggers urine myoglobin.)

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

Table 7. Laboratory Abnormality Criteria

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<1000/mm^3; <1.0 x10^9/L
Hemoglobin	<8.0 g/dL; <4.96 mmol/L; <80 g/L
Platelet count	<75,000/mm^3; <75.0x10^9/L
Lymphocytes	<500/mm^3; <0.5x10^9/L
Chemistry	
AST	>2.5x ULN
ALT	>2.5x ULN
Total bilirubin	>1.5x ULN
CK	>10x ULN

6.1.6.3. Vital Signs

Absolute values and changes from baseline in systolic and diastolic blood pressure, respiratory rate, pulse rate and temperature will be summarized by treatment and time post-dose, according to sponsor reporting standards. Baseline is as defined in Section 3.6.3.

6.1.6.4. Electrocardiogram

Categorical summary tables will be summarized by treatment and time post-dose using sponsor reporting standards. Baseline is as defined in Section 3.6.4. A listing of ECG comments on findings and normal/abnormal results will be provided.

6.1.6.5. Physical Examination

All physical exam data will be provided in the listings.

6.2. Analyses and Summaries During the Single-Blind Extension Period

At Week 24, subjects will be evaluated for eligibility of entering the Single-Blind Extension Period and be assigned to receive either Placebo or Active treatments at Week 28. Post Week 28, subjects who started with placebo at Week 28 may be re-treated with active treatment if pre-specified criteria are met. See details in Appendix 4. Below lists the routes subjects may go through.

Initial 24-Week Treatment Period → Single-Blind Extension Period → (may go to) Active Treatment	**Description**
Placebo → PF-06651600	**Placebo Non-responders**. The subjects initially treated with placebo in the Treatment Period will be assigned to the active treatment in the Single-Blind Extension Period.
Placebo → PF-06700841	
PF-06651600 → PF-06651600	**Active Non-responders**. The subjects initially treated with active treatment in the Treatment Period will be continued with active treatment in the Single-Blind Extension Period if Week 24 SALT 30 = 0.
PF-06700841 → PF-06700841	
PF-06651600 → Placebo	**Responders**. The subjects initially treated with active treatment in the Treatment Period will be assigned to Placebo in the Single-Blind Extension Period if SALT 30 =1.
PF-06700841 → Placebo	
PF-06651600 → Placebo → PF-06651600	**Responders with Retreatment**. The subjects initially treated with active treatment in the Treatment Period will be assigned to Placebo in the Single-Blind Extension Period if SALT 30 = 0, and be re-treated with active treatment post Week 28 if PCB (Week 24) – PCB (post Week 24) >30.
PF-06700841 → Placebo → PF-06700841	

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

For safety endpoints and pharmacodynamics endpoints, analyses and summaries will be presented by visit and treatment; presentations will be shown separately for the Single-Blind Extension Period Week 28 – Week 52 visits (when all subjects are first treated with either an active drug or placebo in the Single-Blind Extension Period) and Active Treatment Visits (when Responders are re-retreated with active drugs). Baseline will be the same as baseline in Treatment Period.

6.2.1. Primary Endpoints (Safety)

A set of safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of administering the study medication. All clinical AEs, SAEs, on-treatment AEs, 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, standard deviation etc.

Change from baseline and percent change from baseline on selected safety endpoints may be additionally 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 6.1.6 (except for the 3-tier analysis which does not need to be conducted in the Single-Blind Extension Period) for the analysis during Treatment Period.

6.2.2. Exploratory Efficacy Analysis

6.2.2.1. Continuous Endpoints

Endpoints:

- Change from baseline in SALT;
- Change from baseline in Pruritus Numerical Rating Scale;
- Change from baseline in AASIS.

Analysis time points: All time points during the complete study including Treatment and Single-Blind Extension Period.

Analysis population: All Placebo Non-responders, Active Non-responders, and Responders with Retreatment who have received at least one dose of planned investigational product in the Single-Blind Extension Period.

Analysis methodology:

- Summary statistics will be provided;
- For the Single-Blind Extension Period, change from baseline will be analyzed using a MMRM model (specified in Section 5.2.2) to compare Non-responders and Responders with Retreatment.

