



**A 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**

<b>Investigational Product Number:</b>	PF-06651600; PF-06700841
<b>Investigational Product Name:</b>	Not Applicable (N/A)
<b>United States (US) Investigational New Drug (IND) Number:</b>	CCI [REDACTED]
<b>European Clinical Trials Database (EudraCT) Number:</b>	2016-004048-13
<b>Protocol Number:</b>	B7931005
<b>Phase:</b>	2a



**Document History**

Document	Version Date	Summary of Changes and Rationale
Amendment 4	06 June 2018	<ul style="list-style-type: none"> <li data-bbox="740 369 1414 653">• In the Title, Schedule of Activities, Section 2 Study Objectives and Endpoints, Section 3 Study Design, Section 6 Study Procedures, and Section 9 Data Analysis, added a 4-week Drug Holiday Period #2 and a 6-month Cross-Over Open Label Extension Period for subjects who complete the segment for non-responder in Single-Blind Extension Period.  Rationale: The objective of the 6 months Cross-Over Open Label Extension Period is to provide opportunity for non-responders to one active study treatment to receive the opposite active study treatment.</li> <li data-bbox="740 911 1414 1194">• In the Title, Schedule of Activities, Section 2 Study Objectives and Endpoints, Section 3 Study Design, Section 6 Study Procedures, and Section 9 Data Analysis, changed the Extension Period to Single-Blind Extension Period including a segment for non-responder and a Withdrawal/Retreatmetn segment for responder and included general outline of the interim CSR.  Rationale: Due to lack of clinical research in the area of Alopecia Areata, there is a strong scientific rationale to summarize and share the results from the 24 week Treatment Period, as that period of the study has been completed.</li> <li data-bbox="740 1453 1414 1526">• In the Section 1 Introduction, mechanism of action of PF-06651600 is updated.  Rationale: Based on the new pre-clinical work, mechanism of action of PF-06651600 is updated.</li> <li data-bbox="740 1667 1414 1803">• In the Section 1.2 Background and Rationale, added information from other studies that investigate PF-06651600 and/or PF-06700841 in different therapeutic areas.  Rationale: To provide updated information for</li> </ul>

		<p>PF-06651600 and/or PF-06700841 in different therapeutic areas.</p> <ul style="list-style-type: none"> <li>In the Section 8 Adverse Event Reporting, added a special safety concern, fetal cleft lip which was reported in study B7931004, a trial investigating PF-06700841 in psoriasis patients affecting a singleton pregnancy of a subject on concomitant medications including herbal supplement which carried a pregnancy warning.</li> </ul> <p>Rationale: To include a special safety concern reported in Study B7931004, a trial investigating PF-06700841 in psoriasis patients.</p> <ul style="list-style-type: none"> <li>In the Section 9.7 Data Monitoring Committee, IRC information is updated.</li> </ul> <p>Rationale: The committee will have completed its work and been dissolved once the database lock and data release occurs for the initial 24-week Treatment Period and the study team becomes unblinded. Unblinded study team will continue monitoring of the safety of subjects in the study.</p> <ul style="list-style-type: none"> <li>In the Section 11 Data Handling and Record Keeping and Section 12.3 Subject information and Consent, new requirements are incorporated.</li> </ul> <p>Rationale: To align with the EU General Data Protection Regulation (GDPR) the appropriate verbiage is incorporated in the protocol.</p> <ul style="list-style-type: none"> <li>Minor administrative changes and sentence revisions made throughout the document.</li> </ul> <p>Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.</p>
Amendment 3	02 August 2017	<ul style="list-style-type: none"> <li>In the Schedule of Activities, Section 2 Study Objectives and Endpoints, Section 3 Study Design, and Section 6 Study Procedures, added a 4-week Drug Holiday Period and an up to 12 months Extension Period.</li> </ul> <p>Rationale: To provide opportunities for subjects</p>

		<p>to receive additional study treatment as to date no medications approved for treatment of alopecia areata.</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities and Section 6 Study Procedures, added medical history at the Baseline Visit.</li></ul> <p>Rationale: Any adverse events occurred prior to first dosing should be reflected on the medical history.</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities, Section 6 Study Procedures, and Section 7.4.2 Laboratory Tests, added urine myoglobin at Screening, Week 28 and in case of CK &gt;3x ULN.</li></ul> <p>Rationale: Urine myoglobin is added to ensure subject safety is fully evaluated prior to study entry and monitored during the study.</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities and Section 6 Study Procedures, added instruction to provide and review dosing instruction.</li></ul> <p>Rationale: Adding instruction to provide and review dosing instruction to prevent medication error and ensure patient safety.</p> <ul style="list-style-type: none"><li>• Section 4.1 Inclusion Criteria, added SALT score 50 to inclusion criteria #5.</li></ul> <p>Rationale: To provide clarification of the definition of moderate to severe AA.</p> <ul style="list-style-type: none"><li>• Section 4.2, Exclusion Criteria, added the following exclusions: subjects with CK &gt;3x ULN and positive urine myoglobin.</li></ul> <p>Rationale: Subjects with elevated CK and positive urine myoglobin will be excluded from participation to ensure subject safety is fully evaluated prior to study entry.</p> <ul style="list-style-type: none"><li>• Section 4.4, Lifestyle Requirements, added requirements for subjects to avoid excessive exercise during the study, especially within one</li></ul>
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		<p>week prior to the scheduled study visits and maintain adequate hydration, if possible.</p> <p>Rationale: to ensure subject safety is fully evaluated during the study.</p> <ul style="list-style-type: none"><li>• Section 6 Study Procedures, added instructions that IP should be administered from the previous container.</li></ul> <p>Rationale: to provide clarification and to be consistent with IP manual.</p> <ul style="list-style-type: none"><li>• Section 9.6 Interim Analysis, updated the interim analysis time point from 24 weeks to 12 weeks.</li></ul> <p>Rationale: the interim analysis time point is updated based on results from an investigator initiated research investigating tofacitinib for 12 weeks.</p> <ul style="list-style-type: none"><li>• Appendix 6 Guidelines for Subject Safety Monitoring and Discontinuation, added that subjects with lymphocytes less than <math>0.6 \times 10^9 /L</math> or CK <math>&gt;3x</math> ULN will be re-tested.</li></ul> <p>Rationale: Subjects who experience decreased lymphocytes less than <math>0.6 \times 10^9 /L</math> or CK <math>&gt;3x</math> ULN will be monitored to further evaluate subject safety.</p> <ul style="list-style-type: none"><li>• Appendix 6 Guidelines for Subject Safety Monitoring and Discontinuation, added that subjects with CK <math>&gt;10x</math> ULN will be discontinued.</li></ul> <p>Rationale: Subjects who experience elevated CK <math>&gt;10x</math> ULN will be discontinued from the study to ensure subject safety.</p> <ul style="list-style-type: none"><li>• Minor administrative changes and sentence revisions made throughout the document.</li></ul> <p>Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.</p>
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<p>Amendment 2</p>	<p>17 February 2017</p>	<ul style="list-style-type: none"> <li>• In the Schedule of Activities, Section 6 Study Procedures, and Section 7.3.5 Audiogram, added audiogram assessments at Week 12 Visit.  Rationale: To monitor for potential changes in hearing during study conduct.</li> <li>• In the Schedule of Activities, Section 6 Study Procedures, and Section 7.4.2 Laboratory Tests, added serum cystatin C and cystatin C based eGFR at various time points.  Rationale: Serum cystatin C and cystatin C based eGFR assessed at additional time points to facilitate interpretability of any findings in individual subjects.</li> <li>• In the Schedule of Activities, Section 7.3.7.2 Creatinine, Cystatin C, and eGFR, Section 8.4.3 Potential Cases of Decreased eGFR, and Appendix 6 Guidelines for Subject Safety Monitoring and Discontinuation, removed statement that a creatinine increase above the ULN will trigger a reflex test for serum cystatin C in order to facilitate both serum cystatin C based, and serum creatinine based eGFR calculation.  Rationale: Serum cystatin C and cystatin C based eGFR assessed at additional time points to facilitate interpretability of any findings in individual subjects.</li> <li>• In the Schedule of Activities, Section 6 Study Procedures, IGA is removed from the Screening Visit.  Rationale: IGA is removed from the Screening Visit to ensure the overall hair growth will be evaluated at baseline and each follow-up visit(s).</li> <li>• Section 4.2, Exclusion Criteria, added the following exclusions: subjects with active renal disease or recent kidney stones.  Rationale: Subjects with active renal disease or</li> </ul>
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		<p>recent kidney stones are excluded from participation to ensure subject safety is fully evaluated prior to study entry.</p> <ul style="list-style-type: none"><li>• Section 4.2, Exclusion Criteria, modified the lymphocyte count for study entry.</li></ul> <p>Rationale: The lymphocyte count is modified to ensure that subjects entering the study are not put at additional risk of experiencing CTCAE Grade 3 adverse events by entering the study with these laboratory values on the lower end of the normal range.</p> <ul style="list-style-type: none"><li>• Section 4.2, Exclusion Criteria, modified the eGFR for study entry.</li></ul> <p>Rationale: The eGFR is modified to allow elderly subjects with lower age adjusted eGFR to enter the study.</p> <ul style="list-style-type: none"><li>• Section 4.4, Lifestyle Requirements, added requirements for subjects who undergo color application to their hair.</li></ul> <p>Rationale: Subjects who undergo color application to their hair, it is recommended that the color application will be performed within one week prior to the scheduled study visits, if possible. This will facilitate the consistency of SALT assessment.</p> <ul style="list-style-type: none"><li>• Section 5.8.2 Prohibited Medications and Treatments and Appendix 2 Prohibited Concomitant Medications, excluded substrates of CYP3A.</li></ul> <p>Rationale: Subjects receiving drugs that are substrates of CYP3A (simvastatin or simvastatin containing products) are excluded from participation in the study to limit any potential interactions with the investigational product.</p> <ul style="list-style-type: none"><li>• Section 7.3.7.2 Creatinine, Cystatin C, and eGFR clarified that creatinine elevations above the ULN will be followed until resolution or</li></ul>
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		<p>baseline.</p> <p>Rationale: Creatinine levels above the ULN will be followed until resolution or baseline to monitor subject safety.</p> <ul style="list-style-type: none"> <li>Section 7.5. 1 Severity of Alopecia Tool, added a sentence that male pattern alopecia scoring may be considered for final adjudication by alopecia areata expert(s).</li> </ul> <p>Rationale: For any male subject, male pattern alopecia scoring may be considered for final adjudication by alopecia areata expert(s). The adjudication is needed to ensure the assessment of complete hair growth.</p> <ul style="list-style-type: none"> <li>Section 9.6 Data Monitoring Committee, added a statement that the IRC will review accumulating renal safety data and may propose changes to the protocol as needed to ensure subject safety.</li> </ul> <p>Rationale: Additional monitoring of safety data to ensure patients' safety.</p> <ul style="list-style-type: none"> <li>Appendix 6, Guidelines for Subject Safety Monitoring and Discontinuation, added that any clinically meaningful, treatment related decline in hearing from baseline will result in the subject being discontinued from treatment with investigational product.</li> </ul> <p>Rationale: Subjects who develop a clinically meaningful, treatment related decline in hearing from baseline will be discontinued from treatment and to further evaluate subject safety.</p> <ul style="list-style-type: none"> <li>Minor administrative changes and sentence revisions made throughout the document.</li> </ul> <p>Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.</p>
Amendment 1	10 November 2016	<ul style="list-style-type: none"> <li>In the Schedule of Activities, Section 6 Study Procedures, and Section 7.3.5. Audiogram, added audiogram assessments.</li> </ul>



		<p>Rationale: To monitor for potential changes in hearing between baseline (between Visit 1 and Visit 2 [inclusive]) and at the end of the study (between Visit 10 and Visit 12 [inclusive]).</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities and Section 6 Study Procedures, remove time requirement for PK on early termination visit.</li></ul> <p>Rationale: Additional time requirement of PK is removed to clarify that only one sample for PK will be collected on early termination visit.</p> <p>CCI [REDACTED]</p> <p>CCI [REDACTED]</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities, Section 2, Study Objectives and Endpoints, Section 6 Study Procedures, CCI [REDACTED]</li></ul> <p>CCI [REDACTED]</p> <ul style="list-style-type: none"><li>• In the Schedule of Activities and Section 6 Study Procedures, added lesional biopsy at W32.</li></ul> <p>Rationale: Lesional biopsy at W32 is added to help understand the post-treatment effect of investigational products in alopecia areata at cellular and molecular level at W32.</p> <ul style="list-style-type: none"><li>• Section 3 Study Design and Section 4.1, Inclusion Criteria, added definition for current episode of fixed hair loss.</li></ul>
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		<p>Rationale: Subjects with current episode of fixed hair loss <math>\leq 7</math> years will be enrolled to study. Subjects with waxing and waning hair loss pattern have no limitation.</p> <ul style="list-style-type: none"> <li>Section 7.8, Photography of Alopecia Areata Treated with Study Drug, added photographs of CCI [REDACTED]</li> <li>CCI [REDACTED]</li> </ul> <p>Appendix 2, Prohibited Concomitant Medications, added strong P-gp inhibitors and substrates of MDRI (eg, digoxin), OCT2 or MATE (dofetilide).</p> <p>Rationale: Subjects receiving strong P-gp inhibitors and drugs that are substrates of MDRI (eg, digoxin), OCT2 or MATE (dofetilide) are excluded from participation in the study to limit any potential interactions with the investigational product.</p> <ul style="list-style-type: none"> <li>Minor administrative changes and sentence revisions made throughout the document.</li> </ul> <p>Rationale: Revisions made for clarity and to correct minor grammatical or spelling errors.</p>
Original protocol	29 August 2016	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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## PROTOCOL SUMMARY

### Background and Rationale:

The janus kinase (JAK) family, including JAK1, JAK2, JAK3 and tyrosine-protein kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function. Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK dimer combination to transduce their signal. JAK1 pairs with JAK3 to mediate  $\gamma$ -common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL) -2, -4, -5, -6, -12, -13, -15, -21, -23, -31, interferon gamma (IFN $\gamma$ ), and interferon alpha (IFN $\alpha$ ). Following cytokine activation, receptor-associated JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs.<sup>16</sup> Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription.<sup>18</sup> The tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family consists of five members including TEC, Bruton's tyrosine kinase (BTK), bone marrow-expressed kinase (BMX), inducible T-cell kinase (ITK) and resting lymphocyte kinase (RLK/TXK), that are primarily expressed in hematopoietic cells. TEC kinases play an important role in antigen receptor signaling and BTK and ITK regulate the signal transduction pathways initiated by the activation of B cell receptor (BCR) and T cell receptor (TCR), respectively.<sup>31,27</sup>

PF-06651600 is an orally bioavailable small molecule that inhibits irreversibly JAK3 with selectivity over the other three JAK isoforms, JAK1, JAK2 and TYK2. PF-06651600 also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, BMX, ITK, TEC, TXK), with high selectivity over the broader kinome. PF-06651600 inhibits the cytotoxic function of CD8+ T cells and NK cells which have been implicated in the pathogenic process of AA.<sup>34,30</sup> This inhibition may be mediated through mechanisms dependent on JAK3 and TEC kinase family members.<sup>33,28,29</sup> PF-06651600 also potently inhibits signaling of the JAK3-dependent receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of AA.<sup>32</sup>

PF-06700841 is a dual TYK2/JAK1 inhibitor with a good selectivity profile over the other human kinases including JAK2. TYK2/JAK1 are critical signaling kinases that regulate the signal transduction pathways triggered by several cytokines implicated in the pathogenesis of AA, including IFN $\gamma$ , IL-2, IL-15, IL-12, and IL-23.<sup>4,25,6</sup>

Both compounds will be investigated in patients with AA.

## Objectives and Endpoints





### Study Objectives and Endpoints during Treatment Period

<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Primary Endpoint:</b></p> <ul style="list-style-type: none"> <li>Change from baseline of Severity of Alopecia Tool (SALT) score at Week 24.</li> </ul>
<p><b>Secondary Objectives:</b></p>	<p><b>Secondary Endpoints:</b></p>
<p><b>Key Secondary Efficacy Objective:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Key Secondary Efficacy Endpoint:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at Week 24.</li> </ul>
<p><b>Other Secondary Efficacy Objectives:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Other Secondary Efficacy Endpoints:</b></p> <ul style="list-style-type: none"> <li>Change from baseline in Investigator Global Assessment (IGA) at all time points up to Week 24 as specified in the <a href="#">Schedule of Activities</a> (SoA).</li> <li>Change from baseline in SALT at intermediate time points up to Week 24 as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at intermediate time points up to Week 24 as specified in the <a href="#">SoA</a> except for Week 24.</li> <li>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 <a href="#">SoA</a>.</li> <li>Percentage change in SALT from baseline to Week 24 at intermediate time points as specified in the <a href="#">SoA</a>.</li> </ul>
<p><b>Safety Objectives:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Safety Endpoints:</b></p> <ul style="list-style-type: none"> <li>Incidence of treatment-emergent adverse events (AEs) up to Week 24.</li> <li>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.</li> </ul>

CCI [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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**Study Objectives and Endpoints during Single-Blind Extension Period**

Primary Objective:	Primary Endpoint:
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of treatment-emergent adverse events (AEs) during the Single-Blind Extension Period.</li> <li>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.</li> </ul>
<p>CCI</p> 	
	<ul style="list-style-type: none"> <li>Change from baseline in SALT during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving SALT 30 during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving SALT 50, SALT 75, SALT 100 during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> </ul> <p>CC I</p>  <ul style="list-style-type: none"> <li>Time to achieve the retreatment criteria during the Withdrawal/Retreatment part of the Extension Period among subjects who achieved primary endpoint at Week 24.</li> </ul>

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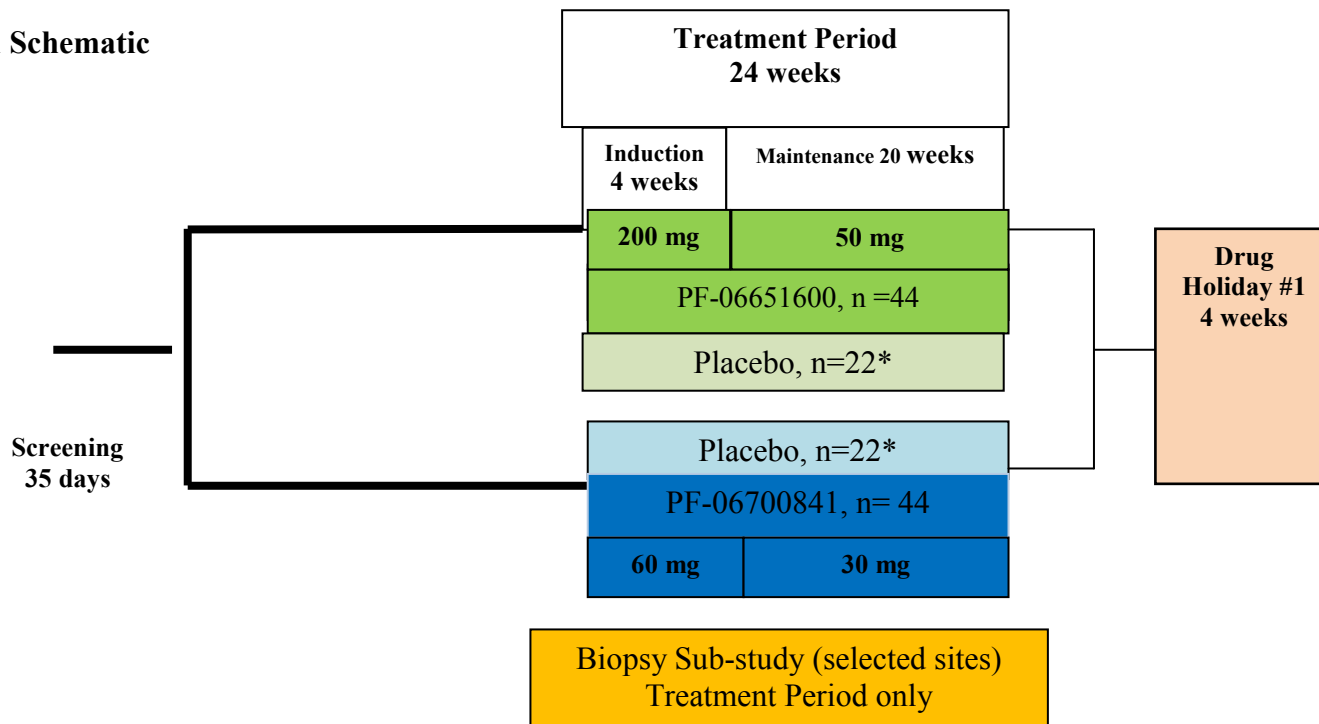
### Study Objectives and Endpoints during Cross-Over Open Label Extension Period

Primary Objective:	Primary Endpoint:
<ul style="list-style-type: none"><li>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.</li></ul>	<ul style="list-style-type: none"><li>Incidence of treatment-emergent adverse events (AEs) during the Cross-Over Open Label Extension period.</li><li>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.</li></ul>
CCI [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