Note that, in the above descriptive summary and MMRM model, subjects will be broken down by the following

4 reporting groups:

Placebo → PF-06651600 and PF-06651600 → PF-06651600;

Placebo → PF-06700841 and PF-06700841 → PF-06700841;

PF-06651600 → Placebo → PF-06651600;

PF-06700841 → Placebo → PF-06700841, and

visits:

Week 30/ AT Week 2, Week 32/ AT Week 4, Week 34/ AT Week 6, Week 36/ AT Week 8, Week 40/ AT Week 12, Week 44/ AT Week 16, Week 48/ AT Week 20, Week 52/ AT Week 24.

To examine the initial placebo subjects responses after treated with active drugs when entering Single-Blind Extension Period, a MMRM model for Placebo Non-responders (only subjects eligible and entered the Single-Blind Extension Period) will be performed.

Placebo → PF-06651600 (Single-Blind Extension Period: Week 28 – Week 52)	vs	Placebo (Treatment Period: Day 1 – Week 24)
Placebo → PF-06700841 (Single-Blind Extension Period: Week 28 – Week 52)		

Note that, subjects will be broken down by the following:

4 reporting groups:

Placebo (randomized to pair with PF-06651600);

Placebo (randomized to pair with PF-06700841);

Placebo → PF-06651600;

Placebo → PF-06700841, and

visits:

Week 2/ Week 30, Week 4/ Week 32, AT Week 6/ Week 34, AT Week 8/ Week 36, Week 12/ Week 40, Week 16/ Week 44, Week 20/ Week 48, Week 24/ Week 52.

Reporting results:

- Raw data: n, mean, standard deviation, median, minimum and maximum at baseline and post-baseline visits will be presented;

- Change from baseline: n, mean, standard deviation, median, minimum and maximum will be presented. The LS means, 90% 2-sided confidence interval for the LS means; difference between the LS means for each pair of reporting groups and the corresponding 90% 2-sided confidence interval will also be presented.

Figures:

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

- LS mean of treatment difference in change from baseline and corresponding 90% 2-sided confidence interval by visit and reporting group for the Non-responders and Responders with Retreatment.

  Note that Non-responders and Responders will be both plotted in the figures above and the Active Treatment (AT) visits will be aligned with Week 28 – Week 52 to compare the trajectory of 24-week response in the Single-Blind Extension Period, ie, Week 30/AT Week 2, …, Week 52/AT Week 24.

- LS mean of treatment difference in change from baseline and corresponding 90% 2-sided confidence interval by visit and reporting group for the initial placebo treated subjects (only subjects eligible and entered the Single-Blind Extension Period).

  Note that the timepoints will be aligned as Week 2/Week 30, …, Week 24/Week 52 to indicate subjects' visits in Treatment Period and their visits in the Single-Blind Extension Period.

- In addition, the active vs placebo comparisons in both the Treatment Period and the Single-Blind Extension Period will be presented in the same figure. That is, the LS mean change from baseline and the LS mean of treatment difference of the following comparisons will be plotted.

PF-06651600 (Treatment Period: Day 1 – Week 24)	vs	Placebo (Treatment Period: Day 1 – Week 24)
PF-06700841 (Treatment Period: Day 1 – Week 24)		
Placebo → PF-06651600 (Single-Blind Extension Period: Week 28 – Week 52)	vs	Placebo (Treatment Period: Day 1 – Week 24)
Placebo → PF-06700841 (Single-Blind Extension Period: Week 28 – Week 52)		

Note that the Single-Blind Extension Period visits will be aligned with the Treatment Period visits to compare the trajectory of 24-week response, ie, Week 2/ Week 30, …, Week 24/Week 52.

6.2.2.2. Binary Endpoints

Endpoints:

- SALT 30, SALT 50, SALT 75, SALT 90 and SALT 100;
- Proportion with one grade improvement in eyelash assessment scale;
- Proportion with one grade improvement in eyebrow assessment scale.

The following descriptions use SALT 30 as an example. The analyses for all binary endpoints are identical.

Analysis time points: All time points during the complete study including the Treatment and Single-Blind Extension Periods.

Analysis population: All Placebo Non-responders, Active Non-responders, and Responders with Retreatment who have received at least one dose of planned investigational product in the Single-Blind Extension Period.

Analysis methodology:

- The number and percentage achieving a 30% improvement in SALT will be provided.
- For the Single-Blind Extension Period, proportion of subjects achieving a 30% improvement in SALT will be analyzed using a repeated measures GLMM model (specified in Section 5.2.1) for Non-responders and Responders with Retreatment. If the GLMM model does not converge, only the estimates using exact method will be presented.

  Note that, in the above descriptive summary and analyses, subjects will be broken down by the following

  4 reporting groups:

  Placebo → PF-06651600 and PF-06651600 → PF-06651600;

  Placebo → PF-06700841 and PF-06700841 → PF-06700841;

  PF-06651600 → Placebo → PF-06651600;

  PF-06700841 → Placebo → PF-06700841, and

  visits:

  Week 30/ AT Week 2, Week 32/ AT Week 4, Week 34/ AT Week 6, Week 36/ AT Week 8, Week 40/ AT Week 12, Week 44/ AT Week 16, Week 48/ AT Week 20, Week 52/ AT Week 24.
- To examine the initial placebo subjects responses after treated with active drugs when entering the Single-Blind Extension Period, a GLMM model for Placebo Non-responders (only subjects eligible and entered the Single-Blind Extension Period) will be performed.

Placebo → PF-06651600 (Single-Blind Extension Period: Week 28 – Week 52)	vs	Placebo (Treatment Period: Day 1 – Week 24)
Placebo → PF-06700841 (Single-Blind Extension Period: Week 28 – Week 52)		

Note that, subjects will be broken down by the following:

4 reporting groups:

Placebo (randomized to pair with PF-06651600);

Placebo (randomized to pair with PF-06700841);

Placebo → PF-06651600;

Placebo → PF-06700841, and

visits:

Week 2/ Week 30, Week 4/ Week 32, AT Week 6/ Week 34, AT Week 8/ Week 36, Week 12/ Week 40, Week 16/ Week 44, Week 20/ Week 48, Week 24/ Week 52. If the GLMM model does not converge, the estimates using exact method will be performed.

Reporting results:

- Raw data: The number and percentage of subjects meeting SALT 30 will be presented;
- Risk differences: The risk differences and the 90% 2-sided confidence interval for risk difference will be presented.

Figures:

- Plot of the proportion of subjects meeting SALT 30 in the Single-Blind Extension Period by visit and by reporting group;
- Risk difference between each pair of reporting groups with corresponding 90% 2-sided confidence interval will be plotted for the Non-responders and Responders with Retreatment;

  Note that Non-responders and Responders will be both plotted in the figures above and the Active Treatment (AT) visits will be aligned with Week 28 – Week 52 to compare the trajectory of 24-week response in the Single-Blind Extension Period, ie, Week 30/AT Week 2, …, Week 52/AT Week 24;

- Risk difference between each pair of reporting groups with corresponding 90% 2-sided confidence interval will be plotted for the initial placebo treated subjects (only subjects eligible and entered the Single-Blind Extension Period).

  Note that the timepoints will be aligned as Week 2/Week 30, …, Week 24/Week 52 to indicate subjects' visits in Treatment Period and their visits in the Single-Blind Extension Period.

- In addition, the active vs placebo comparisons in both the Treatment Period and the Single-Blind Extension Period will be presented in the same figure. That is, the risk differences of the following comparisons will be plotted.

PF-06651600 (Treatment Period: Day 1 – Week 24)	vs	Placebo (Treatment Period: Day 1 – Week 24)
PF-06700841 (Treatment Period: Day 1 – Week 24)		
Placebo → PF-06651600 (Single-Blind Extension Period: Week 28 – Week 52)	vs	Placebo (Treatment Period: Day 1 – Week 24)
Placebo → PF-06700841 (Single-Blind Extension Period: Week 28 – Week 52)		

Note that the Single-Blind Extension Period visits will be aligned with the Treatment Period visits to compare the trajectory of 24-week response, ie, Day 1/Week 28, …, Week 24/Week 52.

CCI [redacted]

CCI [redacted]

[redacted]

6.2.2.4. Placebo Treatment Duration: Time to Event (Retreatment) and Change from Baseline for Single-Blind Extension in SALT Endpoints

Endpoint:

- Time to achieve the pre-specified retreatment criteria (see Appendix 4) during the Single-Blind Extension Period;

[redacted]

Analysis time points: All visits when subjects are treated with placebo during the Single-Blind Extension Period.

Analysis population: All Responders including Responders with and without retreatment .

Analysis methodology:

- Kaplan-Meier analysis will be performed for time to reach the retreatment criteria (see Appendix 4).