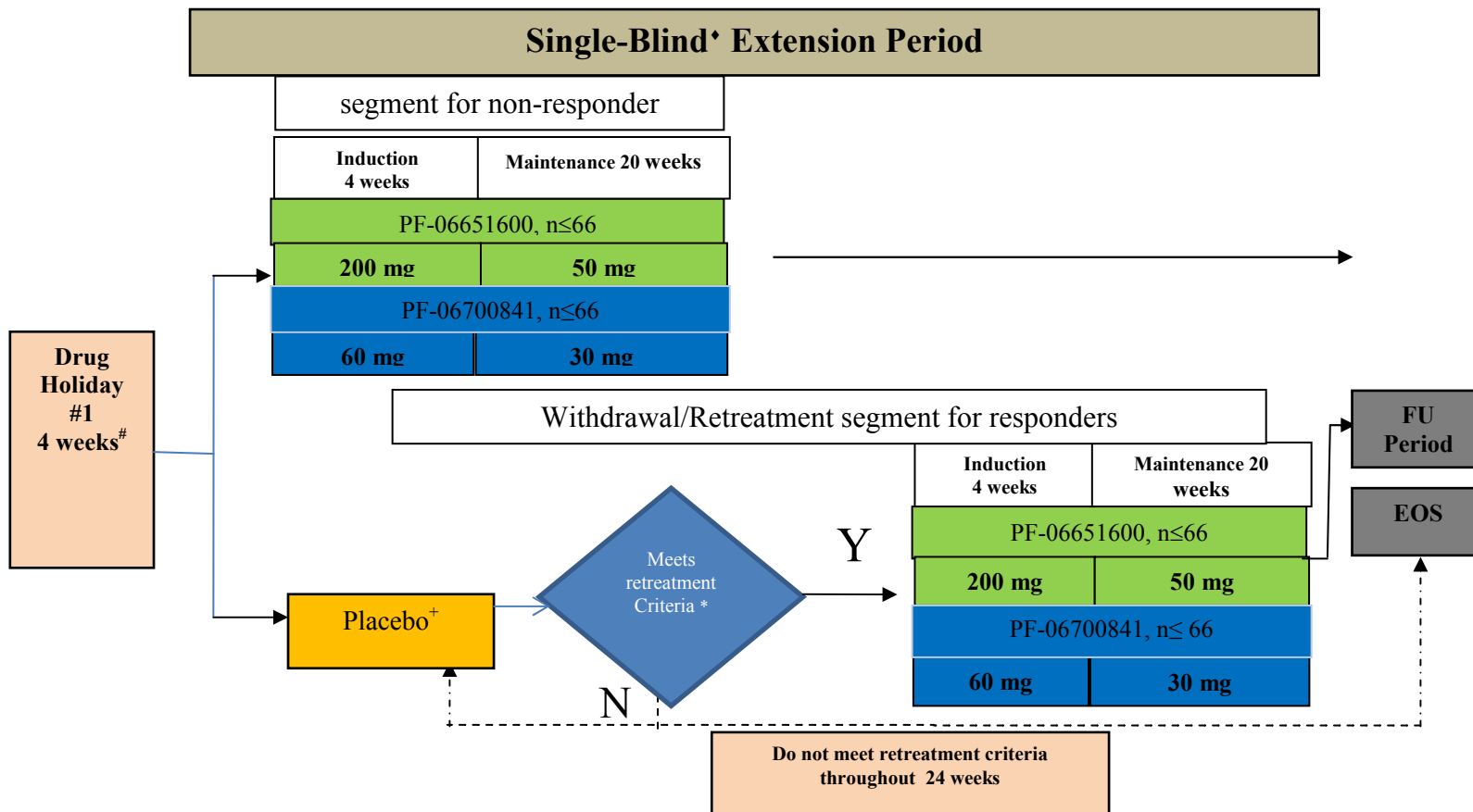


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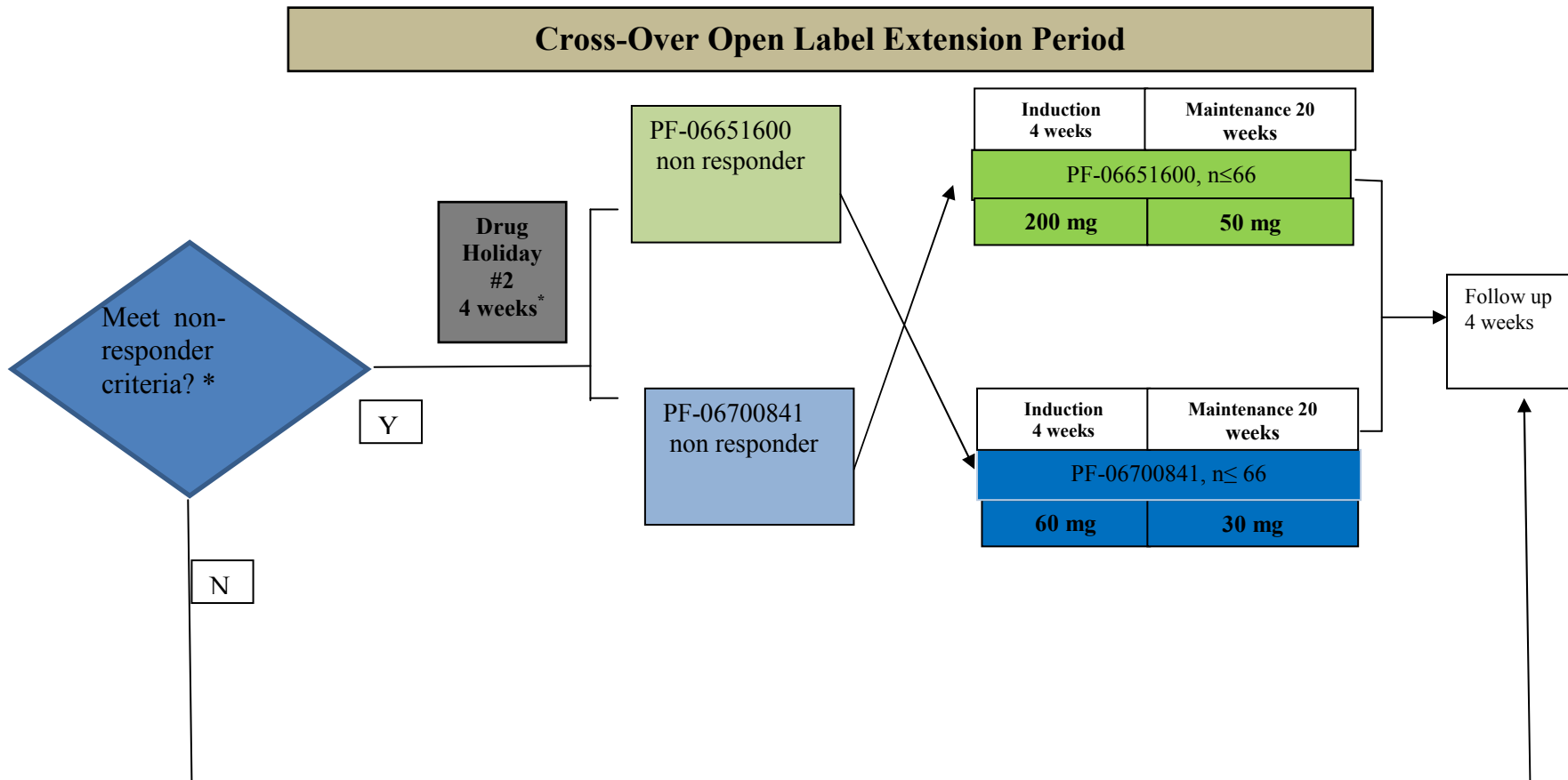
### Study Design Schematic



**\* 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-responder 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 Period and will not participate 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.

### **Study Design and Treatments:**

Study B7931005 will investigate the JAK3 inhibitor PF-06651600 and TYK2/JAK1 inhibitor PF-06700841 in 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 weeks Screening Period, a 24-week Treatment Period, a 4-week Drug Holiday #1, an up to 12 months 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.

Subjects who have moderate to severe alopecia areata ( $\geq 50\%$  hair loss of the scalp [SALT score  $\geq 50$ ] and without evidence of hair regrowth within the previous 6 months; current episode of fixed hair loss  $\leq 7$  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 ( $\geq 50\%$  hair loss of the scalp). 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 in the initial Treatment Period. During the data analysis, 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 24-week treatment period consists of a 4-week induction treatment period and a 20-week maintenance treatment period.

An induction dose of 200 mg once daily (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 Treatment Period of 24 weeks. 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. An 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 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 are met and the audiogram result does not preclude patient's entrance in the 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 will be described in the statistical analysis plan (SAP). The study designee(s), who are independent of the study team, will provide the site with a treatment assignment when investigational product (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%. 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 the SAP.

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 the SAP. 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 end of study (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 Cross-Over Open Label Extension Period.

Any subject that has completed the initial 24 weeks of the Protocol B7931005 prior to 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 at Week 52 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 4-week 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 active 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 subjects 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.

### **Statistical Methods:**

A comprehensive overall Statistical Analysis Plan (SAP) will be provided prior to the un-blinding of the trial.

The sample size is based on the primary efficacy endpoint, mean change from baseline in SALT score at Week 24.

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 randomized study medication) will be included in the efficacy data analyses.

The primary efficacy endpoint is change from baseline in the SALT score for the Treatment Period. The primary time point is Week 24. CCI [REDACTED]

The safety analysis set will include all subjects who have received at least one dose of the study drug or placebo.

Pharmacokinetic concentrations in treatment period will be summarized and presented with summary statistics and, if appropriate, non-compartmental pharmacokinetic (PK) parameter estimates will be provided. There will not be any PK assessments during the Single-Blind Extension Period.

Details regarding the analysis procedures to be used for the interim analysis will be provided in the interim analysis plan (IAP). The interim analysis may be performed when approximately 50% of subjects have completed or had the chance to complete the Week 12 visit. Additional interim analyses may be performed based on emerging data.

CCI [REDACTED]



This study will use an internal review committee (IRC). The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The IRC will review accumulating renal safety data and may propose changes to the protocol as needed to ensure subject safety. There will be a separate Internal Review Committee to review the results of any interim analyses. The committee will have completed its work and been dissolved once the database lock and data release occurs for the initial 24-week Treatment Period and study team becomes unblinded. Unblinded study team will continue monitoring of the safety of subjects in the study.

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Protocol Activity	Screening Period	Treatment Period										Drug Holiday #1 <sup>aa</sup>
		Treatment Period Induction Phase				Treatment Period Maintenance Phase						
Visit Identifier	1	2	3	4	5	6	7	8	9	10		
Visit Day <sup>a</sup>	Day -35 to -1	Day 1	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169		
Week	N/A		W2	W4	W6	W8	W12	W16	W20	W24		
Visit Window	N/A		±2 Days based on Day 1 visit			±3 Days based on Day 1 visit						4 weeks
Enrollment procedure												
Informed consent	X											
Inclusion/Exclusion criteria	X	X									X <sup>aa</sup>	
Demographics	X											
Medical history and AA disease history <sup>c</sup>	X	X										
Medical procedures												
Complete physical examination <sup>d</sup>	X	X								X		
Targeted physical examination <sup>e</sup>			X	X	X	X	X	X	X			
Vital signs <sup>f</sup>	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG <sup>g</sup>	X	X								X		
Height <sup>h</sup>	X											
Weight <sup>h</sup>	X	X										
Chest radiographs <sup>i</sup>	X											
Audiogram <sup>j</sup>	X						X			X		
Laboratory												
Hematology	X	X	X	X	X	X	X	X	X	X		
Blood chemistry	X	X	X	X	X	X	X	X	X	X		
Fasting lipid Panel <sup>k</sup>		X				X				X		
Cystatin C (and eGFR) <sup>l</sup>		X	X	X	X	X	X	X	X	X		

Protocol Activity	Screening Period	Treatment Period									Drug Holiday #1 <sup>aa</sup>
		Treatment Period Induction Phase				Treatment Period Maintenance Phase					
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Visit Day <sup>a</sup>	Day -35 to -1	Day 1	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169	
Week	N/A		W2	W4	W6	W8	W12	W16	W20	W24	
Visit Window	N/A	±2 Days based on Day 1 visit			±3 Days based on Day 1 visit					4 weeks	
Urinalysis <sup>m</sup>	X	X	X	X	X	X	X	X	X	X	
Urine Myoglobin <sup>dd</sup>	X										
Serum FSH (WONCBP only) or serum pregnancy test (WOCBP) <sup>n</sup>	X										
Urine pregnancy test (WOCBP) <sup>o</sup>		X	X	X	X	X	X	X	X	X	
HIV testing <sup>p</sup>	X										
HBsAg, HBcAb, (HepB reflex testing), and HCVAb <sup>q</sup>	X										
Tuberculosis test <sup>r</sup>	X										
Viral Surveillance: EBV, CMV, HSV1, HSV2, and VZV		X	X	X			X			X	
Laboratory Pharmacodynamics											
IP-10 (CXCL10)		X		X			X			X	
CCI											
FACS-TBNK		X		X			X			X	
Immunoglobulins (total Ig, IgA, IgG, IgM)		X		X						X	
IgE		X		X						X	
CCI											
Trial treatment											
Impala registration	X										
Randomization		X									
Investigational product dispensing		X	X	X	X	X	X	X	X		
Investigational product administration <sup>s</sup>		X	→	→	→	→	→	→	→	X	

Protocol Activity	Screening Period	Treatment Period									Drug Holiday #1 <sup>aa</sup>
		Treatment Period Induction Phase				Treatment Period Maintenance Phase					
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Visit Day <sup>a</sup>	Day -35 to -1	Day 1	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169	
Week	N/A		W2	W4	W6	W8	W12	W16	W20	W24	
Visit Window	N/A		±2 Days based on Day 1 visit			±3 Days based on Day 1 visit					4 weeks
Investigational product accountability			X	X	X	X	X	X	X	X	
Clinical assessments											
IGA		X	X	X	X	X	X	X	X	X	
SALT	X	X	X	X	X	X	X	X	X	X	
CCI	X	X	X	X	X	X	X	X	X	X	
Photograph <sup>1</sup>	X	X		X		X	X	X	X	X	
CCI	X	X	X	X	X	X	X	X	X	X	
Patient reported outcome											
CCI	X	X	X	X	X	X	X	X	X	X	
SBQ-R <sup>u</sup>	X										
PHQ-8 <sup>u</sup>	X										
CCI		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
		X	X	X	X	X	X	X	X	X	
Other											
Prior and current concomitant Treatment(s)	X	→	→	→	→	→	→	→	→	→	
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	

Protocol Activity	Screening Period	Treatment Period									Drug Holiday #1 <sup>aa</sup>
		Treatment Period Induction Phase				Treatment Period Maintenance Phase					
Visit Identifier	1	2	3	4	5	6	7	8	9	10	
Visit Day <sup>a</sup>	Day -35 to -1	Day 1	Day 15	Day 29	Day 43	Day 57	Day 85	Day 113	Day 141	Day 169	
Week	N/A		W2	W4	W6	W8	W12	W16	W20	W24	
Visit Window	N/A		±2 Days based on Day 1 visit		±3 Days based on Day 1 visit					4 weeks	
Contraception check	X	X	X	X	X	X	X	X	X	X	
Biopsy sub-study											
Non-lesional biopsy <sup>y</sup>		X									
Lesional biopsy for cellular and molecular analyses <sup>y</sup>		X		X <sup>z</sup>			X			X	



Protocol Activity	Single-Blind Extension Period								
	Induction Phase			Maintenance Phase					
	11	12	13	14	15	16	17	18	19
Visit Identifier	W28 <sup>bb</sup>	W30	W32	W34	W36	W40	W44	W48	W52
Week									
Visit Window	±3 Days based on Day 1 visit	±3 Days based on W28 visit							
Clinical assessments									
IGA	X	X	X	X	X	X	X	X	X
SALT	X	X	X	X	X	X	X	X	X
CCI [REDACTED]	█	█	█	█	█	█	█	█	█
Photograph <sup>1</sup>	X		X		X	X	X	X	X
CCI [REDACTED]	█	█	█	█	█	█	█	█	█
Patient reported outcome									
CCI [REDACTED]	█	█	█	█	█	█	█	█	█
CCI [REDACTED]									
[REDACTED]	█	█	█			█			█
Other									
Prior and current concomitant Treatment(s)	→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring	→	→	→	→	→	→	→	→	→
Contraception check	X	X	X	X	X	X	X	X	X







For subjects in the Cross-Over Open Label Extension Period

Protocol Activity	Drug Holiday#2	Cross-Over Open Label Extension Period								
		Induction Phase			Maintenance Phase					
Visit Identifier		29	30	31	32	33	34	35	36	37
Week		COD1	COW2	COW4	COW6	COW8	COW12	COW16	COW20	COW24/COEOT
Visit Window	4 weeks	±3 Days based on COD1 visit								
Inclusion/Exclusion criteria	X <sup>gg</sup>									
<b>Medical procedures</b>										
Complete physical examination <sup>d</sup>		X								X
Targeted physical examination <sup>e</sup>			X	X	X	X	X	X	X	
Vital signs <sup>f</sup>		X	X	X	X	X	X	X	X	X
12-Lead ECG <sup>g</sup>		X								X
Audiogram <sup>h</sup>							X			X
<b>Laboratory</b>										
Hematology		X	X	X	X	X	X	X	X	X
Blood chemistry		X	X	X	X	X	X	X	X	X
Fasting lipid Panel <sup>k</sup>		X				X				X
Cystatin C (and eGFR) <sup>l</sup>		X	X	X	X	X	X	X	X	X
Urinalysis <sup>m</sup>		X	X	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP) <sup>o</sup>		X	X	X	X	X	X	X	X	X
<b>Laboratory Pharmacodynamics</b>										
CCI [REDACTED]		█		█			█			█
FACS-TBNK		X		X			X			X
CCI [REDACTED]		█		█			█			█
<b>Trial treatment</b>										
Provide and review dosing instructions		X	X	X	X	X	X	X	X	
Investigational product dispensing		X	X	X	X	X	X	X	X	
Investigational product administration		X	→	→	→	→	→	→	→	X

Protocol Activity	Drug Holiday#2	Cross-Over Open Label Extension Period								
		Induction Phase			Maintenance Phase					
Visit Identifier		29	30	31	32	33	34	35	36	37
Week		COD1	COW2	COW4	COW6	COW8	COW12	COW16	COW20	COW24/COEOT
Visit Window	4 weeks	±3 Days based on COD1 visit								
Investigational product accountability			X	X	X	X	X	X	X	X
Clinical assessments										
IGA		X	X	X	X	X	X	X	X	X
SALT		X	X	X	X	X	X	X	X	X
CCI ██████████		█	█	█	█	█	█	█	█	█
Photograph <sup>1</sup>		X		X		X	X	X	X	X
CCI ██████████		█	█	█	█	█	█	█	█	█
██████████		█	█	█	█	█	█	█	█	█
Pharmacokinetic										
Pre-dose PK <sup>v</sup>		X		X			X			X
Full PK <sup>w</sup>				X						X
CCI ██████████										
██████████		█		█			█			█
██████████		█		█			█			█
Other										
Prior and current concomitant Treatment(s)		→	→	→	→	→	→	→	→	→
Serious and non-serious adverse event monitoring		→	→	→	→	→	→	→	→	→
Contraception check		X	X	X	X	X	X	X	X	X

Protocol Activity	Follow- up Period		Early Termination Visit <sup>b</sup>
	38	39	
Visit Identifier	38	39	
Week	FU1 <sup>cc</sup>	EOS <sup>ff</sup>	ET
Visit Window			
<b>Medical procedures</b>			
Complete physical examination <sup>d</sup>		X	X
Targeted physical examination <sup>e</sup>	X		
Vital signs <sup>f</sup>	X	X	X
12-Lead ECG <sup>g</sup>			X
Weight <sup>h</sup>		X	
Audiogram <sup>i</sup>			X
<b>Laboratory</b>			
Hematology	X	X	X
Blood chemistry	X	X	X
Fasting lipid Panel <sup>k</sup>		X	X
Cystatin C (and eGFR) <sup>l</sup>	X	X	X
Urinalysis <sup>m</sup>	X	X	X
Urine pregnancy test (WOCBP) <sup>o</sup>	X	X	X
Viral Surveillance: EBV, CMV, HSV1, HSV2, and VZV			X
<b>Laboratory Pharmacodynamics</b>			
CCI [REDACTED]			
FACS-TBNK		X	X
CCI [REDACTED]			
[REDACTED]			
<b>Trial treatment</b>			
Investigational product accountability			X
<b>Clinical assessments</b>			
IGA	X	X	X
SALT	X	X	X
CCI [REDACTED]			
Photograph <sup>l</sup>		X	X

Protocol Activity	Follow- up Period		Early Termination Visit <sup>b</sup>
	38	39	
Visit Identifier	38	39	
Week	FU1 <sup>ee</sup>	EOS <sup>ff</sup>	ET
CCI			
Patient reported outcome			
CCI			
Pharmacokinetic			
PK <sup>w</sup>			X
CCI			
Other			
Prior and current concomitant Treatment(s)	→	X	X
Serious and non-serious adverse event monitoring	→	X	X
Contraception check	X	X	X
Lesional biopsy for cellular and molecular analyses <sup>y</sup>			X
PK <sup>w</sup>			X

Abbreviations: →= ongoing/continuous event; AA = alopecia areata; CCI; AT = Active Treatment; CCI CMV = Cytomegalovirus; CO = Cross-Over; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; ET = Early Termination; FACS = fluorescence-activated cell sorting; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; CCI HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; IG = Immunoglobulin; IGA = Investigator Global Assessment; IP10 = Interferon gamma-induced protein 10; CCI PHQ-8 = patient health questionnaire – 8 items; CCI SALT = Severity of Alopecia Tool; SBQ-R = Suicidal behaviors questionnaire –revised; TBNK = T, B, and NK cells; VZV = varicella zoster virus; WOCBP = women with childbearing potential; WONCBP = women of non-childbearing potential.

- a. Day relative to start of study treatment (Day 1).
- b. For subjects who discontinue early from the treatment period prior to Week 24 visit or subjects who discontinue early from the Single-Blind Extension Period prior to Week 52 Visit or AT Week 24 visit or subjects who discontinue early from the Cross-Over Open Label Extension Period prior to Cross-Over Week 24 Visit, the procedures scheduled for ET Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Subject will then enter into the Follow-up Period with their first follow-up visit occurring 1 week after their last dose whenever possible.
- c. Medical history and AA disease history includes detailed histories of conditions specified in Study Procedures [Section 7.3.2](#).

- d. Complete physical examination consists of general appearance, skin, head, eyes, ears, nose and throat (HEENT); mouth, heart, lungs, breast (optional), abdomen, external genitalia (optional), extremities, neurologic function, back, and lymph nodes. In addition, **dermatological full body exam** must be performed. Dermatological examinations should include visual inspection of the breasts and external genitalia.
- e. Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the subject.
- f. Vital signs should be performed before laboratory blood collection as specified in [Section 7.3.1](#).
- g. ECG should be performed before laboratory blood collection.
- h. Height and weight will be measured without shoes.
- i. Chest X-ray or other appropriate diagnostic imaging (ie, CT or MRI) may be performed within 12 weeks prior to Day 1. Official reading must be located in the source documentation.
- j. Audiogram testing may be performed within 8 weeks prior to Day 1. Audiogram for Screening must be completed for all subjects and results available prior to Day 1. Audiogram testing at Week 12 must be completed and results available by the Week 16 Visit. Audiogram testing at Week 24 must be completed and results available by the Week 28 Visit. For subjects who are assigned to the placebo group and meet retreatment criteria, audiogram testing must be completed and results available by the AT D1 Visit unless an audiogram testing has been performed within 8 weeks prior to AT D1 Visit. For Cross-Over Open Label Extension Period, audiogram testing must be completed and results available by the CO D1 Visit unless an audiogram testing has been performed within 8 weeks prior to CO D1 Visit. For subjects that terminate early from the study, efforts must be made to complete the audiogram testing and obtain the results.
- k. Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.
- l. Serum cystatin C will be measured and cystatin C based eGFR will be calculated.
- m. Urinalysis will be performed by the central laboratory. Dipstick in all cases; microscopy analysis is indicated if urinalysis is positive for blood, nitrite, leukocyte esterase and/or protein. Urine culture is performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.
- n. Serum pregnancy testing at screening is required for female subjects of childbearing potential. Follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months.
- o. Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential.
- p. Subjects who are positive for HIV will be screen-failed.
- q. Subjects who are HBsAg positive will be screen-failed. Subjects who are HBsAg negative but HBcAb positive will be reflex-tested for HBsAb and, if HBsAb positive, may enroll; if HBsAb negative, they will be screen-failed. Subjects who are positive for HCVAb will be screen-failed.
- r. A documented TB Interferon Gamma Release Assay (IGRA) test performed within 12 weeks prior to Day 1 is acceptable. Documentation of IGRA product used and the test result must be located in source documentation. Subjects with a history of tuberculosis will be screen-failed as per protocol [Section 7.3.6](#).
- s. Subjects should take the medication. Subjects will be encouraged to take the medication after breakfast whenever possible. However, at study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic.
- t. Photographs of treatment-eligible AA will be obtained at Screening to verify eligibility. Scalp areas photographed should be recorded in study documents so that the same scalp region(s) will be photographed. Photographs of **CCI** will also be taken. Additional photographs may also be taken at the investigator's discretion.