[redacted]

CCI

Reporting results:

- The Kaplan-Meier estimator will be provided for each reporting group;
- The raw number and percentage of subjects achieving pre-specified retreatment criteria will be presented over time by reporting group;

CCI

Figures:

- The Kaplan-Meier estimator will be plotted for each treatment group;

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CCI

[redacted]

6.3. Analyses and Summaries During the Cross-over Open-Label Extension Period

6.3.1. Primary Endpoints (Safety)

The analyses for safety endpoints for the Cross-over Open Label Extension Period will be the same as those for the Single-Blind Extension Period (see Section 6.2.1). Descriptive summaries will be presented by treatment groups. The 3-tier analysis for adverse events will not be performed.

For change from baseline and percent change from baseline on selected safety endpoints, baseline is defined as the last measurement at the end of the Single-Blind Withdrawal/Retreatment Extension Period (ie, Week 52 visit).

[redacted]

6.4. Interim Clinical Study Report

After the last subject last visit for the initial 24-week Double-Blind Treatment Period is achieved, data will be cleaned, a snapshot of the database will be created, and all the efficacy and safety data from the 24-week Treatment Period will be summarized in an interim clinical study report (CSR) and published. The analyses and summaries for the Double-Blind Treatment Period described in Section 6.1 will be performed. The interim CSR may be shared with the principal investigator (PI) when it is available.

7. INTERIM ANALYSES

7.1. Introduction

A separate interim analysis plan for this protocol will include an interim analysis using SALT total for both active treatments. Details regarding the analysis procedures to be used for the interim analysis will be provided in the interim analysis plan (IAP). The interim analysis will be performed when approximately 50% of subjects have completed the Week 12 visit or discontinued from the study.

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 is based on predicted power conducted on a total of approximately 66 subjects who have completed the Week 12 visit or discontinued from the study. A non-informative prior will be used for the interim analysis. The decision at the end of the study is being at least 95% confident that active treatment will be superior to placebo (DC1).

The study will be stopped for futility for that active treatment arm if predictive power of meeting DC1 at the end of study is <10% for that active arm. Due to the nature of the analyses the overall Type 1 error for the study is maintained. If the futility condition is met for both active arms, the study will be stopped at the interim point.

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 in order to protect the integrity of the study. This list of individuals will be provided in the interim analysis plan. 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. REFERRENCES

1. Olsen, E. A. (2011). "Investigative guidelines for alopecia areata." Dermatologic Therapy 24(3): 311-319.

2. B7931005 protocol amendment 3. August 02, 2017.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Appendix 1.1. Summary of Efficacy Analyses in the Treatment Period

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Change from baseline in SALT at Week 24 and at intermediate time points	FAS	Summary statistics	None	None	Primary and Secondary
Change from baseline in SALT at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Primary and Secondary
Change from baseline in SALT at Week 24 and at intermediate time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	Multiple Imputation	Sensitivity
Change from baseline in SALT at Week 24 and at intermediate time points	FAS	Linear mixed effect model for longitudinal data regarding visit as a continuous variable	Treatment, Visit, Treatment* Visit, baseline SALT	None	Sensitivity
SALT 30 at Week 24 and at intermediate time points	FAS	Summary statistics	None	None	Secondary
SALT 30 at Week 24 and at intermediate time points	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Secondary
SALT 30 at Week 24 and at intermediate time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
IGA	FAS	Summary statistics	None	None	Secondary
Percent Change from baseline in SALT at all	FAS	Summary	None	None	Secondary

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
time points		statistics			
Percent Change from baseline in SALT at all time points	FAS	MMRM	None	None	Secondary
SALT 50 at all time points	FAS	Summary statistics	None	None	Secondary
SALT 50 at all time points	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Secondary
SALT 50 at all time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
SALT 75 at all time points	FAS	Summary statistics	None	None	Secondary
SALT 75 at all time points	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Secondary
SALT 75 at all time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
SALT 90 at all time points	FAS	Summary statistics	None	None	Secondary
SALT 90 at all time points	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Secondary
SALT 90 at all time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
SALT 100 at all time points	FAS	Summary statistics	None	None	Secondary
SALT 100 at all time points	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline	None	Secondary