- C**  
**C**
- v. Blood sample for PK will be collected pre-dose at each visit as specified in SOA in Treatment Period and Cross-Over Open Label Extension Period. No PK samples are collected for Single-Blind Withdraw/Retreatment Extension Period.
- w. Blood samples for PK will also be collected at 0.5 hours post dose on Weeks 8 and 20; 0.5 and 1 hour on Week 12 during Treatment Period, and 0.5, 1, 2, and 4 hours post dose on Weeks 4 and 24 during Treatment Period and Cross-Over Open Label Extension Period. Blood sample for PK will be collected at early termination visit for subjects who discontinue early from the Treatment Period prior to Week 24 visit or during the Cross-Over Open Label Extension Period only if the most recent dose taken prior to ET visit was within 48 hours. No PK samples will be collected at ET visit for subjects who discontinue early from the Single-Blind Extension Period.

- C**  
**C**
- y. Biopsy samples will be collected only on subjects who provide consent to participate in the biopsy sub-study at selected biopsy sites. Biopsies of the lesional and non-lesional scalp (in subjects that have non-lesional scalp) will be obtained. Biopsies of the lesional scalp at ET visit will only be obtained for subject who discontinue early from the Treatment Period prior to Week 24 visit. No biopsies will be obtained at ET visit for subjects who discontinue early from the Extension Periods.
- z. Biopsy at Week 4 is optional.
- aa. 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. 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 are met and the audiogram result does not preclude patient's entrance in the Single-Blind Extension Period. Subjects who meet Exclusion #9, #10, or #26 will be discontinued and enter the Follow-up Period.
- bb. From Week 28, subjects who are assigned to active treatment group will receive the same respective active compound (PF-06651600 or PF-06700841), dose, and treatment duration as the original Treatment Period which consists of a 4-week induction period and a 20-week maintenance period, if any of the Exclusion criteria #9, #10, and #26 are not met and the audiogram result does not preclude patient's entrance. From Week 28, subjects who are assigned to the placebo group will receive placebo for up to 24 weeks until they meet the retreatment criteria.
- cc. For subjects who are assigned to the placebo group **and** meet the retreatment criteria, providing none of the Exclusion criteria #9, #10, and #26 are met and the audiogram result does not preclude patient's entrance in the Extension Period (audiogram result available within 8 weeks is acceptable).
- dd. Urine myoglobin will be measured at Screening, Week 28, and in case of CK >3x ULN during the study.
- ee. FU Visit 1 will occur 2 weeks after Cross-Over Week 24 Visit. For early terminated subjects from the initial treatment period or the Single-Blind Extension Period or the Cross-Over Open Label Extension Period, FU Visit 1 will occur 1 week after their last dose whenever possible.
- ff. End of Study Visit will occur 2 weeks after FU Visit 1.
- gg. 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 Extension Period as well as the non-responder criteria is met. Audiogram result available within 8 weeks is acceptable.

## 1. INTRODUCTION

### 1.1. Mechanism of Action/Indication

PF-06651600 is an orally bioavailable small molecule that inhibits irreversibly JAK3 with selectivity over the other three JAK isoforms, JAK1, JAK2 and TYK2. PF-06651600 also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, BMX, ITK, TEC, TXK), with high selectivity over the broader kinome. PF-06700841 is a dual inhibitor of human tyrosine-protein kinase 2 (TYK2) and Janus kinase 1 (JAK1). Both compounds will be investigated in patients with alopecia areata (AA).

### 1.2. Background and Rationale

#### 1.2.1. Drug Development Rationale

The JAK family, including JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function. Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK dimer combination to transduce their signal. JAK1 pairs with JAK3 to mediate  $\gamma$ -common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL) -2, -4, -5, -6, -12, -13, -15, -21, -23, -31, interferon gamma (IFN $\gamma$ ), and interferon alpha (IFN $\alpha$ ). Following cytokine activation, receptor-associated JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs.<sup>16</sup> Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription.<sup>18</sup>

The tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family consists of five members including TEC, Bruton's tyrosine kinase (BTK), bone marrow-expressed kinase (BMX), inducible T-cell kinase (ITK) and resting lymphocyte kinase (RLK/TXK), that are primarily expressed in hematopoietic cells. TEC kinases play an important role in antigen receptor signaling and BTK and ITK regulate the signal transduction pathways initiated by the activation of B cell receptor (BCR) and T cell receptor (TCR), respectively.<sup>31,27</sup>

PF-06651600 is an orally bioavailable small molecule that inhibits irreversibly JAK3 with selectivity over the other three JAK isoforms, JAK1, JAK2 and TYK2. PF-06651600 also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (BTK, BMX, ITK, TEC, TXK), with high selectivity over the broader kinome. PF-06651600 inhibits the cytotoxic function of CD8+ T cells and NK cells which have been implicated in the pathogenic process of AA.<sup>34,30</sup> This inhibition may be mediated through mechanisms dependent on JAK3 and TEC kinase family members.<sup>33,28,29</sup> PF-06651600 also potently inhibits signaling of the JAK3-dependent receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of AA.<sup>32</sup>



PF-06700841 is a dual TYK2/JAK1 inhibitor with a good selectivity profile over the other human kinases including JAK2. TYK2/JAK1 are critical signaling kinases that regulate the signal transduction pathways triggered by several cytokines implicated in the pathogenesis of AA, including IFN $\gamma$ , IL-2, IL-15, IL-12, and IL-23.<sup>4,25,6</sup>

### 1.2.2. Study Background

Alopecia areata is an autoimmune T-cell mediated disease characterized by non-scarring hair loss.<sup>5</sup> The disease includes the following forms: limited patchy hair loss (patchy alopecia areata), complete loss of hair on the scalp (alopecia totalis) and complete loss of hair on the scalp and the body (alopecia universalis). Even though the patches are well-circumscribed, short fragile hairs are often seen in the periphery of lesions. Nail changes are also seen in AA patients. Pruritus is sometimes reported in AA patients although the affected skin usually does not have signs of inflammation. Both males and females of all ages and races can be affected.<sup>9</sup> Alopecia areata is associated with immune diseases including asthma, allergic rhinitis, atopic dermatitis, thyroid disease, and autoimmune diseases such as thyroiditis and vitiligo.<sup>9</sup>

The complex pathophysiology of AA is still not completely understood. CD8<sup>+</sup> T cells, natural killer (NK) cells, and mast cells are involved in the pathogenesis of alopecia areata. The possible cytokine pathways of the disease include a role for cytokines from type 1 helper T cell (T<sub>H</sub>1) axis, including IL-1, IFN- $\gamma$  and interferon  $\gamma$ -induced protein 10 (IP-10) that take part in the hair follicle cycle and immune-privilege collapse. Mouse models have shown that IL-2 and IL-15 play a role in the initiation of auto-reactive CD8<sup>+</sup> cells. Recent studies have demonstrated AA signature with type 2 helper T cell (T<sub>H</sub>2), T<sub>H</sub>1, IL-23, and IL-9/T<sub>H</sub>9 cytokine activation in scalp lesions of patients with AA.<sup>24</sup>

To date, there is no cure for AA. Current treatment options are limited and include topical, intralesional, and systemic agents. Topical treatments usually have low efficacy and are not suitable for large areas or long-term use. Intralesional steroids are also not applicable for large areas. Healthcare providers have been using oral broad immunosuppressants including cyclosporine A, oral corticosteroids, mycophenolate mophetil, and azathioprine. None of these immunosuppressive medications have been approved by the regulatory agency(ies) for treatment for AA. The off-label use of immunosuppressive therapies is often associated with adverse events and side effect profiles that prevent their long-term use.<sup>4</sup> Spontaneous hair growth is rare in moderate to severe AA patients. The lack of effective treatments causes psychosocial distress with high prevalence rates of depression and anxiety in AA patients.<sup>1</sup> There is an unmet need for targeted therapy in patients with moderate to severe AA.

Recent studies have suggested potential utility of JAK inhibitors in the treatment of AA. Baricitinib, a JAK1/2 inhibitor, has reversed AA in a subject.<sup>11</sup> Treatment with ruxolitinib, a JAK1/2 inhibitor, resulted in hair regrowth in a patient with AA and vitiligo.<sup>7</sup> Tofacitinib, a pan JAK inhibitor, was reported to provide therapeutic effect in a patient with alopecia universalis.<sup>2</sup>

### **1.2.3. Non-Clinical Pharmacokinetics and Metabolism**

#### **1.2.3.1. Non-Clinical Pharmacokinetics and Metabolism of PF-06651600**

Following intravenous and oral administration of PF-06651600 to rats and dogs, absorption was rapid with high bioavailability in both species (approximately 85-100%). The high oral bioavailability indicated high absorption from the gut, consistent with its high in-vitro passive permeability properties. Plasma clearance (CL) was approximately 69 and 13 mL/min/kg in rat and dog respectively. Half-life was approximately 0.33 and 1.1 hour in rat and dog respectively. Systemic exposures of PF-06651600 as measured by maximum concentration ( $C_{max}$ ) and area under the concentration-time curve ( $AUC_{24}$ ) in repeat oral pivotal toxicology studies increased with increasing dose in rats (up to 400 mg/kg/day) and dogs (up to 45 mg/kg/day). Renal excretion of parent PF-06651600 was limited in the rat and dog. Biliary excretion of parent PF-06651600 was limited in the rat.

PF-06651600 binding to plasma proteins was approximately 10 to 30% across species (fraction unbound values for rat, dog, and human were 0.67, 0.82 and 0.86 respectively). In vitro and in vivo metabolite profiling suggested that the primary clearance mechanisms for PF-06651600 were cytochrome P450 mediated oxidation and glutathione related conjugation. No unique human metabolites were observed in vitro compared to metabolite profiles in rat and dog. Reaction phenotyping in recombinant enzyme systems identified CYP3A4 as the predominant CYP450 isoform responsible for the metabolism of PF-06651600, with minor contributions from CYP2C19 and CYP3A5. In addition, glutathione-S-transferase (GST) conjugate was formed in a time dependent manner in recombinant GST mu 1-1 and pi 1-1 incubations.

PF-06651600 showed a low risk of inhibition and induction of the major CYP450 enzymes as well as the major uridine 5'-diphospho-glucuronosyltransferase enzymes. However, in the presence of nicotinamide adenine dinucleotide phosphate, PF-06651600 showed evidence of time-dependent inhibition of CYP3A4. This CYP3A4 inhibition indicated a potential for pharmacokinetic drug interactions for which CYP3A constitutes the primary mechanism of clearance.

Please refer to the Investigator's Brochure (IB) for more details on the non-clinical pharmacokinetics and metabolism of PF-06651600.

#### **1.2.3.2. Non-Clinical Pharmacokinetics and Metabolism of PF-06700841**

The pharmacokinetic (PK) of PF-06700841 have been studied in rat where the compound has shown a plasma clearance of 31 mL/min/kg, a volume of distribution of 2.0 L/kg, and oral bioavailability of approximately 80-100%. The high oral bioavailability indicated high absorption from the gut, consistent with its high in-vitro passive permeability properties. Rat in vivo clearance was predicted within approximately 2-fold by both in vitro rat liver microsomes and hepatocyte intrinsic clearance highlighting the importance of CYP450 metabolism. Systemic exposures of PF-06700841 as measured by  $C_{max}$  and  $AUC_{24}$  in repeat oral pivotal toxicology studies increased with increasing dose in rats (up to 55 mg/kg/day) and monkeys (up to 45 mg/kg/day). Renal and biliary elimination of parent PF-06700841 was limited in rat.

Plasma protein binding of PF-06700841 was consistent across rat, monkey, and human with a fraction unbound (fu) of approximately 0.6-0.7. Values of fu were lower in mouse (fu = 0.51) and rabbit (fu = 0.36).

Oxidative metabolites of PF-06700841 accounted for the primary routes of biotransformation in rat, monkey, and human consistent with CYP450 as the primary clearance route. No unique human metabolites of PF-06700841 were evident compared to the safety species of rat and monkey.

Clearance phenotyping of PF-06700841 indicated that CYP3A4 will be the predominant mediator of human metabolism with minor contributions from CYP1A2, 2C19, and 2D6.

PF-06700841 showed a low risk of CYP450 inhibition and induction, UDP-glucuronosyltransferase (UGT) inhibition, OATP1B1/1B3 inhibition, and multi-drug resistance 1 (MDR1) inhibition. PF-06700841 showed some potential to inhibit metformin mediated transport by organic cation transporter 2 (OCT2) (IC<sub>50</sub>=1.1 µM), multidrug and toxin extrusion 1 (MATE1) (IC<sub>50</sub>=7.7 µM) and MATE2K (IC<sub>50</sub>=17 µM) in vitro. The respective unbound I<sub>max</sub>/IC<sub>50</sub> ratios are 0.65, 0.09, and 0.04 for a predicted 60 mg clinical dose of PF-06700841 (unbound C<sub>max</sub>=0.72 µM). SimCYP modeling indicated a low risk of drug-drug interactions (DDI) perpetrated by a 60 mg once daily (QD) dose of PF-06700841 (C<sub>max</sub>/AUC ratios 1.19/1.20).

## **1.2.4. Safety Data**

### **1.2.4.1. Non-Clinical Safety**

#### **1.2.4.1.1. Non-Clinical Safety of PF-06651600**

The nonclinical safety profile of PF-06651600 was characterized through the conduct of single- and repeat-dose studies of up to 6 months (rats) and 9 months (dogs) in duration, in vivo and in vitro safety pharmacology (neurofunctional, pulmonary, and cardiovascular), and in vivo and in vitro genetic toxicology studies. Dose range-finding and definitive embryo-fetal development studies in rats and rabbits were also conducted. In addition, an in vivo immunotoxicity study was done to characterize the risk for hypersensitivity, and phototoxicity was evaluated in rats. The no observed adverse effect level (NOAEL) in the 9-month toxicity study in dogs was 5 mg/kg/day, based on the finding of axonal dystrophy and associated auditory effects. In the 9-month study in dogs, an adverse, PF-06651600-related dose-dependent finding of bilateral axonal dystrophy was observed within the olivary nuclei of the brainstem of male and female dogs administered ≥20 mg/kg/day. Auditory testing (Brainstem Auditory Evoked Potential [BAEP]) testing performed on recovery control and high dose animals showed severe to mild hearing loss and waveform defects, with partial recovery in the histological lesions and functional auditory effects indicated at the end of the 3-month recovery period. The lowest observed adverse effect level (LOAEL) was 20 mg/kg/day. The data from the 9-month dog study represent the limiting exposure.

The current planned Phase 2 clinical study in AA include doses up to 200 mg QD (steady state unbound  $C_{\max}$  1078 ng/mL and  $AUC_{\text{last}}$  3192 ng•h/mL). Axonal dystrophy was not observed in the 8-week repeat dose dog study, and exposure at the NOAEL in the 8-week dog study was approximately 14x the predicted human exposure at the 4-week 200 mg clinical dose.

The most commonly observed findings in the repeat-dose toxicity studies were effects on bone marrow and the immune and hematolymphopoietic systems that were consistent with the known pharmacological activity of JAK inhibitors. Except at the high dose in the 9-month dog toxicity study, which was associated with signs indicative of infection, no adverse clinical signs, clinical pathology, or microscopic evidence of infection were observed in repeat dose toxicity studies, and effects related to the pharmacological activity of PF-06651600 were judged to be nonadverse.

PF-06651600 was not mutagenic but was aneugenic in assays in vitro. In vitro aneugenicity with kinase inhibitors is a common observation and is probably the consequence of off-target inhibition of kinases involved in cellular division.<sup>19</sup> PF-06651600 did not induce micronuclei in vivo in rats at exposures 18x and 42x, respectively, the predicted human unbound  $C_{\max}$  and area under the plasma concentration time curve from time zero extrapolated to the last quantifiable concentration ( $AUC_{\text{last}}$ ) values at the highest dose of 200 mg once daily (QD) in planned Phase 2 studies.

PF-06651600 is a covalent inhibitor of JAK3 and an integrated assessment of its potential to induce hypersensitivity and/or nonspecific toxicity reactions resulting from covalent interactions with other proteins was conducted. The nonspecific reactivity potential of PF-06651600 was evaluated by assessing CYS containing kinase selectivity, human serum albumin binding, human hepatocyte recovery, and the modified mouse allergy model for hypersensitivity. These assessments demonstrated a high level of specificity for the JAK3 enzyme, minimal covalent binding to serum albumin, high recovery following human hepatocyte incubations (ie, minimal persistent binding to hepatocytes), and no evidence of hypersensitivity response in the modified mouse allergy model.

In an embryo-fetal development study in rats, the maternal NOAEL was 175 mg/kg/day. Skeletal malformations and variations, and lower fetal body weights occurred at 175 and 325 mg/kg/day. The exposure margins at the developmental NOAEL of 75 mg/kg/day were 7.2x and 5.3x, respectively, the predicted steady state human unbound  $C_{\max}$  (1078 ng/mL) and  $AUC_{\text{last}}$  (3192 ng•h/mL) values at the highest daily dose of 200 mg in planned Phase 2 studies. In an embryo-fetal development study in rabbits, lower mean fetal body weights and higher incidences of visceral and skeletal malformations and skeletal variations were observed at 75 mg/kg/day. The exposure margins at the developmental NOAEL of 25 mg/kg/day in rabbits were 4.1x the predicted steady state human unbound  $C_{\max}$  (1078 ng/mL) and  $AUC_{\text{last}}$  (3192 ng•h/mL) values at the highest daily dose of 200 mg in planned Phase 2 studies. Please refer to [Section 4.4.1](#) on the contraception requirements for participation in this study.

There was no evidence of cutaneous or ocular phototoxicity following oral administration to rats for 3 days at doses up to 200 mg/kg/day.

In summary, the nonclinical safety profile of PF-06651600 has been adequately characterized to support progression into this Phase 2 study. Adequate safety margins based on planned maximum doses and predicted exposures in patients were determined for effects observed in nonclinical studies.

Please refer to the IB for more details on the non-clinical information with PF-06651600.

#### **1.2.4.1.2. Non-Clinical Safety of PF-06700841**

PF-06700841 was evaluated in single-dose and repeat-dose toxicity studies up to 6 months (rats) and 9 months (monkeys) in duration. Dose range-finding and pivotal embryo-fetal development studies (EFD) were conducted with PF-06700841 in rats and rabbits. Target organs identified with PF-06700841 administration in rats and cynomolgus monkeys include the immune and hemolymphatic systems (thymus, spleen, lymph nodes, and bone marrow), gastrointestinal tract (body weight and weight gain effects), and adrenal gland (vacuolation). The findings in the thymus, spleen, lymph nodes, and bone marrow are consistent with the pharmacological activity of PF-06700841 and were not adverse because they were not associated with adverse clinical signs or adverse changes in hematology parameters, and there was no evidence of test article-related infections in these animals. Gastrointestinal and adrenal effects were not adverse because they were either transient, of small magnitude and/or severity, and/or lacked associated tissue injury or inflammation, or changes in clinical pathology parameters. In addition, there were inconsistent findings in the bone, liver, lung and prostate where the relationship to PF-06700841 is less clear. Adverse findings in the central nervous system (decreased activity, mortality, prostration, convulsions) were observed at high exposures in pregnant rabbits, and emesis was observed in monkeys at high doses in studies  $\leq 1$  month in duration. In safety pharmacology assessments PF-06700841-related effects were observed in the cardiovascular system (blood pressure, heart rate, QTc interval) and central nervous system (decreased locomotor activity). Based on the lack of adverse findings at any dose, the NOAELs in the 6-month rat and 9-month monkey studies were 45 mg/kg/day in rats and 20 mg/kg in cynomolgus monkeys. Exposures at these doses were 6.2x to 40x the predicted efficacious human exposure ( $C_{max}=218$  ng/mL and  $AUC_{24}=1730$  ng•h/mL) from a 50 mg dose.

In the pivotal EFD study in rats, there were no PF-06700841-related maternal effects. However, higher incidences of fetal skeletal malformations (in long bones, scapulae, sternbrae or palatine bones) and variations (in the ribs, cervical vertebrae or sternbrae) occurred at  $\geq 2$  mg/kg/day, and delays in the ossification of the axial and appendicular skeleton occurred at 15 mg/kg/day. In addition, lower embryo-fetal viability; lower mean fetal body weights, external malformations (cleft palate) and variations (whole body subcutaneous edema or edematous neck) occurred at 15 mg/kg/day. The maternal NOAEL in rats was 15 mg/kg/day (13x and 11x the predicted efficacious human  $C_{max}$  and  $AUC_{24}$  exposure from a 50 mg dose) and the developmental NOAEL was not determined but was  $< 2$  mg/kg/day, the lowest dose tested (2.2x and 1.3x the predicted efficacious human  $C_{max}$  and  $AUC_{24}$  exposure from a 50 mg dose). In the pivotal EFD study in rabbits, there were no

PF-06700841-related maternal effects. However, test article-related higher incidences of late resorptions and post-implantation loss occurred at  $\geq 3$  mg/kg/day and lower mean numbers of viable fetuses occurred at 7 mg/kg/day. Test article-related skeletal variations were observed at  $\geq 3$  mg/kg/day, but were not adverse because most of these findings represent delays in ossification that would resolve with further growth and development. The maternal NOAEL in rabbits was 7 mg/kg/day, the highest dose tested, (6.6x and 3.2x the predicted efficacious human  $C_{max}$  and  $AUC_{24}$  exposure from a 50 mg dose) and the developmental NOAEL was 1 mg/kg/day (0.8x and 0.4x the predicted efficacious human  $C_{max}$  and  $AUC_{24}$  exposure from a 50 mg dose). Please refer to [Section 4.4.1](#) on the contraception requirements for participation in this study.

PF-06700841 was negative for mutagenicity in the bacterial reverse mutation assays. Although PF-06700841 was positive in the in vitro micronucleus assays in both CHO and TK6 cells, and was aneugenic in vitro (at 72,100 nM), it did not induce micronuclei, in vivo, in reticulocytes in the 1-month study in rats (at exposures 35x to 51x the predicted human efficacious exposure (unbound  $C_{max}$ =218 ng/mL and  $AUC_{24}$ =1730 ng•h/mL) from a 50 mg dose.