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
			SALT*treatment		
SALT 100 at all time points	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
Eyelash assessment scale	FAS	Summary statistics	None	None	Exploratory
One grade improvement in Eyelash assessment	FAS	GLMM	None	None	Exploratory
One grade improvement in Eyelash assessment	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
Eyebrow assessment scale	FAS	Summary statistics	None	None	Exploratory
One grade improvement in Eyebrow assessment	FAS	GLMM	None	None	Exploratory
One grade improvement in Eyebrow assessment	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Secondary
AASIS	FAS	Summary statistics	None	None	Exploratory
Change from baseline in AASIS at all time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Exploratory
C-SSRS	FAS	Summary statistics	None	None	Exploratory
NRS	FAS	Summary statistics	None	None	Exploratory
Change from baseline in NRS at all time points	FAS	MMRM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Exploratory

Appendix 1.2. Summary of Efficacy Analyses in the Single-Blind Extension Period

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
Change from baseline in SALT, NRS, AASIS	FAS	Summary statistics	None	None	Exploratory
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SALT 30, SALT 50, SALT 75, SALT 90, SALT 100, CCI [redacted]	FAS	Summary statistics	None	None	Exploratory
SALT 30, SALT 50, SALT 75, SALT 90, SALT 100, CCI [redacted]	FAS	GLMM	Treatment, Visit, Treatment* Visit, baseline SALT, baseline SALT*treatment	None	Exploratory
SALT 30, SALT 50, SALT 75, SALT 90, SALT 100, CCI [redacted]	FAS	Chan and Zhang's exact test	None	Non-Responder Imputation	Exploratory
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to retreatment	FAS (all Responders at Week 24)	Kaplan-Meier	None		Exploratory

Endpoint	Analysis Set	Statistical Method	Model	Missing Data Imputation	Interpretation
CCI					

CCI

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting the Initial Treatment Period

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 -35	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 36
Visit 5 (Day 43, Week 6)	Day 37	Day 50
Visit 6 (Day 57, Week 8)	Day 51	Day 71
Visit 7 (Day 85, Week 12)	Day 72	Day 99
Visit 8 (Day 113, Week 16)	Day 100	Day 127
Visit 9 (Day 141, Week 20)	Day 128	Day 155
Visit 10 (Day 169, Week 24)	Day 156	Day 176

Appendix 2.2. Definition and Use of Visit Windows in Reporting the Single-Blind Extension Period

Visit	Target Day	Start Day	End Day
Visit 11 (Week 28) / Visit 20 (AT Day 1)	Week 28 Day 1/ AT Day 1		
Visit 12 (Week 30) / Visit 21 (AT Week 2)	Week 28 Day 1/ AT Day 1 + 14	Target Day -6	Target Day +7
Visit 13 (Week 32) / Visit 22 (AT Week 4)	Week 28 Day 1/ AT Day 1 + 28	Target Day -6	Target Day +7

Visit 14 (Week 34) / Visit 23 (AT Week 6)	Week 28 Day 1/ AT Day 1 + 42	Target Day -6	Target Day +7
Visit 15 (Week 36) / Visit 24 (AT Week 8)	Week 28 Day 1/ AT Day 1 + 56	Target Day -6	Target Day +7
Visit 16 (Week 40) / Visit 25 (AT Week 12)	Week 28 Day 1/ AT Day 1 + 84	Target Day -6	Target Day +7
Visit 17 (Week 44) / Visit 26 (AT Week 16)	Week 28 Day 1/ AT Day 1 + 112	Target Day -6	Target Day +7
Visit 18 (Week 48) / Visit 27 (AT Week 20)	Week 28 Day 1/ AT Day 1 + 140	Target Day -6	Target Day +7
Visit 19 (Week 52) / Visit 28 (AT Week 24)	Week 28 Day 1/ AT Day 1 + 168	Target Day -6	Target Day +7

CCI [redacted]

[redacted]			
[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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; and using ilink option in GLIMMIX will generate the estimate for proportions. The variance of risk difference (proportion difference) cannot be directly obtained by GLIMMIX procedure using link=logit. This appendix describes how to obtain the estimate and the confidence interval (CI) for risk difference (proportion difference) by 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).