Although PF-06700841 absorbs in the ultraviolet A (UVA) and ultraviolet B (UVB) range, PF-06700841 ( $\leq 100$  mg/kg/day [unbound  $C_{max}$  and  $AUC_{24}$  were 46x and 82x the predicted efficacious human exposure from a 50 mg dose]) had no evidence of phototoxicity in the skin or eyes of pigmented Long Evans rats in a 3-day phototoxicity study. This demonstrates that PF-06700841 was not a phototoxicant, in vivo.

In summary, the nonclinical studies adequately support the planned clinical trials with PF-06700841.

Please refer to the IB for more details on the nonclinical information with PF-06700841.

#### **1.2.4.2. Clinical Experience**

##### **1.2.4.2.1. Clinical Experience with PF-06651600**

As of April 27, 2016, 74 subjects have received at least one active dose of oral PF-06651600. This accounts for 60 subjects from the first-in-human (FIH) B7981001 study who received active solution and 14 subjects from the bioavailability (BA) B7981003 study who received solution/tablet.

The FIH study is a Phase 1, randomized, double blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult subjects. During the single dose period, subjects received doses of 5, 20, 50, 100, 200, 400, or 800 mg of PF-06651600 in a dose escalation format. Subjects returned for the multiple dose periods to receive doses of 50, 200, or 400 mg QD or 100 or 200 mg twice a day (BID) for 14 days.

### 1.2.4.2.1.1. Clinical Safety Experience with PF-06651600

Eighty (80) subjects were enrolled into the FIH study. Single doses up to 800 mg and multiple doses up to 400 mg daily, as both 400 mg QD and 200 mg BID were administered. PF-06651600 appears to be generally safe and well-tolerated. No clinically significant changes in vital signs, electrocardiogram or laboratory data were observed. No dose limiting adverse events were reported and no subjects met the protocol prescribed individual stopping rules. There were no deaths in the study.

The most commonly reported all causality treatment emergent adverse events (TEAEs) across both single ascending dose (SAD) and multiple ascending dose (MAD) PF-06651600 cohorts were gastrointestinal (GI) disorders including diarrhea (9 subjects), abdominal pain (6 subjects), abdominal discomfort (2 subjects), and flatulence (3 subjects). Change of bowel habit, constipation, fecal volume increased, discolored feces, nausea, paresthesia oral, and vomiting have each also been reported (1 subject each event). All cases were mild in severity with the exception of 1 moderate TEAE each of abdominal pain, dysphagia, and vomiting.

Skin and subcutaneous tissue disorders including, but not limited to rash, maculopapular rash, dermatitis acneiform, and erythema of mild to severe intensity were reported in the PF-06651600 cohorts and are summarized in Table 1 below. There were no skin and subcutaneous tissue disorders reported in the 5, 20, 50, 200, 400, and 800 single dose cohorts; nor were there any skin and subcutaneous tissue disorders reported in the 50 mg QD multiple dose cohort.

**Table 1. Skin and Subcutaneous Tissue Disorder Occurrence**

N= # of subjects	SAD 50 mg N=8		SAD 100 mg N=8		MAD 100 mg BID N=8		MAD 200 mg QD N=8		SAD 400 mg N=16		MAD 400 mg QD N=24		MAD 200 mg BID N=8	
	A	P	A	P	A	P	A	P	A	P	A	P	A	P
Acne	0	0	0	0	0	0	0	0	0	0	2*	1*	0	0
Dermatitis acneiform	0	0	0	0	2*	0	0	0	0	0	0	0	1*	0
Dry Skin	0	1**	0	0	0	0	0	0	0	0	2*	1*	0	0
Eczema	0	0	0	0	0	0	0	0	0	0	0	1*	0	0
Erythema	0	0	0	0	1*	0	2*	1*	0	1*	1*	0	1**	0
Rash	0	0	1*	0	0	0	0	0	0	0	1*	0	0	0
Rash macular	0	0	1*	0	0	0	0	0	0	0	3*	0	0	0
Rash maculopapular	0	0	1**	0	1**	0	0	0	0	0	0	0	2 (1**/ 1***)	0
Rash pruritic	0	0	0	0	0	0	0	0	0	0	0	0	1**	0
Seborrhoeic dermatitis	0	0	0	0	1*	0	0	0	0	0	0	0	0	0
Skin induration	0	0	0	0	0	0	0	0	0	0	0	0	0	1*

Abbreviations: A = active, P = placebo.

\*- Mild \*\*- Moderate \*\*\*- Severe

Three (3) serious adverse events (SAEs) were reported in the FIH trial.

The first event was a cutaneous abscess on the left buttock during the 200 mg single dose period in a subject who entered the study with a pre-existing boil on the left buttock. This was assessed 19 days after the single dose was administered and was considered related to the study drug. The subject was discontinued from treatment. The SAE criterion was met as the incision and drainage procedure was performed in a hospital setting.

The second SAE was a sacrococcygeal cyst/pilonidal sinus abscess during the 400 mg single dose period. This was assessed 19 days after the single dose was administered and was considered related to the study drug. The SAE criterion was met as the incision and drainage procedure was performed in a hospital setting.

The third SAE was a varicella infection during the 400 mg QD MAD dose period. The start date was 11 days after the last dose and was considered related to the study drug. The source of the infection is unknown; however, a second subject, who had a reactivation of varicella zoster, may be the source as the subjects were confined during the same time. The varicella infection resolved in 51 days.

Please refer to the IB for more details on the clinical safety information with PF-06651600.

#### 1.2.4.2.1.2. Clinical Pharmacokinetics Experience with PF-06651600

The PK parameters from the 5, 20, 50, 100, 200, 400 and 800 mg single dose levels are summarized below in Table 2. In general, PF-06651600 area under the plasma concentration-time curve from time zero to infinity ( $AUC_{inf}$ ) increased in a dose related manner over the 5 to 800 mg dose range with a slightly greater than proportional increase observed over the 200 mg to 400 mg dose range.  $C_{max}$  increased with dose in an apparent dose proportional manner.

CCI [REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]





CL/F = apparent total body clearance;  $V_z/F$  = apparent volume of distribution;  $Ae_\tau\%$  = Percent of dose recovered unchanged in urine over the dosing interval  $\tau$ ; CL<sub>r</sub> = Renal clearance.

Urinary recovery of PF-06651600 was low, with approximately <8% of the dose recovered unchanged in urine on Day 14 across all doses (geometric mean  $Ae_\tau\%$  of 4.1% to 7.0%). Renal clearance ranged from 42.9 mL/min to 63.1 mL/min.

CCI



#### **1.2.4.2.1.3. Phase 2 Studies Safety Data**

PF-06651600 is currently being investigated in patients with rheumatoid arthritis, alopecia areata, ulcerative colitis, and Crohn's disease.

Further details of the Phase 2 programs are provided in the IB.

#### **1.2.4.2.2. Clinical Experience with PF-06700841**

The B7931001 FIH study is the single clinical trial of PF-06700841 completed to date. Of the 96 subjects randomized, 74 subjects have received at least one active dose of oral PF-06700841 in study B7931001. This accounts for 41 healthy subjects who participated in the single and multiple ascending dose period of the trial who received active solution/suspension, 12 healthy subjects from the BA study who received suspension/tablet, and 21 subjects with chronic plaque psoriasis who were randomized to receive active solution/suspension over a 28 day treatment period.

The FIH study was a Phase 1, randomized, double blind, third party open, placebo controlled, single and multiple dose escalation, parallel group study in healthy adult subjects and subjects with plaque psoriasis, with a relative bioavailability and food effect assessment of a tablet formulation of PF-06700841 in healthy adult subjects. During the SAD period, 41 healthy subjects received doses of 1, 3, 10, 30, 100, or 200 mg of PF-06700841 in a dose escalation format. Twenty-one healthy subjects received doses of 10, 30, 100, or 175 mg QD for 10 days during the MAD period. Subjects participating in the 100 mg multiple dose cohort returned for a third period to receive 50 mg PF-06700841 BID for 10 days. Thirty subjects with moderate to severe chronic plaque psoriasis were also randomized into study B7931001, to receive once daily placebo (n=9), 30 mg (n=14), or 100 mg (n=7) PF-06700841 for 28 days, and underwent safety monitoring and clinical efficacy assessments. An additional healthy volunteer cohort was included to support the evaluation of the relative BA of a tablet formulation of PF-06700841, and assessment of a high fat meal on tablet BA. Twelve healthy subjects participated in this BA assessment, and received single doses of open label PF-06700841 in a 3-way cross over design (PF-0670841 tablet

fasted, PF-06700841 solution/suspension fasted, and PF-06700841 tablet under fed conditions).

#### **1.2.4.2.2.1. Clinical Safety Experience with PF-06700841**

PF-06700841 was generally safe and well tolerated in the Phase 1 clinical study B7931001, which included both healthy subjects (n=66 randomized) and subjects with plaque psoriasis (n=30 randomized). There were no deaths in the study, no serious adverse events, and no severe adverse events. Subjects reported 11 TEAEs in the SAD phase, 22 TEAEs in the MAD phase, 39 TEAEs in the psoriasis phase, and 3 TEAEs in the BA phase. All AEs were mild or moderate in severity. Dose escalation stopping rules were not triggered at any dose level.

The most commonly reported all causality TEAEs across active subjects in both SAD and MAD cohorts were blood creatinine increased (reported in 2 subjects during the SAD period and 11 subjects during the MAD period), and neutropenia/neutrophil count decreased (reported in 4 subjects during the MAD period), which belong to the System Organ Class (SOC) categories of Investigations and Blood and Lymphatic System Disorders, respectively.

During the SAD/MAD, the AEs of blood creatinine increased were reported across dose levels from 10 mg up to 200 mg of PF-06700841, and occurred with greatest frequency in the 175 mg QD and 50 mg BID MAD cohorts. Neutropenia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3) occurred at the 175 mg QD and 50 mg BID dose levels during the MAD period. All laboratory abnormalities reported as AEs were mild in severity, except for one case of neutropenia which was reported as moderate in severity (Grade 3 neutropenia). No neutrophil counts reached, or fell below 500 cells/mm<sup>3</sup>.

Other commonly reported all causality TEAEs during the SAD/MAD by SOC were Nervous System Disorders (2 events of headache and 1 event each of dizziness and presyncope during the SAD period, and 1 event each of headache, presyncope, and syncope reported during the MAD period), and Infections and Infestations (upper respiratory tract infection reported in 2 subjects during the MAD period). The AEs of upper respiratory tract infection were reported in 1 subject who received 10 mg PF-06700841 QD and 1 subject who received 100 mg PF-06700841 QD. These infections did not require antibiotic therapy (1 subject received symptomatic treatment), and did not require study treatment discontinuation.

The most commonly reported all causality TEAEs across active subjects in the psoriasis cohorts treated with either 30 mg or 100 mg PF-06700841 were blood creatinine increased (reported in 7 subjects in the 30 mg dose group and 6 subjects in the 100 mg dose group), neutrophil count decreased ( reported in 1 subject in the 30 mg dose group and 1 subject in the 100 mg dose group), which belong in the SOC category of Investigations.

Other commonly reported AEs by SOC in the psoriasis cohorts included Nervous System Disorders (headache reported in 1 subject in the 30 mg dose group and 1 subject in the 100 mg dose group, and paresthesia reported in 1 subject in the 100 mg dose group), Gastrointestinal Disorders (constipation reported in 3 subjects in the 30 mg dose group), and

Infections and Infestations (1 report of upper respiratory tract infection and 1 report of herpes zoster infection, both in the 100 mg dose group).

The AE of herpes zoster occurred in a single subject after completing 28-day treatment with PF-06700841 at the 100 mg QD dose level. The subject had non-disseminated, herpetiform rash on the upper left back and left arm that was reported to have presented on Study Day 30 (2 days after the last dose of PF-06700841). The AE was mild in severity and was treated with acyclovir and Vicodin by the Investigator.

In the BA cohort, the SOCs with subjects reporting AEs were Gastrointestinal Disorders, Injury, Poisoning, and Procedural Complications, and Nervous System Disorders, each reported by 1 subject. The reported AEs were nausea, contusion, and headache, each of which was experienced by 1 subject. Subjects in the PF-06700841 100 mg oral solution/suspension fasted group reported treatment-related TEAE each of nausea and headache. All TEAEs were mild in severity.

Despite the AEs of blood creatinine increased observed in the healthy subjects (n=13 in the SAD/MAD cohorts) and psoriasis patients (n=13), the review of clinical laboratory parameters from study B7931001 confirmed there have been no noted clinically meaningful changes in the blood urea nitrogen, serum electrolytes, urinalysis, or cystatin-c based estimated glomerular filtration rate (eGFR) in subjects with elevated serum creatinine.

Serum creatinine is primarily filtered by the kidney however; approximately 10-20% is actively secreted into the renal proximal tubules. The active tubular secretion is mediated by transporters such as OCT2, organic anion transporter 2 (OAT2), and MATEs. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport (ie, transporter-mediated rather than direct nephrotoxicity), and is based on PF-06700841 potential to inhibit OCT2 creatinine transporter ( $IC_{50}=1.1 \mu M$ ; unbound  $I_{max}/IC_{50}$  ratio=0.25). To differentiate from direct nephrotoxicity, the B7931001 protocol was amended (Protocol Amendment 2) to include collection of serum cystatin C. Serum cystatin C was used to calculate eGFR in order to monitor for nephrotoxicity during the trial. Elevated serum creatinine in the absence of clinically meaningful changes in serum cystatin C based estimates of GFR during study B7931001 supports the transporter inhibition hypothesis. Following the implementation of cystatin C-based kidney safety monitoring, no subjects were discontinued from treatment/study due to renal concerns.

Proof of mechanism was achieved in study B7931001. CCI



Please refer to the IB for more details on the clinical safety information with PF-06700841.





The total sample size for the study is computed to be approximately 132 randomized.

The dose selection strategy was designed to balance pharmacology and safety. A global PK model for each asset was developed using the data from the FIH studies for PF-06651600 (Protocol B7981001) and PF-06700841 (Protocol B7931001), respectively. Pharmacokinetic was assumed to be similar between healthy subjects and subjects with AA. The activity of the JAK inhibitors was assessed by measurement of various PD markers and markers of safety that were collected in the FIH studies and analyzed using indirect response modeling. The magnitude of change in these markers required for efficacy and/or safety is poorly understood.

By including two investigational drugs in a single study, the placebo group can be shared by both, resulting in fewer subjects being exposed to placebo and smaller overall study size. The inclusion of these two investigational drugs is appropriate as the target population for both is identical as are the efficacy outcome measures. The current non-clinical toxicology packages for both PF-06651600 and PF-06700841 support the treatment duration.

By including a 4-week induction period and a 20-week maintenance period, this 24-week treatment study will determine the clinically relevant efficacy and safety of PF-06651600 and PF-06700841 in patients with moderate to severe AA. The biopsy sub-study will establish the effects of JAK3 and TYK2/JAK1 suppression on modulation of immune pathways involved in AA.

In the PF-06700841 FIH study B7931001, serum creatinine elevation was reported across dose levels in healthy volunteer and psoriasis patients ([Section 1.2.4.2.2.1](#)) but the review of clinical laboratory parameters confirmed there have been no noted clinically meaningful changes in the blood urea nitrogen, serum electrolytes, urinalysis, or cystatin-c based eGFR in the subjects with elevated serum creatinine. In order to monitor for any potential cases of decreased eGFR during this trial serum cystatin C will be collected to calculate eGFR in addition to serum creatinine.

Currently there is no medications approved for treatment for AA. The two Extension Periods will provide an opportunity for subjects to receive additional active study treatment and active treatment with different MOA.

This study includes a Single-Blind Extension Period to evaluate additional safety and tolerability of PF-06651600 and PF-06700841. After the 4-week Drug Holiday #1, subjects who complete the initial 24 weeks of the protocol may enter the up to 12 months Single-Blind Extension Period. Subjects who discontinue prior to Week 24 will enter the Follow Up period and will not be eligible for the Single-Blind Extension Period.

The study includes a Cross-Over Open Label Extension Period to evaluate the safety and tolerability of PF-06651600 and PF-06700841 for initial non-responders to either active treatment who will receive the opposite active treatment. Subjects who complete the segment for non-responders in Single-Blind Extension Period may be evaluated for potential entry into the Cross-Over Open Label Extension Period and receive opposite active treatment. Subjects who discontinue prior to Week 52 will enter the Follow Up period and

will not be eligible for the Cross-Over Open Label Extension Period. Subjects who complete the Withdrawal/Retreatment segment for responder in Single-Blind Extension Period will go directly to the 4-week Follow-up Period. After the 4-week Drug Holiday #2, the 6-month Cross-Over Open Label Extension Period is followed by a 4-week Follow-up Period.

### 1.2.5.1. PF-06651600 Dose Rationale

The predicted total PK parameters for PF-06651600 based on simulations using the global PK model are provided in Table 6.

**Table 6. Summary of Predicted Steady State Plasma PF-06651600 Pharmacokinetic and Pharmacodynamic Parameters**

Dose mg QD	Total C <sub>max</sub> ng/mL	Predicted C <sub>max</sub> Margins <sup>a</sup>	Total AUC <sub>tau</sub> ng·hr/mL	Predicted AUC Margins <sup>a</sup>	% Reduction from Baseline IP-10
<b>Induction Treatment Period</b>					
200	1254 (2.1)	12	3712 (14)	14	42 (19)
<b>Maintenance Treatment Period</b>					
50	259.5 (3.4)	5 <sup>b</sup>	662.0 (20)	7 <sup>b</sup>	18 (39)
<p>AUC<sub>tau</sub> = Area under the concentration-time curve from zero to 24 hours postdose at steady state; C<sub>max</sub> = Peak plasma concentration; QD = Once daily; ( ) = Coefficient of variation expressed as a percent; human unbound fraction (fu) = 0.86; 1 ng/mL = 3.504 nM.</p> <p>a. <u>Induction treatment period</u>: NOAEL-highest dose in dogs, 45 mg/kg/day; Week 8 mean male and female C<sub>max</sub> (free) = 12,000 ng/mL; C<sub>max</sub> (total) = 14,634 ng/mL; AUC<sub>tau</sub> (free) = 44,100 ng·h/mL; AUC<sub>tau</sub> (total) = 53,780 ng·h/mL.</p> <p>b. <u>Maintenance treatment period</u>: 9 month oral dog NOAEL-5 mg/kg; mean male and female C<sub>max</sub>(free) = 1115 ng/mL; C<sub>max</sub> (total) = 1297 ng/mL; AUC<sub>tau</sub> (free) = 4018 ng·h/mL; AUC<sub>tau</sub> (total) = 4672 ng·h/mL, dog (fu) = 0.82.</p>					

The induction dosing period (4 weeks) is supported by the nonclinical safety profile of PF-06651600 in dogs in a trial of 8 weeks duration. The margins during the induction period are based on the NOEAL exposure from the highest dose (45 mg/kg). The NOAEL in the 9-month toxicity study in dogs was 5 mg/kg/day, based on the finding of axonal dystrophy and associated auditory effects. The lowest observed adverse effect level (LOAEL) was 20 mg/kg/day. Thus, the data from the 9-month dog study represent the limiting exposure for chronic dosing.

The predicted exposure during the induction treatment period at the top dose of 200 mg QD for 4 weeks is projected to maintain 12- and 14-fold safety margins for C<sub>max</sub> and AUC<sub>tau</sub>, respectively. During the maintenance treatment period the 50 mg dose administered QD for 20 weeks is projected to maintain safety margin for C<sub>max</sub> and AUC<sub>tau</sub> of 5- and 7-fold, respectively.



PF-06651600 inhibits signaling of the common- $\gamma$  chain receptors for IL-15 and IL-21, which have been implicated in the pathogenic pathways of AA. In lymphocytes, PF-06651600 inhibited JAK1/JAK3-dependent STAT5 and STAT3 phosphorylation by IL-15 and IL-21 respectively, with  $IC_{50}$ s of 56.5 ng/mL and 103 ng/mL, respectively. All other pathways were inhibited at  $IC_{50}$ s >5708 ng/mL. There is evidence of modulation of IP-10 a marker related to IFN- $\gamma$ .

The predicted in vitro average percent inhibition of IL-15 and IL-21 signaling in human whole blood based on human PK for the selected dosing period is provided in Table 7.

**Table 7. Summary of the Predicted In Vitro Average Percent Signaling Inhibition Based on Steady State Pharmacokinetics of PF-06651600**

Cytokine	Average Percent Signaling Inhibition	
	50 mg	200 mg
IL-15	44	81
IL-21	30	71

Pharmacological modulation of the target can be inferred from the predictions in Table 7.

#### 1.2.5.2. PF-06700841 Dose Rationale

The predicted total PK parameters for PF-06700841 based on simulations using the global PK model are provided in Table 8.

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]	[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]	[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]

The predicted exposure during the loading treatment period for PF-06700841 at the top dose of 60 mg QD for 4 weeks is projected to maintain 7.2- and 3.9-fold safety margins for  $C_{max}$  and  $AUC_{tau}$ , respectively. During the stable dosing treatment period the 30 mg dose administered QD for 20 weeks is projected to maintain safety margin for  $C_{max}$  and  $AUC_{tau}$  of 15- and 9.3-fold, respectively.

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[REDACTED] were measured in healthy subjects. Based on indirect response modeling, the predicted percent reductions in the CCI [REDACTED]. Similarly, the predicted reduction of IP-10 levels was 47% and 51%, respectively for 30 and 60 mg QD. The predicted maximum percent reduction in neutrophils and reticulocytes was 32% and 50%, respectively during the induction period and 30% and 36%, during the chronic dosing period.

Subjects with moderate to severe psoriasis received doses of 30 mg or 100 mg QD or placebo for 28 days (B7931001). Significant psoriasis disease modification as measured by placebo adjusted psoriasis area and severity index (PASI) change from baseline (mean change from baseline >-9 at 30 mg and mean change from baseline >-11 at 100 mg) was observed in the patients.

Overall, the doses selected in this study are expected to demonstrate clinically relevant efficacy in subjects with AA.

#### 1.2.6. Summary of Benefits and Risks

Overall, the safety profile observed during the Phase 1 program for PF-06651600 appears to be acceptable at dosages up to 200 mg administered orally. The safety profile observed during the Phase 1 program for PF-06700841 appears to be acceptable at dosages up to 175 mg administered orally.

Additional information for these compounds may be found in the single reference safety document (SRSD), which for this study are the IBs of PF-06651600 and PF-06700841.

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[REDACTED]

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[REDACTED]

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Study Objectives and Endpoints During Treatment Period

<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Primary Endpoint:</b></p> <ul style="list-style-type: none"> <li>Change from baseline of Severity of Alopecia Tool (SALT) score at Week 24.</li> </ul>
<p><b>Secondary Objectives:</b></p> <p><b>Key Secondary Efficacy Objective:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Secondary Endpoints:</b></p> <p><b>Key Secondary Efficacy Endpoint:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at Week 24.</li> </ul>
<p><b>Other Secondary Efficacy Objectives:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Other Secondary Efficacy Endpoints:</b></p> <ul style="list-style-type: none"> <li>Change from baseline in Investigator Global Assessment (IGA) at all time points up to Week 24 as specified in the <a href="#">Schedule of Activities (SoA)</a>.</li> <li>Change from baseline in SALT at intermediate time points up to Week 24 as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving a 30% improvement in SALT (SALT 30) at intermediate time points up to Week 24 as specified in the <a href="#">SoA</a> except for Week 24.</li> <li>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 <a href="#">SoA</a>.</li> <li>Percentage change in SALT from baseline to Week 24 at intermediate time points as specified in the <a href="#">SoA</a>.</li> </ul>
<p><b>Safety Objectives:</b></p> <ul style="list-style-type: none"> <li>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.</li> </ul>	<p><b>Safety Endpoints:</b></p> <ul style="list-style-type: none"> <li>Incidence of treatment-emergent adverse events (AEs) up to Week 24.</li> <li>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.</li> </ul>
<p>CCI [REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

	<ul style="list-style-type: none"><li>• C</li><li>C</li><li>I</li></ul>	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

## 2.2. Study Objectives and Endpoints during Single-Blind Extension Period

Primary Objective:	Primary Endpoint:
<ul style="list-style-type: none"> <li>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.</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of treatment-emergent adverse events (AEs) during the Single-Blind Extension Period.</li> <li>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.</li> </ul>
<p>CCI</p>	
<p>█</p>	<ul style="list-style-type: none"> <li>Change from baseline in SALT during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving SALT 30 during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> <li>Proportion of subjects achieving SALT 50, SALT 75, SALT 100 during the Single-Blind Extension Period at all time points as specified in the <a href="#">SoA</a>.</li> </ul> <p>CCI</p> <ul style="list-style-type: none"> <li>Time to achieve the retreatment criteria during the Withdrawal/Retreatment part of the Extension Period among subjects who achieved primary endpoint at Week 24.</li> </ul>
<p>CCI</p>	<p>█</p> <p>█</p>
<p>█</p>	<p>█</p>

<p>• C C I</p> <p>[Redacted]</p>	<p>[Redacted]</p> <p>[Redacted]</p> <p>[Redacted]</p>
<p>[Redacted]</p>	<p>[Redacted]</p>
<p>[Redacted]</p>	<p>[Redacted]</p> <p>[Redacted]</p>

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

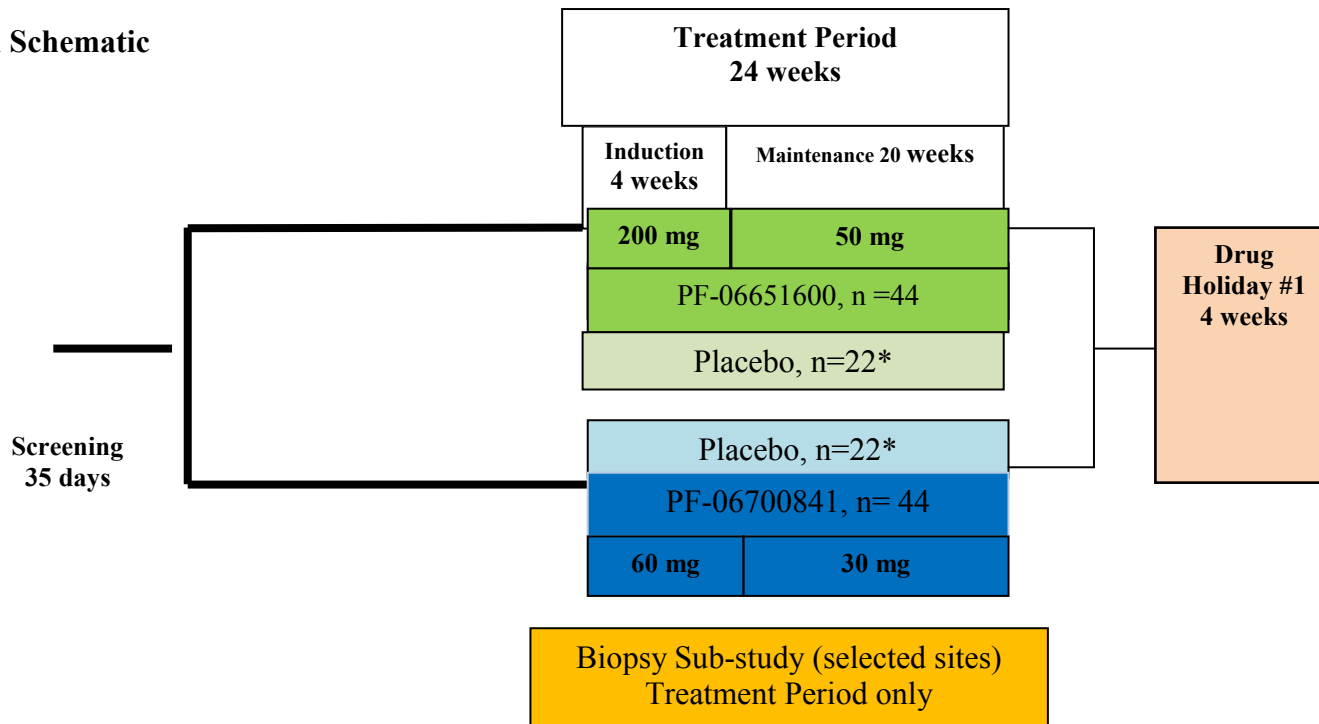
Primary Objective:	Primary Endpoint:
<ul style="list-style-type: none"><li>To evaluate the safety and tolerability of PF-06651600 and PF-06700841 over time in subjects who are non-responders to PF-06700841 and PF-06651600, respectively, during the Cross-Over Open Label Extension Period.</li></ul>	<ul style="list-style-type: none"><li>Incidence of treatment-emergent adverse events (AEs) during the Cross-Over Open Label Extension Period.</li><li>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.</li></ul>
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[Redacted]	[Redacted]
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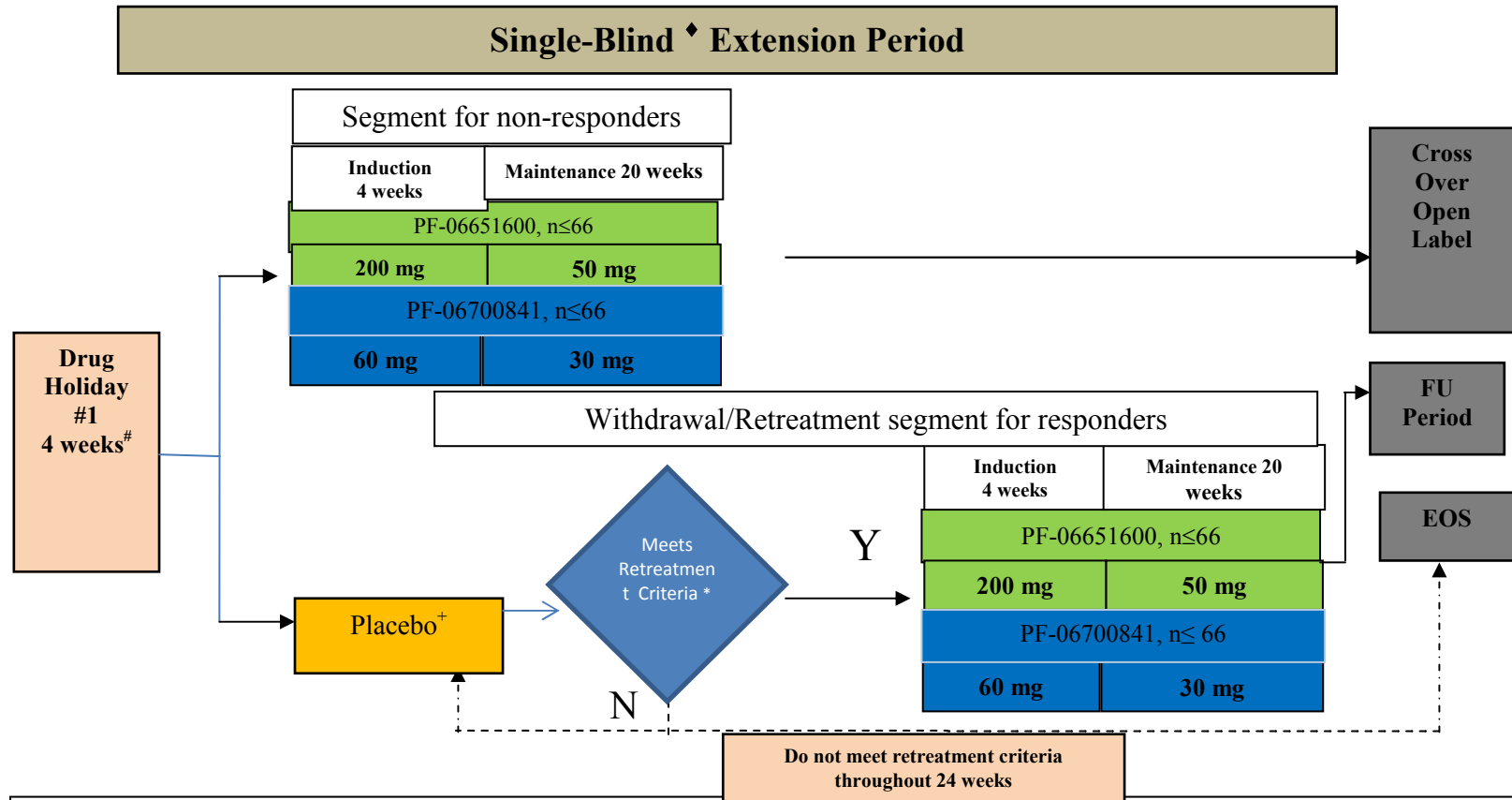


### 3. STUDY DESIGN

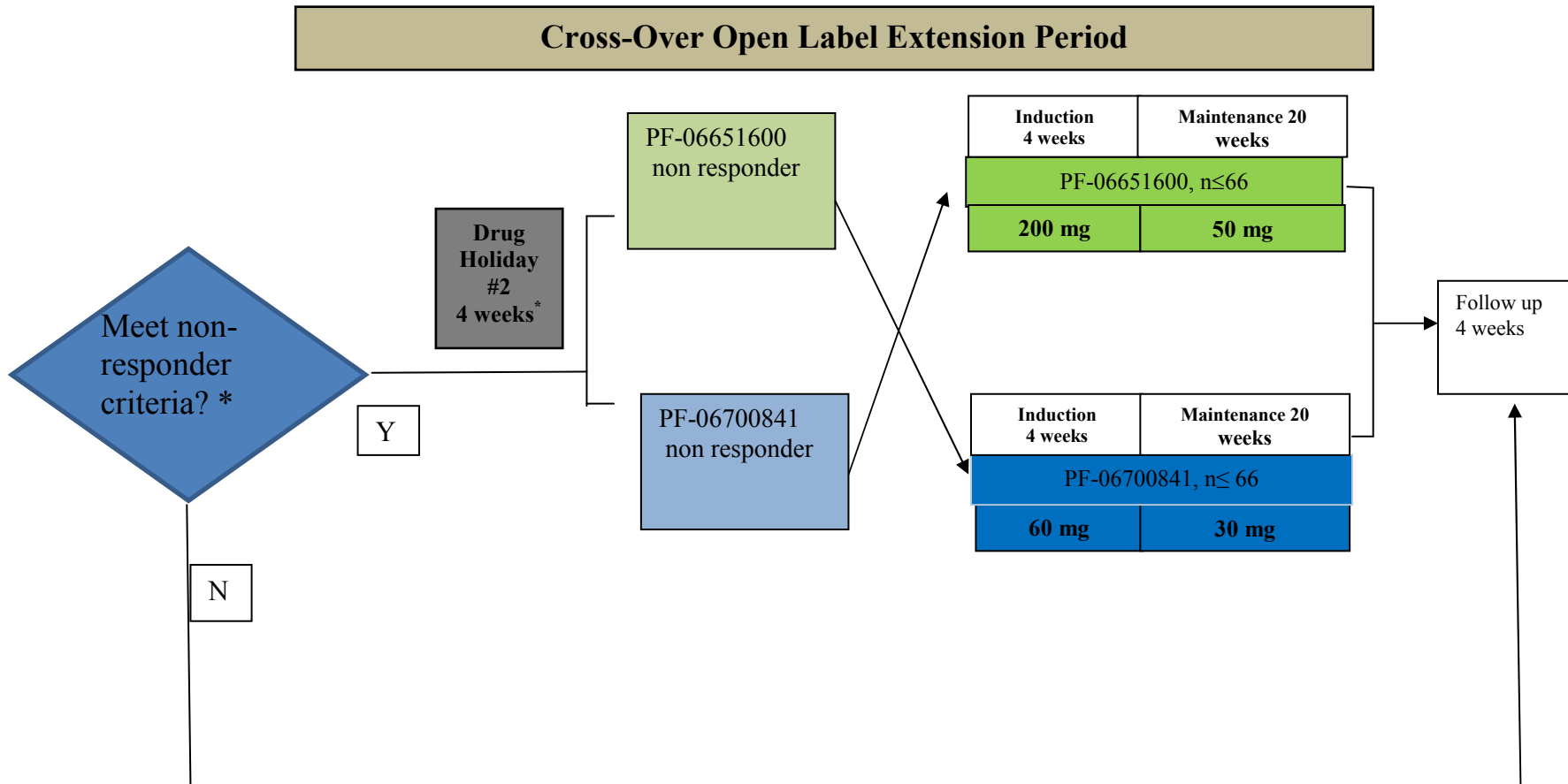
#### Study Design Schematic



**\* 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 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 for non-responder or placebo at Week 28 (after the 4-week Drug Holiday #1) to start the Withdrawal/Retreatment segment for responder.  
 + 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 Period and will not participate 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.

Study B7931005 will investigate the JAK3 inhibitor PF-06651600 and TYK2/JAK1 inhibitor PF-06700841 in 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 weeks Screening Period, a 24-week Treatment Period, a 4-week Drug Holiday (#1), an up to 12 month Single-Blind (investigator open, sponsor 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.

Subjects who have moderate to severe alopecia areata ( $\geq 50\%$  hair loss of the scalp [SALT score  $\geq 50$ ] without evidence of hair regrowth within the previous 6 months; current episode of fixed hair loss  $\leq 7$  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 ( $\geq 50\%$  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 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.

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### Single-Blind Extension Period

Alopecia Areata is a disease with high unmet medical need. Currently there are no approved medications for treatment of AA. An 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 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 will be described in the SAP. 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%. 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 the SAP.

During the Single-Blind Extension Period, subjects who are assigned to the active treatment (PF-06651600 or PF-06700841) at Week 28 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 to start the segment for non-responder.

Subjects who are assigned to the placebo group at Week 28 to start the Withdrawal/Retreatment segment for responder will receive placebo for up to 24 weeks until they meet the retreatment criteria described in the SAP. 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 Cross-Over Open Label Extension Period.

Any subject that has completed the initial 24 weeks of the Protocol B7931005 prior to 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 at Week 52 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 4-week 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 active 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 subjects 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.

#### **4. SUBJECT ELIGIBILITY CRITERIA**

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

##### **4.1. Inclusion Criteria**

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
3. Male or female subjects between 18-75 years of age, inclusive, at time of informed consent.
4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use **two** highly effective method of contraception (per [Section 4.4.1](#)) throughout the study and for at least 28 days after the last dose of assigned treatment.

Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

- a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
- b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

5. Must meet the following alopecia areata criteria:
  - a. Have a clinical diagnosis of moderate to severe alopecia areata ( $\geq 50\%$  hair loss of the scalp [defined as SALT  $\geq 50$ ] without evidence of hair regrowth within 6 months) at the screening and baseline visits;
  - b. Current episode of fixed hair loss  $\leq 7$  years.
6. If receiving concomitant medications for any reason other than AA, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1. Subject must be willing to stay on a stable regimen during the duration of the study ([Section 5.8](#)).
7. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

#### **4.2. Exclusion Criteria**

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
2. Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or sponsor, would make the subject inappropriate for entry into this study.



3. Any psychiatric condition including recent or active suicidal ideation or behavior meets any of the following criteria:

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[REDACTED]

- Any lifetime history of serious or recurrent suicidal behavior.
  - Suicidal behaviors questionnaire –revised (SBQ-R) ([Appendix 9](#)) total score  $\geq 8$ .
  - Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) ([Appendix 10](#)) total score  $\geq 15$ .
  - The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.
  - In the opinion of the investigator or Pfizer (or designee) exclusion is required.
4. Subjects considered in imminent need for surgery or with elective surgery scheduled to occur during the study.
5. Subjects have other types of alopecia (including but not limited to traction, scarring alopecia).
6. Currently have active forms of other inflammatory skin disease(s) or evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of the Screening or Day 1 Visit that in the opinion of the investigator would interfere with evaluation of AA or response to treatment.
7. Have received any of the following treatment regimens specified in the timeframes outlined below:

Within 6 months of first dose of study drug:

- Any cell-depleting agents including but not limited to rituximab: within 6 months of first dose of study drug, or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer.

Within 12 weeks of first dose of study drug:

- Use of JAK inhibitors.

- Other biologics: within 12 weeks of first dose of study drug or 5 half-lives (if known), whichever is longer.

Within 8 weeks of first dose of study drug:

- Systemic treatments that could affect AA within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.
- Use of oral immune suppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, systemic corticosteroids, mycophenolate-mofetil,) within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.
- Intralesional steroid injection within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.
- Participation in other studies involving investigational drug(s) within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.

Note: Any investigational or experimental therapy taken or procedure performed for rheumatoid arthritis, psoriasis, vitiligo, thyroid disease, allergic rhinitis, or atopic dermatitis in the previous 1 year should be discussed with the Pfizer Medical Monitor (or designee). Subjects cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

Within 6 weeks of first dose of study drug:

- Have been vaccinated with live or attenuated live vaccine.

Within 4 weeks of first dose of study drug:

- Ultra-Violet B (UVB) phototherapy, Psoralen Ultra-Violet A therapy, or other phototherapy.

Within 2 weeks of first dose of study drug:

- Topical treatments that could affect AA (eg, steroid cream; medicated shampoo; or herbal hair care that could affect AA).

Within 1 week of first dose of study drug:

- Herbal medications with unknown properties or known beneficial effects for AA.

8. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use two highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
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.
11. Have a history of any lymphoproliferative disorder such as Epstein Barr Virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.
12. Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.
13. Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1 (for exception regarding Tuberculosis (TB) infection see Exclusion Criterion 24 or skin infections that lead to hospitalizations see Exclusion Criterion 14).
14. Have active acute or chronic skin infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1, or superficial skin infections within 2 weeks prior to Day 1.  
NOTE: patients may be rescreened after the infection resolves.
15. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator or Pfizer (or designee) will preclude participation in the study.
16. A Screening 12-lead electrocardiogram (ECG) that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome).

17. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.
18. Abnormal findings on the Screening chest radiographs (eg, chest x-ray) including, but not limited to, presence of TB, general infections, heart failure, or malignancy. Chest radiographs examination may be performed up to 12 weeks prior to Day 1. Documentation of the official reading must be available in the source documentation.
19. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
20. Have undergone significant trauma or major surgery within 1 month of the first dose of study drug.
21. Require treatment with prohibited concomitant medication(s) ([Section 5.8.2](#) and [Appendix 2](#)) or have received a prohibited concomitant medication within 7 days or 5 half-lives (whichever is longer) prior to Day 1.
22. History of human immunodeficiency virus (HIV) or positive HIV serology at screening.
23. Infected with hepatitis B or hepatitis C viruses. For Hepatitis B, all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) during Screening. Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb) and if HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the subject is not eligible for the study. For Hepatitis C, all subjects will undergo testing for Hepatitis C antibody (HCVAb) during Screening. Subjects who are HCVAb positive are not eligible for the study.
24. Infected with Mycobacterium tuberculosis (TB) as defined by the following:
  - a. A positive Interferon Gamma Release Assay (IGRA) test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. It is recommended that subjects with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the IGRA test since the Mantoux/PPD tuberculin skin test may be positive due to vaccination. See [Section 7.3.6](#) for requirements for Mantoux/PPD tuberculin skin testing. The following are acceptable IGRA assays: QuantiFERON<sup>®</sup> - TB Gold test (QFT-G), QuantiFERON<sup>®</sup> - TB Gold In-Tube test (QFT-GIT) and T-SPOT<sup>®</sup>.
    - If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

- Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant treatment without additional action).
  - Subjects who test positive for QFT-G/ QFT-GIT test, but in the opinion of the principal investigator (PI) are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and may have the IGRA test repeated once. Subjects will be eligible if the repeat test is negative before the randomization.
- b. Chest radiograph taken at screening with changes suggestive of active TB infection, unless previously performed and documented within 3 months prior to Day 1.
- c. A subject who has been treated or is currently being treated for active or latent TB infection is to be excluded.
- d. A history of either untreated or inadequately treated latent or active TB infection is to be excluded.
25. Donation of blood in excess of 500 mL within 8 weeks prior to Day 1.
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  $<2.5 \times 10^9/L$  ( $<2500/mm^3$ );
  - Hemoglobin  $<10.0$  g/dL or hematocrit  $<30\%$ ;
  - Platelet count below the lower limit of normal (LLN) at Screening;
  - Absolute lymphocyte count of  $<0.8 \times 10^9/L$  ( $<800/mm^3$ );
  - serum creatinine  $>$  upper limit of normal (ULN) or eGFR  $<80$  ml/min/1.73m<sup>2</sup> based on the age appropriate calculation;
  - enzymes aspartate transaminase (AST) or alanine transaminase (ALT) values  $>2$  times the ULN;
  - Total bilirubin  $\geq 1.5$  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  $\leq$  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.

#### **4.3. Randomization Criteria**

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. This study will enroll a total of approximately 132 subjects (expected to provide approximately 90 completers). Eligible subjects will be randomly assigned to a treatment group through the sponsor's interactive response technology (IRT) system in the allocation ratio stratified by the disease subtype.

Eligible 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 in the 24 week Treatment Period. For analyses purposes, the two placebo arms will be combined during the treatment period.

A biopsy sub-study will be performed at selected sites. 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 during the treatment period.

Eligible subjects will be stratified by the status of agreeing to participate in the biopsy sub-study and the disease sub-type. Specifically there will be two strata for disease sub-type: AA (not totalis/universalis) and AA (totalis/universalis). The study will be first stratified by the status of the biopsy sub-study and within each stratum for the status of the biopsy sub-study it will be further stratified by the disease sub-type.

Subjects will be assigned to receive either active treatment (PF-06651600 or PF-06700841) or placebo at Week 28 (after the 4-week Drug Holiday #1 that follows completion of Week 24) by the study designee(s). The study designee(s), who are independent of study team, will provide the site with a treatment assignment when IP is being supplied via the IRT system post Week 24.

#### **4.4. Lifestyle Requirements**

In order to participate in the study, subjects must be aware of the following lifestyle guidelines and restrictions that apply during and after the study period.