Appendix 4. Criteria for Treatment Assignment/Subject Retreatment during the Extension Periods

All subjects who complete the initial 24-week Treatment Period will be evaluated during the Drug Holiday #1 for potential entry into the Single-Blind Extension Period. After the 4-week Drug Holiday, subjects will enter the Extension Period providing none of the Exclusion criteria #9, #10, and #26 (see below) are met and the audiogram results does not preclude patient's entry into the Single-Blind Extension Period. The non-responder criteria will be checked at Week 24 to determine if a subject should enter the segment for non-responder or the Withdrawal/Retreatment segment. Subjects who meet Exclusion criteria #9, #10, or #26 will be directly entered into the Follow-up Period. Please note that all placebo patients in the Treatment Period who are eligible for the Single-Blind Extension Period will be assigned to active treatment.

All subjects who are assigned to receive active treatment (PF-06651600 or PF-06700841) directly and complete the segment for non-responder in Single-Blind Extension Period may be evaluated for potential entry into the Cross-Over Open Label Extension Period during the Drug Holiday #2. Subjects will enter the Cross-Over Open Label Extension Period providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's entrance in the Cross-Over Open Label Extension Period as well as the non-responder criteria is met at Week 52. Subjects who complete the Withdrawal/Retreatment segment will go directly to the Follow-up Period and will not participate in the Cross-Over Open Label Extension Period.

Exclusion criteria #9, #10, #26

#9. Have current or recent history of clinically significant severe, progressive, or uncontrolled renal (including but not limited to active renal disease or recent kidney stones), hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic or neurologic disease; or have any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or interfere with the interpretation of study results; or in the opinion of the investigator or Pfizer (or designee), the subject is inappropriate for entry into this study, or unwilling/unable to comply with Study Procedures and Lifestyle Requirements.

#10. Have current or recent history of clinically significant severe, progressive, or uncontrolled hearing loss or auditory disease.

#26. **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

- Absolute neutrophil count of <2.5 x 109/L (<2500/mm3);
- Hemoglobin <10.0 g/dL or hematocrit <30%;
- Platelet count below the lower limit of normal (LLN) at Screening;

- Absolute lymphocyte count of <0.8 x 109 /L (<800/mm3);
- serum creatinine > upper limit of normal (ULN) or eGFR <80 ml/min/1.73m2 based on the age appropriate calculation;
- enzymes aspartate transaminase (AST) or alanine transaminase (ALT) values >2 times the ULN;
- Total bilirubin ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN;
- CK >3 times the ULN and positive urine myoglobin;
- In the opinion of the investigator or Pfizer (or designee), have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study.

The Responder/Non-responder Criteria

- During Drug Holiday # 1, SALT 30 at Week 24 will be calculated:
  - Calculate % change from baseline: (SALT baseline – SALT Week 24)/SALT baseline X 100%
  - If the % change from baseline ≥30 then SALT 30 = 1 or 0 otherwise
  - If the SALT 30 = 1 then the subject will be assigned to receive placebo at Week 28 and enter the Withdrawal /Retreatment segment for responders in the Single-Blind Extension Period.
  - If the SALT 30 = 0 then the subject will be assigned to receive active treatment at Week 28 and enter the segment for non-responders in the Single-Blind Extension Period.
- During Drug Holiday # 2, SALT 30 at Week 52 will be calculated:
  - Calculate % change from baseline: (SALT baseline – SALT Week 52)/SALT baseline X 100%;
  - If the % change from baseline ≥ 30 then SALT 30 = 1 or 0 otherwise;
  - If the SALT 30 = 0 then the subject is a non-responder and will enter Cross-Over Open Label Extension Period with the treatment alternative to that is used in the Single-Blind Extension Period;
  - If the SALT30 =1 then subject is a responder at Week 52 and will enter the Follow-up Period directly.

The Retreatment Criteria

In the Withdrawal/Retreatment segment of the Single-Blind Extension Period, the responders will be evaluated at each post Week 28 visit to determine if retreatment criteria met:

- PCB (post Week 24): Calculate percent change from baseline as (SALT baseline – SALT post week 24)/SALT baseline X 100%;

- PCB (Week 24): Calculate percent change from baseline as (SALT baseline – SALT week 24)/SALT baseline X 100%;