- On study visit days that include fasting lipid panel, comply with fasting requirement for at least 8 hours prior to the visit.
- On study visit days, do not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements.
- On study visit days, do not take the dose of study drug until instructed to do so by the investigator or designated study site staff.

- During study, discontinue and avoid using certain medications and treatments ([Section 4.2](#), [Section 5.8.2](#), and [Appendix 2](#)).
- Agree to use appropriate contraception methods ([Section 4.4.1](#)).
- Agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
- For subjects who undergo color application to their hair, it is recommended that the color application will be performed within one week prior to the scheduled study visits, if possible. This will facilitate the consistency of SALT assessment.
- Agree to avoid strenuous exercise during the study, especially within one week prior to the scheduled study visits and maintain adequate hydration, if possible.

#### **4.4.1. Contraception**

In this study, fertile male subjects and female subjects who are of childbearing potential will receive PF-06651600 and PF-06700841. PF-06700841 has been associated with demonstrated teratogenicity/fetotoxicity in animals. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the [Schedule of Activities](#), the investigator or designee will inform the subject of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post vasectomy ejaculate.
5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

#### **4.5. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

### **5. STUDY TREATMENTS**

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product(s) are PF-06651600 and PF-06700841.



### **5.1. Allocation to Treatment**

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

### **5.2. Breaking the Blind**

The study will be subject and investigator blinded.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

Details of unblinding plan for interim analysis will be specified in interim analysis plan.

### **5.3. Subject Compliance**

For self-administration of PF-06651600 or PF-06700841 at home, subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the investigational product will be monitored by delegated site personnel by the accounting of unused medication returned by the subject at the study visits. Compliance will be documented on the CRF and source document. If compliance is <80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects interrupting investigational product for more than 4 consecutive days or for a total of more than 7 days between visits are to be discussed with the sponsor for possible withdrawal from the study.

## 5.4. Investigational Product Supplies

### 5.4.1. Dosage Form(s) and Packaging

Blinded PF-06651600 and PF-06700841 tablets and matching placebos will be provided as tablets for oral administration. The designation “PF-06651600-15” and “PF-06700841-15” may appear on labeling and indicates a salt. They are equivalent to “PF-06651600” and “PF-06700841” with regard to this protocol. The PF-06651600 50 mg tablets and their matching placebos will be supplied in blisters and labeled according to local regulatory requirements. The PF-06700841 5 mg and 25 mg tablets and their matching placebos will be supplied in bottles and labeled according to local regulatory requirements. Subjects will receive blinded labeled supplies throughout the study including the Extension Period. Blinding occurs within investigational products, not across investigational products. The Extension Period will become single-blind (investigator open, sponsor open and subject blind) upon approval of Amendment 4. The Cross-Over Extension Period is open label.

### 5.4.2. Preparation and Dispensing

The investigational product (IP) will be dispensed using an IRT drug management system at each visit according to [Schedule of Activities](#). A qualified staff member will dispense the investigational product via unique container numbers on the bottles or blister labels provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in bottles or blisters provided throughout the course of dosing and return the bottles or blisters to the site at the next study visit.

## 5.5. Administration

Subjects will receive IP as outpatients. PF-06651600 tablets and matching placebo for oral administration will be dispensed in blisters while PF-06700841 tablets and matching placebo for oral administration will be dispensed in bottles. Subjects will be provided clear dosing instructions.

Sites will be trained on how subjects should take tablets at home through an IP manual and/or other vehicle(s). Sites are responsible for communicating this information and site staff **should review the dosing instructions with subjects at every study visit.**

Subjects should take the medication orally; Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL; Subjects will swallow the investigational product whole, and will not manipulate or chew the medication prior to swallowing; **Subjects will be encouraged to take the medication after breakfast whenever possible** even though IP may be taken with or without food; however, for **study visit days**, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic.

If a dose is missed and the interval to the next dose is less than 8 hours, the missed dose should not be administered.

Study treatment may be temporarily withheld (or adjusted) for a maximum of 4 consecutive days at the discretion of the investigator. Subjects interrupting investigational product for more than 4 consecutive days are to be discussed with the sponsor for possible withdrawal from the study.

## **5.6. Investigational Product Storage**

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

## **5.7. Investigational Product Accountability**

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All study drug must be returned to the investigator by the subject at every visit and at the end of the trial.

### **5.7.1. Destruction of Investigational Product Supplies**

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

For all blisters/bottles returned to the investigator by the subject, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

## **5.8. Concomitant Treatment(s)**

Medications that are taken in the Screening period (after informed consent is obtained and before the first dose of study drug) will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication, daily dose, and start and stop dates of administration. Subjects will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each study visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

The start date, stop date, and indication for all therapies will be recorded on the CRF.

### **5.8.1. Permitted Concomitant Medications**

Acetaminophen may be used intermittently (not to exceed 1 g/day). For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, and purified food substances with pharmaceutical properties. Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

A subject who is receiving **metformin** as concomitant medication must allow at least two hours to elapse after taking the medication and before taking investigational product.

A subject who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose for the treated indication, and this must be documented in the CRF. Subjects are not allowed any other investigational drugs or treatments during the study.

Subjects should **refrain from starting new or changing doses** of permitted prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and prior to study visits throughout the study, unless otherwise noted below.

Subjects should report any changes to permitted medications during the study to the investigator as soon as they occur. Medication changes must be documented in the subject's record and CRF.

Unless a prohibited medication or treatment, subjects may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1, addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

### **5.8.2. Prohibited Medications and Treatments**

Subjects will abstain from all concomitant medications as described in the [Inclusion](#) and [Exclusion](#) sections of the protocol and [Appendix 2](#) Prohibited Concomitant Medications.

Subjects should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

A subject who is receiving **simvastatin as concomitant medication should be switched at least 7 days prior to baseline to an alternative statin**. Treatment with simvastatin-containing products should not be initiated during participation in this study.

**All medications and treatments that could affect AA must be discontinued.** Subjects must also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.

Herbals supplements are only allowed on a case by case basis; please contact the Pfizer staff. Herbal medications with unknown properties or known beneficial effects for AA or that are known to have an effect on drug metabolism (eg St. John's Wort) must be discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of investigational product.

Restrictions on certain vaccinations are described in [Section 5.8.3](#).

### **5.8.3. Vaccinations**

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study drug, during the study, and for 6 weeks after the last dose of investigational product. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of treatment.

Such vaccines include but are not limited to: FluMist<sup>®</sup> (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

## **6. STUDY PROCEDURES**

Refer to the [Schedule of Activity](#) for a detailed list of study procedures as they should be conducted at each respective visit.

Subjects are required to fast for at least **8 hours** prior to all visits that include fasting lipid profile panel testing. During the fasting period, subjects should refrain from all food and liquids (water and non-study medications are permitted).

Due to possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit within the 35 days prior to the Day 1 visit.

Visits should occur in the morning and prior to the subject's dose. To assure consistency and reduce variability, all study visits should occur in the morning whenever possible. On days of study visits, subjects will receive their dose at the clinic during their study visit.

Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential through end of study (EOS).

The patient report outcome assessments should be completed before the other evaluations or treatments at the clinical visits whenever it is possible.

Refer to [Appendix 6](#) for guidelines on subject safety monitoring and discontinuation.

### **6.1. Screening**

Subjects will have up to 35 days of a screening period confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the [Schedule of Activities](#) section.

If the Mantoux PPD tuberculin skin test is given, the subject must return between 48-72 hours post-injection for induration evaluation.

Screening laboratory tests with abnormal results may be repeated **once** to confirm abnormal results (with the same screening number); the last value will be used to determine eligibility. If results return to normal within the 5-week screening period, the subject may enter the study.

Sites will be permitted to re-screen subjects (with a new screening number) who initially do not meet eligibility criteria **once**.

The following procedures will be completed:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Register subject in Impala.
- Demography.
- Complete AA disease history includes collection of details of AA at Screening: AA 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.
- Complete 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.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 35 days prior to the Screening Visit.
  - In addition, previous drug treatments for AA taken within the 2 years before the Screening visit must be documented including the use of topical treatments, intralesional treatments, systemic treatments and any other treatments.
- Conduct complete physical examination including dermatological full body examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Audiogram.
- Perform single 12-lead electrocardiogram (ECG).
- Obtain weight.

- Obtain height.
- Chest radiograph (if previous chest radiograph has not been performed within 12 weeks of Day 1, may require a visit to a different location).
- Obtain samples for laboratory testing: Blood chemistry, hematology, urinalysis, urine myoglobin, serum FSH (female subjects of non-child bearing potential) or serum pregnancy test (female subjects of childbearing potential), HIV, HBsAg, HBcAb, Hep B reflex testing if applicable, and HCVAb.
- Mantoux Purified Protein Derivative (PPD) skin test or IGRA test (unless performed within 12 weeks of Day 1). If Mantoux PPD tuberculin skin test is performed, the subject must return between 48-72 hours post-injection for evaluation of induration.
- Photographs to verify eligibility.
- Conduct clinical evaluations including SALT, CCI [REDACTED]  
[REDACTED] SBQ-R, and PHQ-8.  
[REDACTED]
- Agree to use proper contraception methods.
- Assess for occurrence of Adverse Events: The reporting period starts with the signing of the informed consent.

## 6.2. Study Period

### 6.2.1. Visit 2, Day 1

- Review of Inclusion/Exclusion Criteria.
- If subject meets all Inclusion/Exclusion criteria, officially randomize subject into the study.
- Review any changes in the subject's prior and concomitant treatment information.
- Review any changes in the medical history (any AEs happened before the first dosing should be reflected on the medical history).
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain weight.
- Conduct complete physical examination.



- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for other laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, Cytomegalovirus (CMV), herpes simplex virus type 1(HSV1), herpes simplex virus type 2 (HSV2), VZV, CCI [REDACTED]
- Photography.  
CCI [REDACTED]
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
CCI [REDACTED]
- Perform single 12-lead ECG.  
CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Confirm proper contraception is being used.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer first dose of study drug to subject.
- Provide and review dosing instruction.
- Dispense study drug supply to the subject.  
CCI [REDACTED]
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.2.2. Visit 3, Day 15/Week 2 (±2 days)

- Conduct targeted physical examination.

- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, EBV, CMV, HSV1, HSV2, VZV, and urine pregnancy test (female subjects of childbearing potential only).
- Obtain Prep B1 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- C [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- **Prior to dosing**, obtain samples for PK analysis.
- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.2.3. Visit 4, Day 29/Week 4 (±2 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED], EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- **Prior to dosing**, obtain samples for PK analysis.

- Photography.
- Obtain Prep B1 and B2 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- **Optional** lesional biopsy (for subjects who consent to participate in biopsy sub-study only).
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Collect blood samples for PK at 0.5, 1, 2, and 4 hours post dose.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.2.4. Visit 5, Day 43/Week 6 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- **Prior to dosing**, obtain samples for PK analysis.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]

**C** [REDACTED]

**C** [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Administer study drug to the subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.2.5. Visit 6, Day 57/Week 8 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- **Prior to dosing**, obtain samples for PK analysis.
- Photography.
- Conduct clinical evaluations including IGA, SALT, **CCI** [REDACTED]

**C** [REDACTED]

**I** [REDACTED]

**I** [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.

- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Collect blood samples for PK at 0.5 hours post dose.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.2.6. Visit 7, Day 85/Week 12 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis and urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED] EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- **Prior to dosing**, obtain samples for PK analysis.
- Audiogram.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- I [REDACTED]
- C [REDACTED]
- Lesional biopsy (for subjects who consent to participate in biopsy sub-study only).
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.

- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Collect blood samples for PK at 0.5 and 1 hour post dose.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

**6.2.7. Visit 8, Day 113/Week 16 (±3 days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- **Prior to dosing**, obtain samples for PK analysis.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI, [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.

- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### **6.2.8. Visit 9, Day 141/Week 20 (±3 days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- **Prior to dosing**, obtain samples for PK analysis.

- Photography.

- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Collect blood samples for PK at 0.5 hours post dose.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### **6.2.9. Visit 10, Day 169/Week 24/End of Treatment (±3 days)**

- Conduct complete physical examination.

- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Perform single 12-lead ECG.
- Audiogram.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- **Prior to dosing**, obtain samples for PK analysis.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Lesional biopsy (for subjects who consent to participate in biopsy sub-study only).
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject (from the previous container).
- Collect blood samples for PK at 0.5, 1, 2, and 4 hours post dose.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"



### 6.2.10. Early Termination Visit

For subjects who discontinue early from the treatment period prior to Week 24 visit or subjects who discontinue early from the Single-Blind Extension Period or Cross-Over Open Label Extension Period, the procedures scheduled for early termination (ET) Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. Subject will then enter into the Follow-up Period with their first follow-up visit occurring 1 week after their last dose whenever possible.

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Perform single 12-lead ECG.
- Audiogram.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Lesional biopsy (for subjects who consent to participate in biopsy sub-study only). Biopsies of the lesional scalp at ET visit will only be obtained for subject who discontinue early from the treatment period prior to Week 24 visit. No biopsies will be obtained at ET visit for subjects who discontinue early in the Extension periods.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.

- Collect blood sample for PK for subjects who discontinue early from the treatment period prior to Week 24 visit or during the Cross-Over Open Label Extension Period only if the most recent dose taken prior to ET visit was within 48 hours. No PK samples will be collected at ET visit for subjects who discontinue early in the Single-Blind Extension period.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

### **6.3. Drug Holiday #1**

All subjects who complete the initial 24-week Treatment Period will be evaluated for potential entry into the Single-Blind Extension Period during the 4-week 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 participation. Subjects who meet Exclusion criteria #9, #10, or #26 will be discontinued and enter the Follow-up Period.

### **6.4. Extension Periods**

#### **6.4.1. Single-Blind Extension Period**

Subjects will be assigned 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 at Week 28 (after the 4-week Drug Holiday #1) by study designee(s) who are independent of study team. The probability to receive active treatment in the Single-Blind Extension Period is approximately 33% to 100%. 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 the SAP.

Subjects who are assigned to the active treatment group during Drug Holiday #1 will enter the Single-Blind Extension Period at Week 28 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 are assigned to the placebo group during Drug Holiday #1 will enter the Single-Blind Extension Period at Week 28 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 are assigned to the placebo group and meet the retreatment criteria will receive active treatment between Week 28 to Week 52 depending on when they meet the retreatment criteria.

##### **6.4.1.1. Visit 11, Week 28 (±3 days)**

- Review any changes in the subject’s prior and concomitant treatment information.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.

- Conduct complete physical examination.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for other laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine myoglobin, urine pregnancy test (female subjects of childbearing potential only), EBV, Cytomegalovirus (CMV), herpes simplex virus type 1(HSV1), herpes simplex virus type 2 (HSV2), VZV, CCI [REDACTED]
- Photography.  
CCI [REDACTED]  
CCI [REDACTED]
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
CCI [REDACTED]
- Perform single 12-lead ECG.
- Obtain Prep B1 and B2 samples.
- Confirm proper contraception is being used.
- Administer study IP to subject.
- Provide and review dosing instruction.
- Dispense study drug supply to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.1.2. Visit 12, Week 30 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, EBV, CMV, HSV1, HSV2, VZV, and urine pregnancy test (female subjects of childbearing potential only).

- Obtain Prep B1 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.3. Visit 13, Week 32 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED] EBV, CMV, HSV1, HSV2, VZV CCI [REDACTED]
- Photography.
- Obtain Prep B1 and B2 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.4. Visit 14, Week 34 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- C [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Administer study IP to subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.5. Visit 15, Week 36 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.6. Visit 16, Week 40 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.

- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis and urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED] EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Audiogram.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]  
C [REDACTED]  
I [REDACTED]  
I [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.7. Visit 17, Week 44 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.

- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

**6.4.1.8. Visit 18, Week 48 (±3 days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.



- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.1.9. Visit 19, Week 52 (±3 days)

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Perform single 12-lead ECG.
- Audiogram.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]  
[REDACTED]
- Obtain Prep B1 and B2 samples.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]  
I [REDACTED]  
I [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.

- Administer study IP to subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.1.10. Active Treatment (AT) Period

Only for subjects who are assigned to the placebo group at Week 28 and meet the retreatment criteria, 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 (audiogram result available within 8 weeks is acceptable).

##### 6.4.1.10.1. Visit 20, AT Day 1

- Review any changes in the subject’s prior and concomitant treatment information.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Conduct complete physical examination.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for other laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, Cytomegalovirus (CMV), herpes simplex virus type 1(HSV1), herpes simplex virus type 2 (HSV2), VZV, CCI [REDACTED]
- Photography.  
C [REDACTED]
- C [REDACTED]
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- Perform single 12-lead ECG.
- Obtain Prep B1 and B2 samples.
- Confirm proper contraception is being used.
- Administer active treatment (PF-06651600 or PF-06700841) to subject.

- Provide and review dosing instruction.
- Dispense study drug supply to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.1.10.2. Visit 21, AT Week 2 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, EBV, CMV, HSV1, HSV2, VZV, and urine pregnancy test (female subjects of childbearing potential only).
- Obtain Prep B1 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- C [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.1.10.3. Visit 22, AT Week 4 ( $\pm 3$ days)

- Conduct targeted physical examination.

- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED] EBV, CMV, HSV1, HSV2, VZV CCI [REDACTED]  
[REDACTED]
- Photography.
- Obtain Prep B1 and B2 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]  
I [REDACTED]  
I [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.10.4. Visit 23, AT Week 6 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).

- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.1.10.5. Visit 24, AT Week 8 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.

- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

**6.4.1.10.6. Visit 25, AT Week 12 (±3 days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis and urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED] EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Audiogram.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.

- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

**6.4.1.10.7. Visit 26, AT Week 16 (±3 days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

**6.4.1.10.8. Visit 27, AT Week 20 ( $\pm 3$  days)**

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

**6.4.1.10.9. Visit 28, AT Week 24/AT End of Treatment ( $\pm 3$  days)**

Subjects who complete the Withdrawal/Retreatment segment for responder will go directly to the Follow-up Period and will not participate the Cross-Over Open Label Extension Period.

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Perform single 12-lead ECG.



- Audiogram.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, CCI [REDACTED]  
[REDACTED]
- Obtain Prep B1 and B2 samples.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]  
C [REDACTED]  
[REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer active treatment (PF-06651600 or PF-06700841) to subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.2. Drug Holiday # 2

Subjects who complete the segment for non-responder in Single-Blind Extension Period will be evaluated during 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 non-responder criteria at Week 52 will enter the Follow-up Period directly. 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.

### 6.4.3. Cross-Over Open Label Extension Period

#### 6.4.3.1. Visit 29, Cross-Over Day 1 (COD1)

- Review any changes in the subject's prior and concomitant treatment information.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Conduct complete physical examination.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for other laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only),  
CCI [REDACTED]
- Photography.  
C [REDACTED]  
C [REDACTED]  
I [REDACTED].
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]
- Perform single 12-lead ECG.
- Obtain Prep B1 and B2 samples.
- Confirm proper contraception is being used.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer study IP to subject.
- Provide and review dosing instruction.
- Dispense study drug supply to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.2. Visit 30, Cross-Over Week 2 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.3. Visit 31, Cross-Over Week 4 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED]
- Photography.
- Obtain Prep B1 and B2 samples.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]

**C** [REDACTED]  
**C**

**I** [REDACTED]

**I** [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer study IP to subject (from the previous container).
- Collect blood samples for PK at 0.5, 1, 2, and 4 hours post dose.
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.4. Visit 32, Cross-Over Week 6 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, SALT, **CCI** [REDACTED]

**C** [REDACTED]  
**C**

**I** [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.

- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Administer study IP to subject (from the previous container).
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.3.5. Visit 33, Cross-Over Week 8 (±3 days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- I [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

#### 6.4.3.6. Visit 34, Cross-Over Week 12 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis and urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Audiogram.
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]  
C [REDACTED]  
C [REDACTED]  
I [REDACTED]  
I [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.7. Visit 35, Cross-Over Week 16 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.8. Visit 36, Cross-Over Week 20 ( $\pm 3$ days)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Photography.

- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- C [REDACTED]
- I [REDACTED]
- [REDACTED]
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study IP to subject (from the previous container).
- Provide and review dosing instruction.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

#### 6.4.3.9. Visit 37, Cross-Over Week 24/Cross-Over End of Treatment ( $\pm 3$ days)

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Perform single 12-lead ECG.
- Audiogram.
- Obtain **fasting** samples for fasting lipid panel.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED]
- Obtain Prep B1 and B2 samples.
- Photography.
- Conduct clinical evaluations including IGA, SALT, NRS for CCI [REDACTED]



**C** [REDACTED]  
**C**

**I** [REDACTED]

**I** [REDACTED]

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- **Prior to dosing**, obtain samples for PK analysis.
- Administer study IP to subject (from the previous container).
- Collect blood samples for PK at 0.5, 1, 2, and 4 hours post dose.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

## 6.5. Follow-up Period

### 6.5.1. Visit 38, Followup 1

Follow up Visit 1 will occur 2 weeks after AT Week 24 or Cross-Over Week 24. For early terminated subjects from the initial treatment period or the Single-Blind Extension Period or the Cross-Over Open Label Extension Period, FU Visit 1 will occur 1 week after their last dose whenever possible.

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, SALT, **CCI** [REDACTED]

**I** [REDACTED]

**I** [REDACTED].

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.

- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

### 6.5.2. Visit 39, End of Study Visit

End of Study Visit will occur 2 weeks after FU Visit 1.

Subjects who are assigned to the placebo group in the Single-Blind Extension Period and do not meet the retreatment criteria throughout 24 weeks will go directly to the EOS visit 1 week after their last visit whenever possible.

The following procedures will be completed:

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, blood chemistry, cystatin C, urinalysis, urine pregnancy test (female subjects of childbearing potential only), CCI [REDACTED]
- Obtain **fasting** samples for fasting lipid panel.
- Prep B1 and B2 samples.
- Obtain weight.
- Conduct clinical evaluations including IGA, SALT, CCI [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Photograph.
- Confirm proper contraception is being used.
- Review any changes in the subject’s concomitant treatments information.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

### 6.5.3. Follow-up Contact

Follow-up contact only applies to subjects who have the EOS Visit taking place less than 28 days after the last dose. Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the [Time Period for Collecting AE/SAE Information](#) section) and to confirm appropriate contraception usage (see the [Contraception](#) section). Contact with the subject may be done via a phone call.

### 6.6. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the [Withdrawal From the Study Due to Adverse Events](#) section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Subjects who are requested to discontinue study treatment from the Treatment Period or Extension Periods will enter into the Follow-up Period **with their first follow-up visit occurring 1 week after their last dose whenever possible** and continue to be followed for protocol specified follow-up procedures. The procedures scheduled for **ET Visit** will be performed on the last day the subject takes the investigational product or as soon as possible thereafter.

See [Appendix 6](#) for guidelines on subject safety monitoring and discontinuation. The ET Visit only applies to subjects who are randomized, received at least one dose of study drug, and then are prematurely withdrawn from the study treatment.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

#### **Withdrawal of consent:**

Subjects who request to discontinue receipt of study treatment from the Treatment Period or Extension Periods will enter the Follow-up Period with their **first follow-up visit occurring 1 week after their last dose whenever possible** and continue to be followed for protocol specified follow-up procedures. The procedures scheduled for **ET Visit** will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is

only from further receipt of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

**Lost to follow-up:**

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

**7. ASSESSMENTS**

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

### 7.1. Pregnancy Testing

Pregnancy tests are required to be done (if applicable) as specified in the [Schedule of Activities](#).

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female subjects of childbearing potential, 2 negative pregnancy tests are required before receiving study treatment(s) (1 negative pregnancy test at screening and 1 at the baseline visit immediately before study treatment administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result will then be required at the baseline visit and within 5 days after the first day of the menstrual period (counting the first day of the menstrual period as Day 1) before the subject may receive the study treatment. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at every visit and at the end of the study to confirm that the subject has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product but may remain in the study for follow up.

CCI



CCI [REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 7.3. Safety Assessments

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. Investigators and Pfizer Clinicians (or designees) will review individual subject data throughout the conduct of the study to ensure subjects' well-being.

### **7.3.1. Vitals 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](#).

Vital signs should be performed before laboratory blood collection.

It is preferred that body temperature be collected using the tympanic or oral methods and that the same method be used consistently throughout the study.

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes based on the arm circumference is the required type of device. The appropriate cuff size for the subject must be used to ensure accurate measurement. The arm circumference at the midpoint of the length of the upper arm should be measured to determine the appropriate cuff size in accordance with the specifications of the BP measuring device. The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time.

Subjects should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc.) and supported at heart level. Measurements should be taken on the same arm at each visit (preferably non-dominant). Subjects should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements. Measurements should begin after at least 5 minutes of rest.

Pulse should be measured at approximately the same time as BP for a minimum of 30 seconds. When the timing of BP and pulse (heart) rate measurements coincides with a blood collection or other study procedure, BP and pulse (heart) rate should be obtained first.

### **7.3.2. Medical History, Physical Exam, Height, and Weight**

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 and baseline (if applicable). Smoking status and average weekly alcohol consumption (units/week) will also be collected.

Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) and weight (lbs or kgs) will be measured and recorded in the source document at the Screening visit. Weight (lbs or kg) will continue to be measured and recorded at various timepoints according to [Schedules of Activities](#).

Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Complete physical examinations consist of assessments of general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth, heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function, back, and lymph nodes. In addition, **dermatological full body exam** must be

performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Dermatological examinations should include visual inspection of the breasts and external genitalia.

Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and should include skin, heart, lung, and abdomen and examination of body systems where there are symptom complaints by the subject.

Complete and Targeted physical examinations are performed at various time points, see [Schedules of Activities](#).

### **7.3.3. Chest Radiography**

Chest X-ray (posterior-anterior and lateral views are recommended, however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) with no evidence of abnormalities including but not limited to current, active TB or previous inactive TB, general infections, heart failure or malignancy taken at Screening or within 12 weeks prior to Study Day 1 and read by a qualified radiologist. Documentation of the official reading must be located and available in the source documentation.

### **7.3.4. Electrocardiogram**

Single 12-lead ECGs should be collected at times specified in the [Schedule of Activities](#).

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position and prior to any blood collection.

The baseline ECG values will serve as each subject's baseline values. To ensure safety of the subjects, a 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.

### **7.3.5. Audiogram**

All subjects will have an audiogram at times specified in the [Schedule of Activities](#). Audiogram testing taken at Screening or within 8 weeks prior to Day 1 must have results available prior to Day 1. Audiogram testing at Week 12 must be completed and results available by the Week 16 Visit. Audiogram testing at Week 24 must be completed and results available by the Week 28 Visit. For subjects who are assigned to the placebo group and meet the pre-specified criteria during the Single-Blind Extension Period, audiogram testing must be completed and results available by the AT D1 Visit unless an audiogram testing has been performed within 8 weeks prior to AT D1 Visit. For Cross-Over Open Label Extension Period, audiogram testing must be completed and results available by the



CO D1 Visit unless an audiogram testing has been performed within 8 weeks prior to CO D1 Visit. For subjects that terminate early from the study, efforts must be made to complete the audiogram testing and obtain the results.

When possible, the subject should have the audiogram performed at the same evaluation center during the study.

If there is a clinically-meaningful, treatment-related decline in hearing from baseline, the subject will be followed off treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable.

The information from the audiogram will be entered into the data collection tool.

Any de-identified audiogram results/reports and any additional relevant test results (if applicable) may be requested to be forwarded to Pfizer (and/or designee) at any time during the study.

### **7.3.6. Tuberculosis Testing**

#### **7.3.6.1. Interferon Gamma Release Assay (IGRA) Tuberculin Test**

Subjects may be screened for TB using an IGRA per local guidelines. Interferon gamma release assay will be tested during screening or within 12 weeks prior to Day 1. The following are acceptable IGRA assays: QuantiFERON<sup>®</sup>-TB Gold test (QFT-G), QuantiFERON<sup>®</sup>-TB Gold In-Tube test (QFT-GIT) and T-SPOT<sup>®</sup> TB test. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

An IGRA is preferred for subjects with a prior BCG vaccination, but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject's source documentation.

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant (eg, anti-TNF) treatment without additional action).

Subjects who test positive for QFT-G/ QFT-GIT test, but in the opinion of the PI are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and potential IGRA test repeated once. Subjects will be eligible if the repeat test is negative before the randomization.

Refer to lab manual for any additional processing information and shipping instructions.

### **7.3.6.2. Mantoux/Purified Protein Derivative (PPD) Tuberculin Skin Test**

Subjects can be TB screened using the Mantoux/PPD Tuberculin Skin Test. Mantoux/PPD testing can also be performed if there are indeterminate QFT-G test results. Subjects must have a Mantoux/PPD tuberculin skin test administered and then evaluated by a health care professional 48 to 72 hours later. A positive Mantoux/PPD tuberculin skin test is exclusionary.

### **7.3.7. Special Safety Assessment**

#### **7.3.7.1. Dermatological Events**

All subjects will have a dermatological full body exam at Screening Visit. Skin lesions will be evaluated as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v 4.0) and managed as [Appendix 4](#).

##### **7.3.7.1.1. Herpetiform Rash**

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), specimens for viral DNA analysis will be obtained: A swab of the affected area will be collected for confirmation; a blood sample for viral surveillance will be collected for the analysis of viral load. Details for these collections will be provided in the laboratory manual.

##### **7.3.7.1.2. Drug-Related Rash**

All potential drug-related reports of rash will be followed up until resolution or clinically stable or in agreement with the sponsor.

All events of rash should be treated according to International and local guidelines for the treatment of rash, eg, where appropriate, topical corticosteroids and/or agents such as antibiotics or antivirals could be prescribed.

All subjects reporting an unexplained skin rash should undergo a formal comprehensive dermatologic evaluation. A 4 mm punch biopsy will be taken unless there is a clear, non-drug related etiology (eg, infection, pre-existing condition) or other clinical rationale (eg, if the rash is present on the face it may not be appropriate to take a biopsy) or subject refuse to have biopsy performed. The biopsy will be sent to the local laboratory for histological investigation of the rash in order to gain insight into potential etiology of the rash. Note: For herpetiform rash, no biopsy is required. Please see [Section 7.3.7.1.1](#).

In addition to a biopsy of suspected drug-related rash, a swab (for microbiological assessment) of the affected area will also be taken for culture and sensitivity to assess (at the local laboratory) for any bacterial, fungal, or viral pathogens, if applicable. A blood sample for viral surveillance will be collected (and sent to the central laboratory) for the analysis of viral load including but not limited to CMV, EBV, HSV1, HSV2, and VZV, if applicable.

CCI



Investigators will complete a questionnaire and take appropriate photographs of the rash.

All de-identified biopsy results, culture results, photographs, and any additional relevant test results will be forwarded to Pfizer (or designee) for review within 30 days of receipt by the PI.

An independent dermatologist contracted by Pfizer will review all relevant data and summarize the data at the end of the study.

### **7.3.7.2. Creatinine, Cystatin C, and estimates of Glomerular Filtration Rate (eGFR)**

Serum creatinine is the best known standard test for monitoring renal function. However, serum creatinine based estimates of glomerular filtration rate (eGFR) may be affected by factors other than renal function, including chronic and acute illness. Serum cystatin C is a test that can be used either as an adjunct to or a replacement for serum creatinine. The most reliable estimates of GFR use both test results.<sup>8</sup>

Serum cystatin C is a low molecular weight protein that is used as an alternative to serum creatinine for monitoring of renal function. It seems to correlate more closely with GFR than serum creatinine concentration and may be a more sensitive detector of early renal dysfunction.<sup>17,3</sup> While use of cystatin C has been limited, its independence of demographic factors (eg, race) has made it an interesting means of determining changes in renal function in clinical settings and it is included in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Estimated GFR may be calculated via the 2012 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine, cystatin C, or creatinine-Cystatin C equations.<sup>10</sup>

Serum creatinine will be measured as part of serum chemistry at times specified in the [Schedule of Activities](#) section of the protocol. Creatinine elevations above the ULN will be followed until resolution or baseline. Serum creatinine based eGFR will be calculated. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at times specified in the [Schedule of Activities](#) section of the protocol.

The eGFR will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.<sup>26</sup>

## **7.4. Clinical Laboratory Tests**

### **7.4.1. Blood Volume**

Total blood sampling volume planned for this study is approximately 1000 mL. Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.

#### **7.4.2. Laboratory Tests**

The following laboratory tests will be performed at time points identified in the [Schedule of Activities](#). Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

Sample collection, labeling, storage, and shipping information can be found in the laboratory manual. All laboratory tests with clinically important changes from baseline identified after administration of investigational product will be followed until the value stabilizes.

- Subjects must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to fasting lipid profile panel collection according to [Schedule of Activities](#). All other labs (including PK sample collections) do not require fasting.

### Laboratory Tests

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

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

Clinically significant abnormal findings should be recorded as AEs. Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Clinically significant laboratory findings at the final assessment should be followed to resolution or until determined by the Investigator to be stabilized. Repeat tests may be indicated to establish this. Refer to [Appendix 6](#) for laboratory discontinuation criteria.

## 7.5. Efficacy Assessments

### 7.5.1. Severity of Alopecia Tool (SALT)

Severity of alopecia tool 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 3](#). **For any male subject, the male pattern alopecia should be permitted to score SALT 0 at the end of trial. Male pattern alopecia scoring may be considered for final adjudication by alopecia areata expert(s).**

**Subject should have a SALT score  $\geq 50\%$  at Screening and Baseline to be eligible for the study.**

The retreatment criteria during the Single-Blind Extension Period will be specified in SAP.

The photos may be reviewed by an independent consultant to confirm the SALT scores.

### 7.5.2. Investigator Global Assessment (IGA)

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 Table 9. This takes into account extent and density of regrowth by the SALT scoring system.

For determination IGA, the SALT score would be determined at baseline and each follow-up visit and the percentage change from baseline determined by the following:  $(\text{SALT}_{\text{baseline}} - \text{SALT}_{\text{follow-up}}) / \text{SALT}_{\text{baseline}} \times 100\% = \% \text{ change from baseline}$ .

Example: 75% hair loss at baseline (SALT score 75%), 50% hair loss at follow-up (SALT score 50%), the percent regrowth =  $(75\% - 50\%) / 75\% \times 100\% = 33\% \text{ regrowth}$ .

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

**Table 9. Investigator Global Assessment (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

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]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 7.7. Patient Report Outcome (PRO)

CCI [REDACTED]

[REDACTED]

CCI

### **7.7.3. Patient Health Questionnaire – 8 items (PHQ-8)**

Patient health questionnaire – 8 items ([Appendix 10](#)) is a patient-report questionnaire consists of 8 items to assess subject depression level.

At Screening Visit, if PHQ-8 total score  $\geq 15$ , the subject will not be included in the study.

### **7.7.4. Suicidal Behaviors Questionnaire-Revised (SBQ-R)**

Suicidal behaviors questionnaire- revised ([Appendix 9](#)) is a patient-report questionnaire consists of 4 items to assess suicidal ideation, suicide attempts, threat of suicidal behavior, and likelihood of suicidal behavior.

At Screening Visit, if SBQ-R total score  $\geq 8$ , the subject will not be included in the study.

### **7.8. Photography of Alopecia Areata Treated with Study Drug**

Photographs of treatment-eligible alopecia areata will be obtained (according to the separately provided Photography Instructions) at various time points as per [Schedule of Activities](#).

Photographs of treatment-eligible AA will be taken at Screening Visit to verify eligibility ( $\geq 50\%$  hair loss of the scalp). Scalp areas photographed should be recorded in study documents so that the same scalp region(s) will be photographed at all time points as applicable. Photographs of CCI will also be taken. Additional photographs may also be taken at the investigator's discretion.

Photographic services may be provided through a central photography lab selected by the sponsor. Detailed procedures to assure consistency will be provided separately in a central photography lab instruction manual.

The photos may be reviewed by an independent consultant to confirm the SALT scores.

CCI



CCI [Redacted]

| [Redacted]

| [Redacted]

| [Redacted]

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CCI



CCI


#### **7.10.8. Shipment of Pharmacodynamic Samples**

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

#### **7.11. Skin Biopsies**

Biopsy samples will be collected only at pre-selected biopsy sites and only on subjects who provide consent to participate in the biopsy sub-study.

The lesion(s) selected for biopsy will be outlined using a black permanent marker on plastic transparency film. An area will be marked on the transparency film for identification and biopsy. The film will be identified with the study number and subject's identification number and retained with subject's clinic/site source documents.

Biopsies of the lesional and non-lesional scalp (in subjects that have non-lesional scalp) will be obtained at each time point as specified in the [Schedule of Activities](#). In case of early termination, a lesional biopsy will be obtained at the ET visit. All skin biopsies will be approximately 5 mm in diameter.

Biopsy samples will be prepared for histopathology and immunohistochemistry and for RNA extraction as described in a separate study manual that will be provided to investigators. Skin biopsies will be sent to designated laboratories for analysis following a schedule to be determined.

The shipment address and laboratory contact information will be provided to the investigator prior to initiation of the study. Details on the procedure for skin biopsy and sample preparation will be provided to investigators in a separate study manual.

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As skin biopsies may be associated with risk of bleeding or infection, subjects will be instructed to contact the investigator or other designated site staff if they experience bleeding, warmth, swelling, tenderness, or erythema at the biopsy site; an unscheduled visit may be required for clinical assessment. If a wound infection occurs at the site of the biopsy, a bacterial culture will be performed as part of standard of care procedures.

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## 7.12. Rater Qualifications

Clinical evaluations of alopecia areata will be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of AA clinical trials may be permitted to perform the clinical evaluations of alopecia areata when designated by primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible;** a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

## 8. ADVERSE EVENT REPORTING

### 8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), <b>except occupational exposure</b>	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the [Serious Adverse Events](#) section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

#### **8.1.1. Additional Details On Recording Adverse Events on the CRF**

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

### **8.1.2. Eliciting Adverse Event Information**

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

### **8.1.3. Withdrawal from the Study Due to Adverse Events (see also the [Subject Withdrawal/Early Termination](#) section)**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the [Requirements](#) section above.

### **8.1.4. Time Period for Collecting AE/SAE Information**

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

#### **8.1.4.1. Reporting SAEs to Pfizer Safety**

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

#### **8.1.4.2. Recording Non-serious AEs and SAEs on the CRF**

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

### **8.1.5. Causality Assessment**

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

### **8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## **8.2. Definitions**

### **8.2.1. Adverse Events**

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

### **8.2.2. Abnormal Test Findings**

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

### **8.2.3. Serious Adverse Events**

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);



- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### **8.2.4. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);

- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.4. Special Situations

#### 8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

#### 8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more

serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal ( $\times$  ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations ( $>2 \times$  ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above  $3 \times$  ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values  $>3 \times$  ULN AND a TBili value  $>2 \times$  ULN with no evidence of hemolysis and an alkaline phosphatase value  $<2 \times$  ULN or not available;
- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values  $>2$  times the baseline values AND  $>3 \times$  ULN; or  $>8 \times$  ULN (whichever is smaller).
  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least  $1 \times$  ULN **or** if the value reaches  $>3 \times$  ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

#### **8.4.3. Potential Cases of Decreased eGFR**

In the PF-06700841 FIH study B7931001, serum creatinine elevation was reported across dose levels in both healthy volunteer and psoriasis patients. The proposed mechanism for the observed serum creatinine increases in study B7931001 is inhibition of creatinine transport in the kidney (ie, transporter-mediated rather than direct nephrotoxicity) ([Section 1.2.4.2.2.1](#)).

All subjects will have serum creatinine based and serum cystatin-C based eGFR calculated at baseline upon entry into the study.

Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, in the absence of other causes of kidney injury, are considered important medical events.

Estimated GFR using serum creatinine (2009 CKD-EPI eGFR)<sup>14</sup> and serum cystatin C (2012 CKD-EPI eGFR)<sup>10</sup> will be determined at times specified in the [Schedule of Activities](#). If an individual subject demonstrates a **CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of  $\geq 30\%$  compared to the subject's baseline eGFR**, then the subject should not be further dosed and adequate, immediate, supportive measures and **immediate evaluation by nephrologist (preferably within 24 hours)** with appropriate management should be taken for evaluation and treatment as clinically indicated. If the subject cannot be seen by a nephrologist within 24 hours, then the subject should be sent to a local emergency room for assessment of renal function. Results should be repeated as

indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline  $\pm 15\%$  or the renal parameters are deemed to be stable by the nephrologist and/or PI. eGFR results will be communicated to the treating physician.

Subjects should return to the investigational site and be evaluated as soon as possible, preferably within **24 to 48 hours** from awareness of the abnormal eGFR (CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of  $\geq 30\%$  compared to the subject's baseline eGFR) result for a safety follow-up visit. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the above pre-set laboratory criteria, with no other cause(s) of laboratory abnormalities identified should be considered as important medical event irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal serum creatinine.

All relevant test results will be forwarded to Pfizer for review within 30 days of receipt by the PI.

This requirement applies to all subjects.

#### **8.4.4. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure**

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

##### **8.4.4.1. Exposure During Pregnancy**

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

A special safety concern (SSC), fetal cleft lip, was reported in the B7931004 (investigating PF-06700841 to treat psoriasis) trial affecting a singleton pregnancy of a subject on concomitant medications including an herbal supplement which carried a pregnancy warning.

#### **8.4.4.2. Exposure During Breastfeeding**

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

#### **8.4.4.3. Occupational Exposure**

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

#### **8.4.5. Medication Errors**

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

<b>Safety Event</b>	<b>Recorded on the CRF</b>	<b>Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness</b>
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

##### **8.4.5.1. Medication Errors**

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

This section outlines the key planned statistical summaries and analyses for the data collected in this study. A comprehensive overall Statistical Analysis Plan (SAP) will be provided prior to the un-blinding of the trial. The SAP may modify the plans outlined in the protocol; however, any major modifications of planned analyses will be reflected in a protocol amendment if it is modified before data un-blinding. If, after the trial is un-blinded, changes are made to the SAP, then these deviations to the plan will be documented, along with an explanation as to why they occurred, in the Clinical Study Report (CSR).

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 PI when it is available.

### **9.1. Sample Size Determination**

The standard deviation of SALT mean change from baseline at Week 24 was calculated by simulating subject level data from the summary data from the open label study in AA using tofacitinib.<sup>12</sup> The adjusted standard deviation (SD) for the change from baseline was calculated to be ~32.43.

The sample size is based on the primary efficacy endpoint, mean change from baseline in SALT score at Week 24. The null hypothesis to be tested for one compound (PF-06700841) is to assess if the difference between PF-06700841 and placebo is less than or equal to 20 vs the alternative hypothesis if the difference between PF-06700841 and placebo is greater than 20. Using a between-group comparison at Week 24, for PF-06700841 vs placebo and PF-06651600 vs placebo, 30 completers in each arm provides approximately 89.9% power to detect a true mean change from baseline in SALT total equal to 15. This is for a test conducted at a one-sided level of significance of 2.5% (adjusted for two active vs placebo comparisons). Assuming a 30% average drop-out in the study the total sample size would be ~132.

For the biopsy sub-study which will be performed at selected sites, approximately 42 subjects will be randomized (30 completers; assuming 30% drop out rate. 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. Due to the exploratory nature of the sub-study, there is no formal sample-size calculation performed for the biopsy sub-study.



There is no re-randomization at the start of the Single-Blind Extension Period or Cross-Over Open Label Extension Period.

## **9.2. Efficacy Analysis During the Treatment Period**

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 randomized study medication) will be included in the efficacy data analyses. Alpha adjustments for primary and secondary endpoints will be described in the SAP.

### **9.2.1. Analysis of the Primary Endpoint During the Treatment Period**

The primary efficacy endpoint is change from baseline in the SALT score. The primary time point is Week 24. Baseline is defined as the last measurement prior to randomization (Day 1 of the Double-Blind Treatment Period). All other collection time points will be considered secondary. A linear mixed-effect repeated measures model with fixed effects for treatment, time (visit), baseline value of SALT and investigator site, and a random effect for subject, will be used to analyze the change from baseline in the SALT score (this will be denoted as the primary analysis). This model may also include effects for treatment by time interaction and baseline value of SALT by treatment interaction and disease sub-type. 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. Using this model, adjusted 95% upper confidence bound comparing the mean change from baseline in SALT estimates at Week 24 for PF-06700841 vs. placebo and PF-06651600 vs placebo will be computed. Alpha adjustments for primary and secondary endpoints will be described in the SAP.

Supplemental analyses of the primary variable will be performed to support the robustness of the conclusions drawn from the primary analysis described above such as, verify assumptions of possible normality violations, sensitivity analyses to account for informative drop-outs. Details of these supplemental analyses will be included in the SAP.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be provided for the baseline and change from baseline values by treatment group and visit.

### **9.2.2. Analysis of Secondary Endpoints During the Treatment Period**

The key secondary efficacy endpoint is proportion of subjects achieving a 30% improvement in SALT (SALT 30) at Week 24. The primary time point is Week 24. All other collection time points will be considered secondary.

The frequency and percentage of SALT 30 responders will be presented at all post-randomization visits as specified in the SoA where SALT is collected. The SALT 30 response rate will be analyzed by a generalized linear mixed model, with fixed factors of treatment, visit, treatment by visit, baseline SALT score. Within-subject covariance structure may be considered by assessing various models (eg, unstructured, Toeplitz and first order autoregressive etc.) and the corresponding results will be compared for the sake of checking

robustness. Comparison to placebo for this key secondary endpoint will be conducted at Week 24 as described by the statistical model above.

Detailed description of analyses for other secondary endpoints will be outlined in the SAP. Continuous and discrete modelling techniques will be applied whenever applicable.