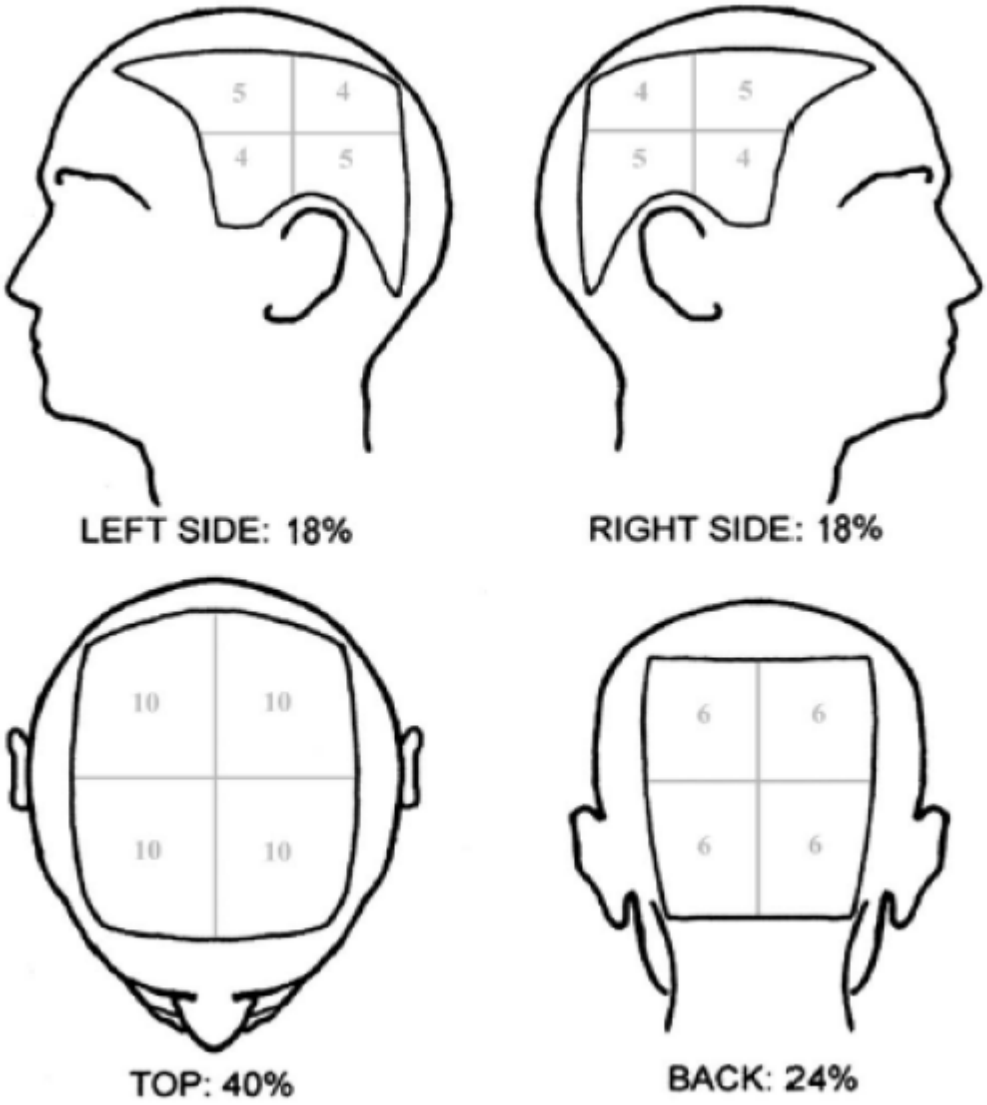
- If PCB (Week 24) – PCB (post Week 24) >30 then the subject will be re-assigned to receive active treatment;

- If PCB (Week 24) – PCB (post Week 24) ≤30 then the subject will continue to receive placebo.

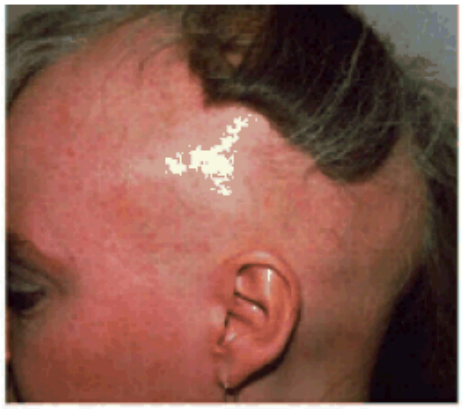
Appendix 5. Severity of Alopecia Tool (SALT)

(Olsen 2011)[1]