### **9.2.3. Analysis of Other Endpoints During the Treatment Period**

CCI



Continuous and discrete modelling techniques will be applied whenever applicable. Distribution summaries will be presented by means of summary tables data visualization methods. Detailed description of analyses for other endpoints will be outlined in the SAP.

CCI



#### **9.2.3.1. Pharmacokinetic Analysis During the Treatment Period**

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.

PK concentrations will be summarized and presented with summary statistics. A population PK model may be developed for the purpose of estimating PK parameters. Any population PK model developed to characterize the PK data will be reported separately.

Data permitting, the relationship between exposure and clinical responses (efficacy and safety) from subjects with AA may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report (CSR) and may be reported separately.

#### **9.2.3.2. PK/PD Unblinding Plan**

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead may be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with applicable Pfizer standard operating procedures (SOPs) for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a fuller interpretation of the study upon completion (at appropriate interim milestone). This group will not serve on the study team during the period of early unblinding. The unblinding may occur after the last subject has been randomized. The details of the procedures will be

described in the PK/PD Unblinding Plan for Modelling and Simulation for study B7931005 which will be finalized prior to the start of the PK/PD unblinding.

CCI



### 9.3. Safety Analysis During the Treatment Period

The safety analysis set will include all subjects who have received at least one dose of the drug or placebo. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Categorical outcomes (eg, AEs) will be summarized by subject counts and percentage. Continuous outcome (eg, BP, heart rate, etc) will be summarized using N, mean, median, standard deviation, etc. Change from baseline in laboratory data and vital signs will also be summarized. Categorical summaries will be produced for ECGs. Subject listings will be produced for these safety endpoints accordingly.

The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP. CCI

There will be no adjustment for multiple comparisons or stratification factor in the analyses unless specified.

CCI



Nominal p-values (Tier 1 events only) and 95% confidence intervals (Tier 1 and Tier 2 events) will be provided for between treatment differences in the percentage of subjects with events. Reporting p-values and confidence intervals will follow Pfizer standard practice in the 3-tier approach.

## 9.4. Analysis During the Single-Blind Extension Period and Cross-Over Open Label Extension Period

### 9.4.1. Exploratory Efficacy Analysis During the Single-Blind Extension Period

Descriptive statistics will be provided for the exploratory efficacy analysis. Binary endpoints will be summarized with frequency and percentage by time point, and the continuous variables will be summarized with n, mean, median, standard deviation, etc. These summaries may be provided by the strata of responding status at entry to the Single-Blind Extension Period.

The efficacy will be compared between subjects who enter the Single-Blind Extension Period non-responder segment to receive active treatment directly and the subjects who are retreated with active treatment in the Single-Blind Extension Period Withdrawal/Retreatment segment. Additionally, for subjects who enter the Single-Blind Extension Period non-responder segment to receive active treatment directly and are initially treated with placebo in the Double-Blind Treatment Period, the active treatment will be compared with placebo in the Double-Blind Treatment Period to examine the efficacy. For continuous endpoints (such as SALT, CCI [REDACTED]) the change from baseline scores will be analyzed using an Mixed effect Model Repeat Measurement (MMRM) model as described for the Treatment Period primary efficacy analysis. The binary endpoints such as SALT30, SALT50, SALT75, SALT100, CCI [REDACTED] [REDACTED] respectively will be analyzed by generalized linear mixed model (GLMM) on observed data, and Chan and Zhang's exact method applied to non-responder imputation (NRI) data. CCI [REDACTED]

[REDACTED] Baseline is defined as the last measurement prior to randomization (Day 1 of the 24 week Double-Blind Treatment Period) when deriving the continuous and binary endpoints.

In addition, for subjects on placebo in the Single-Blind Extension Period, to estimate the maintenance of the efficacy effect, Kaplan-Meier method will be used to analyze the time to event (re-treatment) endpoint; and the change in SALT from Week 24 will be analyzed by MMRM model to explore the magnitude of efficacy over time after stopping active treatment.

All subjects who have received at least one dose of planned investigational product in the Single-Blind Extension Period will be included into the efficacy analyses. Detailed methodologies of these analyses will be described in the SAP.

CCI [REDACTED]  
[REDACTED]  
[REDACTED]

CCI [Redacted]

[Redacted]

CCI [Redacted]

**9.4.4. Safety Analysis for Single-Blind Extension Period and Cross-Over Open Label Extension Period**

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 on selected safety endpoints may be additionally summarized. Tier-1 analyses will not be done for the Single-Blind Extension Period and Cross-Over Open Label Extension Periods. 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 will be described in the SAP.

### **9.5. Interim Analysis During the Treatment Period**

The statistical analysis plan and the interim analysis plan for this protocol may 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 may be performed when approximately 50% of subjects have completed or had the chance to complete the Week 12 visit. Additional interim analyses may be performed based on emerging data.

The objective of this 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 45 subjects who complete or had the chance to complete Week 12. A non-informative prior will be used for the interim analysis. The decision at the end of the study is being at least 90% 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.

### **9.6. Data Monitoring Committee**

This study will use an internal review committee (IRC).

The IRC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The IRC will review accumulating renal safety data and may propose changes to the protocol as needed to ensure subject safety. The IRC may also review results of any interim analyses as described in [Section 9.5](#). The recommendations made by the IRC to alter the conduct of the study will be forwarded to Pfizer management for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

This study will utilize an independent separate Internal Review Committee to review the results of the interim analysis. Details of the logistics and operational aspects of the IA may be documented in an IA charter.

The committee will have completed its work and been dissolved once the database lock and data release occurs for the initial 24-week Treatment Period and study team becomes unblinded. Unblinded study team will continue monitoring of the safety of subjects in the study.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Data Collection Tools/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the

CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

## **11.2. Record Retention**

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.



## **12. ETHICS**

### **12.1. Institutional Review Board/Ethics Committee**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

### **12.3. Subject Information and Consent**

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

#### **12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in a Member State**

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

#### **13.2. End of Trial in All Other Participating Countries**

End of trial in all other participating countries is defined as last subject last visit (LSLV).

## **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06651600 and PF-06700841 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 business days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial US Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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## Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AA	alopecia areata
CCI	
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	active treatment
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC <sub>inf</sub>	area under the plasma concentration-time curve from time zero to infinity
AUC <sub>last</sub>	area under the plasma concentration time curve from time zero extrapolated to the last quantifiable concentration
AUC <sub>τ</sub>	area under the concentration-time curve from zero to 24 hours (QD) or zero to 12 hours (BID) post-dose at steady state
BA	bioavailability
BAEP	Brainstem Auditory Evoked Potential
CCI	
BCG	bacille calmette guérin
BID	twice a day
BP	blood pressure
BUN	blood urea nitrogen
CDS	core data sheet
CK	creatinine kinase
CL	clearance
C <sub>max</sub>	maximum plasma concentration
CMV	cytomegalovirus
CO	cross-over
COEOT	cross-over end of treatment
CRF	case report form
CSA	clinical study agreement
CsA	cyclosporine A
CSF	cerebrospinal fluid
CSR	clinical study report
CCI	
CT	computed tomography
CTA	clinical trial application
CTCAE	common terminology criteria for adverse events
DAI	dosage and administration instructions
DDI	drug-drug interaction

<b>Abbreviation</b>	<b>Term</b>
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EBV	epstein barr virus
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
CCI	
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
fu	fraction unbound
FU	follow up
GCP	good clinical practice
GI	gastrointestinal
CCI	
GM-CSF	granulocyte-macrophage colony-stimulating factor
GST	glutathione-S-transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
CCI	
HSV	herpes simplex virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IFN $\alpha$	interferon alfa

<b>Abbreviation</b>	<b>Term</b>
IFN $\gamma$	interferon gamma
Ig	Immunoglobulin
IGA	investigator's global assessment
IGRA	Interferon Gamma Release Assay
IgE	immunoglobulin E
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IP	investigational product
CCI	
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IVRS	interactive voice response system
IWR	interactive web response
JAK	janus kinase
LFT	liver function test
LLN	lower limit of normal
LOAEL	lowest observed adverse effect level
LPD	local product document
LSLV	last subject last visit
MAD	multiple ascending dose
MATEs	multidrug and toxin extrusion proteins
MDCK/MDR1	Madin Darby canine kidney cell line/multidrug resistance 1 gene
mITT	modified intention-to-treat
MMRM	mixed-effect models repeated measures
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NK	natural killer cells
NOAEL	no observed adverse effect level
NRI	non-responder imputation
CCI	
OAT2	organic anion transporter 2
OBU	oncology business unit
OCT2	organic cation transporter 2
PCD	primary completion date
PD	pharmacodynamic
PI	principal investigator
PFS	pre-filled syringe

<b>Abbreviation</b>	<b>Term</b>
P-gp	P-glycoprotein
PHQ-8	patient health questionnaire – 8 items
PK	pharmacokinetic
POC	proof-of-concept
POM	proof of mechanism
PPD	purified protein derivative
PRO	patient reported outcomes
PT	prothrombin time
PtGA	patient global assessment
QD	once daily
QFT-G	QuantiFERON <sup>®</sup> -TB Gold
QFT-GIT	QuantiFERON <sup>®</sup> -TB Gold In-Tube
R <sub>ac</sub>	accumulation ratio
RNA	ribonucleic acid
RRCK	ralph russ canine kidney cells
SAD	single ascending dose
SAE	serious adverse event
SALT	severity of alopecia tool
SAP	statistical analysis plan
SBQ-R	suicidal behaviors questionnaire –revised
SC	subcutaneous
SCL	supply chain lead
SD	standard deviation
SOA	Schedule of activities
SOC	system organ class
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SSC	special safety concern
STATs	signal transducers and activators of transcription
t <sub>½</sub>	half life
TB	tuberculosis
TBNK	T, B, and natural killer cells
TDAR	T cell-dependent antibody response
TEAE	treatment-emergent adverse event
T <sub>H1</sub>	type 1 helper T cell
T <sub>H2</sub>	type 2 helper T cell
T <sub>max</sub>	the time after administration of a drug when the maximum plasma concentration is reached
TYK2	tyrosine kinase 2
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States

<b>Abbreviation</b>	<b>Term</b>
USPI	United States package insert
UVA	ultraviolet A light
UVB	ultraviolet B light
UVR	ultraviolet radiation
VZV	varicella zoster virus

## Appendix 2. Prohibited Concomitant Medications

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are either moderate to potent CYP3A inhibitors or inducers or substrates, strong P-glycoprotein (P-gp) inhibitors, substrate of MDR1, or substrate of OCT2/MATE.

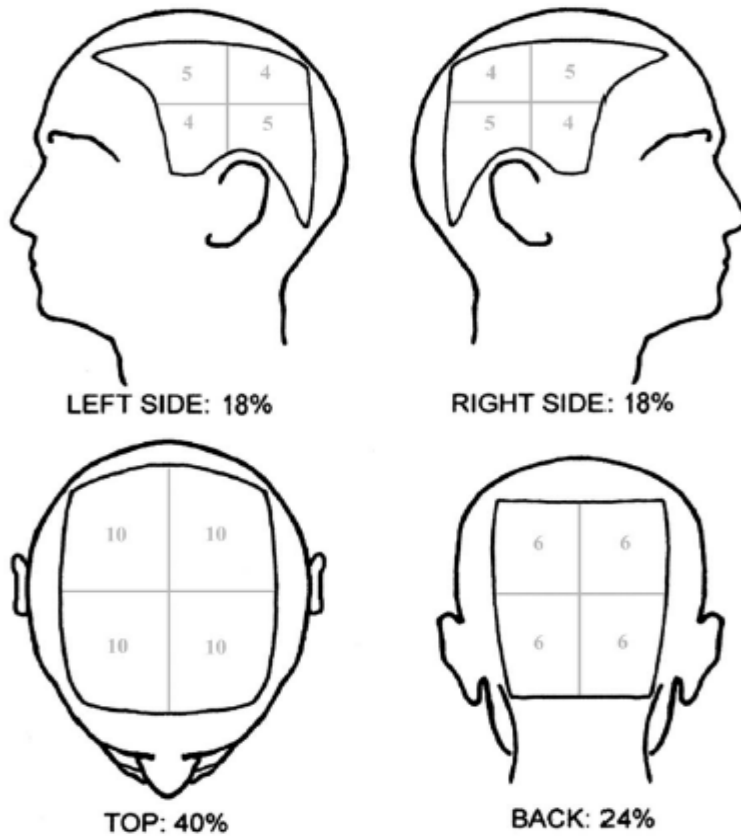
Moderate to Potent CYP3A Inhibitors*	Moderate to Potent CYP3A Inducers**	Substrates of CYP3A	Strong P-gp inhibitors	Substrates of MDR1	Substrates of OCT2/MATE
Amprenavir	Avasimibe#	Simvastatin or Simvastatin-containing products	Quinidine	Digoxin	Dofetilide
Amiodarone	Bosentan				
Aprepitant	Barbiturates				
Atazanavir	Carbamazepine #				
Boceprevir	Efavirenz				
Casopitant	Etravirine				
Cimetidine	Mitotane#				
Ciprofloxacin	Modafinil				
Clarithromycin#	Nafcillin				
Cobicistat#	Phenobarbital#				
Conivaptan#	Phenytoin#				
Darunavir	Rifabutin#				
Diethylthiocarbamate	Rifampin #				
Diltiazem	St. John's Wort#				
Dronedarone	Talviraline				
Elvitegravir#					
Erythromycin					
Fluconazole					
Fluvoxamine					
Imatinib					
Indinavir#					
Itraconazole#					
Ketoconazole#					
Lopinavir#					
Mibefradil#					
Mifepristone (RU486)					
Nefazodone#					
Nelfinavir#					
Norfloxacin					
Posaconazole#					
Ritonavir #					
Saquinavir#					
Schisandra sphenanthera					
Telaprevir					
Telithromycin#					

Tipranavir#					
Tofisopam					
Troleandomycin#					
Verapamil					
Voriconazole#					
<p>* All prohibited drugs that are CYP3A inhibitors require at least a 7 day or 5 half-lives (whichever is longer) prior to the first dose of study drug. Note: Amiodarone requires discontinuation at least 290 days (~5 half-lives, half-life averages ~58 days) prior to the first dose of study drug.</p> <p>** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) prior to the first dose of study drug.</p> <p># Noted as potent inhibitors or inducers.</p> <p>It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.</p> <p><b>In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:</b></p> <p>Moderate to potent inhibitors and inducers of CYP3A are not permitted in the study EXCEPT in emergency situations requiring no more than one day of administration. <i>Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.</i> Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.</p>					

### Appendix 3. Severity of Alopecia Tool (SALT)

(Olsen 2011)<sup>20</sup>

SALT score=  $0.18 \times \text{score\_left side} + 0.18 \times \text{score\_right side} + 0.4 \times \text{score\_top} + 0.24 \times \text{score\_back}$



For example:





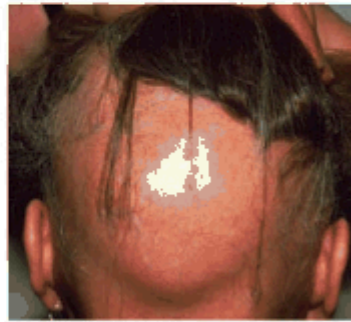
$$80\% \times 0.18 = 14.48\%$$



$$95\% \times 0.18 = 17.1\%$$



$$65\% \times 0.40 = 26\%$$



$$85\% \times 0.24 = 20.4\%$$

SALT score

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



$$95\% \times 0.18 = 17.1\%$$



$$95\% \times 0.18 = 17.1\%$$



$$50\% \times 0.40 = 20.0\%$$



$$65\% \times 0.24 = 15.6\%$$

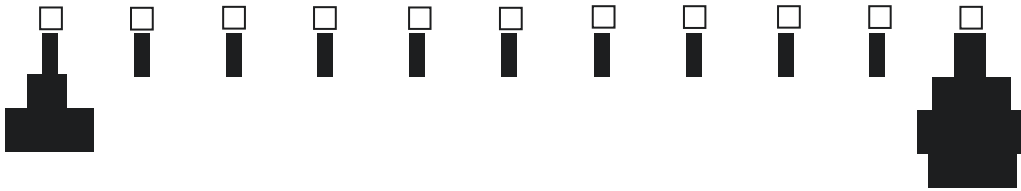
SALT score

$$17.1\% + 17.1\% + 20\% + 15.6\% = 69.8\%$$

#### Appendix 4. Management of Dermatological Events

Dermatologic Event (CTCAE v 4.0)	Course of Management
<b>Acne/Acneiform Rash/Maculopapular Rash</b>	
Grade 1/2	<ol style="list-style-type: none"> <li>1. Investigator's discretion for withdrawing study medication.</li> <li>2. Execute reasonable monitoring.</li> <li>3. Consider treatment with topical agents such as clindamycin or corticosteroids.</li> </ol>
Grade 3	<ol style="list-style-type: none"> <li>1. Discontinue study medication.</li> <li>2. Monitor to resolution (defined as a Return to Baseline status).</li> <li>3. Consider treatment with topical agents such as clindamycin or corticosteroids.</li> </ol>
<b>Pruritus</b>	
Grade 1 Mild or localized	<ol style="list-style-type: none"> <li>1. Investigator's discretion for withdrawing study medication.</li> <li>2. Execute reasonable monitoring.</li> <li>3. Consider treatment with topical agents such as clindamycin or corticosteroids.</li> </ol>
Grade 2 Intense or widespread	<ol style="list-style-type: none"> <li>1. Discontinuation of the study medication may not be required unless condition is sustained &gt;4 days or at the investigator's discretion.</li> <li>2. Execute reasonable monitoring.</li> <li>3. Consider treatment with topical agents such as clindamycin or corticosteroids.</li> </ol>
Grade 3 Intense or widespread and interfering with activities of daily living	<ol style="list-style-type: none"> <li>1. Permanently discontinue study medication.</li> <li>2. Monitor to resolution (Return to Baseline).</li> <li>3. Consider treatment with topical agents such as clindamycin or corticosteroids.</li> </ol>

CCI [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]



## **Appendix 6. Guidelines for Subject Safety Monitoring and Discontinuation**

These guidelines for subject safety monitoring and discontinuation are to be applied to all subjects in study B7931005. Additional individual subject monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

### **Appendix 6.1. Monitoring**

All potential treatment-related reports of rash will be followed up until resolution or agreement with Pfizer.

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

- Absolute neutrophil count  $<2000/\text{mm}^3$  ( $2.0 \times 10^9/\text{L}$ );
- Hemoglobin  $<9.0$  g/dL;
- Platelet count below  $<100,000/\text{mm}^3$  ( $100 \times 10^9/\text{L}$ );
- Lymphocytes  $<600/\text{mm}^3$ ;  $<0.6 \times 10^9/\text{L}$ .
- CK  $>3 \times \text{ULN}$  (this also triggers urine myoglobin).

### **Appendix 6.2. Discontinuation**

**Treatment will be discontinued and the subject withdrawn from this study for:**

**Adverse Events:**

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization;
- Clinically meaningful, treatment related decline in hearing from baseline.
- Other serious or severe AEs, at the discretion of the investigator or sponsor.

**Potential Cases of Potential Drug-Related Rash:**

- Serious or severe drug-related rash at the discretion of the investigator or sponsor ([Appendix 4](#)).

### **Potential Cases of Decreased eGFR:**

If an individual subject demonstrates a CONCOMITANT serum creatinine-based AND serum Cystatin C-based eGFR decline of  $\geq 30\%$  compared to the subject's baseline eGFR, then the subject should not be further dosed and adequate, immediate, supportive measures and **immediate evaluation by nephrologist (preferably within 24 hours)** with appropriate management should be taken for evaluation and treatment as clinically indicated. If the subject cannot be seen by a nephrologist within 24 hours, then the subject should be sent to a local emergency room for assessment of renal function. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline  $\pm 15\%$  or the renal parameters are deemed to be stable by the nephrologist and/or P (see protocol [Section 8.4.3](#)).

### **Psychological Assessment**

At any post-baseline visits, if there are "yes" answers on items 4, 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.

### **Vital Signs:**

The following vital sign abnormality will **require discontinuation** if it is confirmed. Confirmation through re-testing should occur within 1 week:

- Diastolic: recurrent or persistent ( $\geq 24$  hrs) or symptomatic increase from baseline, in same posture, by  $>20$  mmHg.

### **Laboratory Abnormalities:**

All the following laboratory abnormalities **require discontinuation** if they are confirmed. Confirmation through re-testing should occur within 1 week:

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

<sup>a</sup> Total bilirubin ≥1.5 x 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.

**Discontinuation/End of Treatment Monitoring:**

Any subject meeting discontinuation criteria must enter into the Follow-up Period with their first follow-up visit occurring 1 week after their last dose whenever possible, until the event has returned to normal or baseline levels or is deemed clinically stable. The procedures scheduled for ET Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Additional follow-up visits may occur as needed until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable.

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## Appendix 9. Suicidal Behaviors Questionnaire-Revised (SBQ-R)

(Osman, Bagge et al. 2001)<sup>21</sup>

### SBQ-R Suicide Behaviors Questionnaire-Revised

Patient Name \_\_\_\_\_ Date of Visit \_\_\_\_\_

**Instructions:** Please check the number beside the statement or phrase that best applies to you.

**1. Have you ever thought about or attempted to kill yourself?** (check one only)

- 1. Never
- 2. It was just a brief passing thought
- 3a. I have had a plan at least once to kill myself but did not try to do it
- 3b. I have had a plan at least once to kill myself and really wanted to die
- 4a. I have attempted to kill myself, but did not want to die
- 4b. I have attempted to kill myself, and really hoped to die

**2. How often have you thought about killing yourself in the past year?** (check one only)

- 1. Never
- 2. Rarely (1 time)
- 3. Sometimes (2 times)
- 4. Often (3-4 times)
- 5. Very Often (5 or more times)

**3. Have you ever told someone that you were going to commit suicide, or that you might do it?** (check one only)

- 1. No
- 2a. Yes, at one time, but did not really want to die
- 2b. Yes, at one time, and really wanted to die
- 3a. Yes, more than once, but did not want to do it
- 3b. Yes, more than once, and really wanted to do it

**4. How likely is it that you will attempt suicide someday?** (check one only)

- |  |   |
|--|---|
| <input type="checkbox"/> 0. Never            | <input type="checkbox"/> 4. Likely        |
| <input type="checkbox"/> 1. No chance at all | <input type="checkbox"/> 5. Rather likely |
| <input type="checkbox"/> 2. Rather unlikely  | <input type="checkbox"/> 6. Very likely   |
| <input type="checkbox"/> 3. Unlikely         |   |

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## Appendix 10. Patient Health Questionnaire – 8 items (PHQ-8)

(Kroenke K 2002)<sup>13</sup>

### Appendix A: Patient Health Questionnaire eight-item depression measure (PHQ-8) PHQ-8

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
(For office coding: Total Score _____ = _____ + _____ + _____)				



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