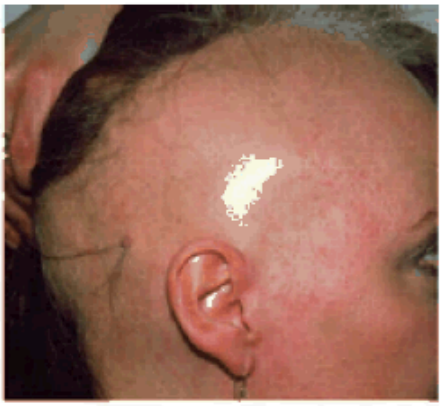
SALT score= 0.18×score_left side + 0.18×score_right side + 0.4×score_top + 0.24×score_back



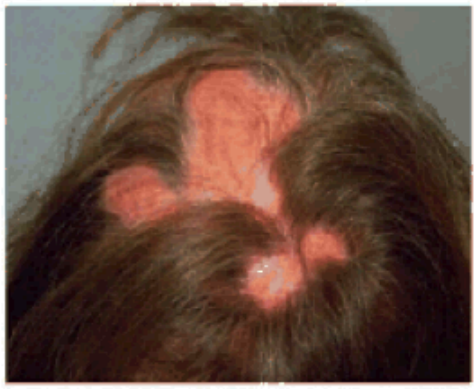
For Example:



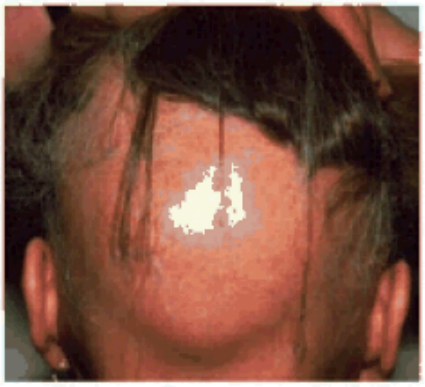
80% X 0.18 =14.48%



95% X 0.18 = 17.1%



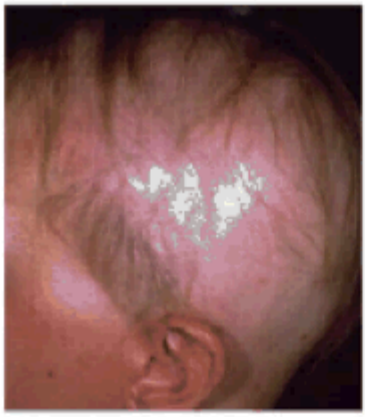
65% X 0.40 = 26%



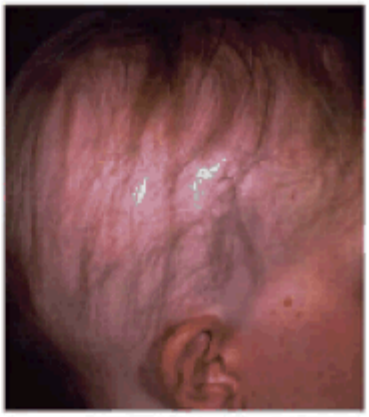
85% X 0.24 = 20.4%

SALT score

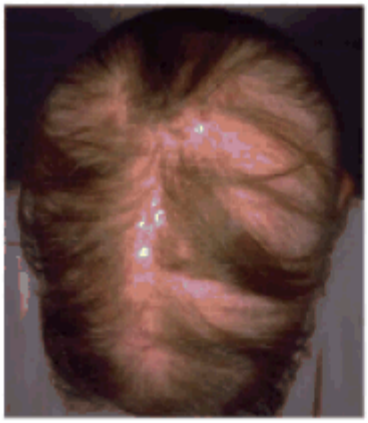
14.5% + 17.1% + 26% + 20.4% = 78%



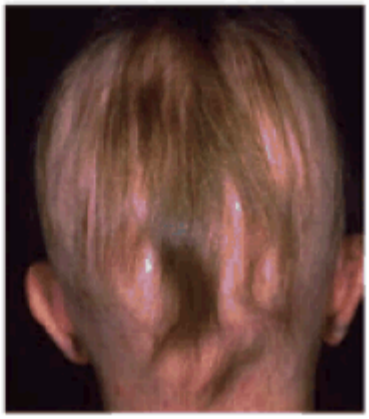
95% x 0.18 = 17.1%



95% x 0.18 = 17.1%



50% x 0.40 = 20.0%



65% x 0.24 = 15.6%

SALT score

17.1% + 17.1% + 20% + 15.6% = 69.8%

CCI

CCI

CCI