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

Investigational Product Number:	PF-06651600 and PF-06700841
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI (PF-06651600) CCI (PF-06700841)
European Clinical Trials Database (EudraCT) Number:	2018-001271-20
Protocol Number:	B7981019
Phase:	2b

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	26 June 2020	• In the Schedule of Activities, Protocol Summary, Section 1.2.4 Study Rationale, Section 2 Study Objectives and Endpoints, Section 3 Study Design, Section 7.4 Clinical Efficacy Assessment, Section 7.7 Photography, and Section 9 Data Analysis/Statistical Methods, added central read Facial Vitiligo Area Scoring Index (facial-VASI) as the new primary endpoint. Added new key secondary endpoint: Proportion of subjects achieving central read facial-VASI75 (defined as at least 75% improvement in central read facial-VASI from baseline) at Week 24. Rationale: As this is an unprecedented indication, there has been limited clinical trial experience with the VASI and facial-VASI scoring for de-pigmented vitiliginous lesions. Discrepancies have been identified by an external blinded expert consultant in preparation for the protocol specified interim analysis. Based on the digital photographs available, total body VASI scores cannot be evaluated by a central reader. Due to this limitation and in order to preserve the scientific integrity of the study, the primary endpoint is changed from the percent change from baseline in total body VASI at Week 24 to percent change from baseline in central read facial-VASI at Week 24. Central read facial-VASI75 score will be added as a key secondary endpoint. • In the Section 2 Study Objectives and Endpoints, added new exploratory endpoint: proportion of subjects achieving “very much improved” on patient global impression of change in vitiligo (PGIC-V). Rationale: This change is to correct the editorial error and to be consistent with the scaling of PGIC on evaluation of improvement assessed as

		"very much improved" and "much improved". • In the Section 7.4.3 Facial Vitiligo Area Scoring Index Site Assessment, clarification added that the site assessment facial-VASI will be performed by the investigator(s). Rationale: To differentiate site assessment and central assessment facial-VASI. • In Section 9.1 Sample Size Determination, the sample size rationale was updated to reflect the assumptions for the new primary endpoint, central read facial-VASI. Rationale: The sample size rationale is updated to be aligned with the new primary endpoint. • In Section 9.2 Efficacy Analysis, the analysis of the primary endpoint and secondary endpoints were updated. Rationale: The analysis is updated to be aligned with the new primary and key secondary endpoint. • In Section 9.5 Safety Analysis during the Dose Ranging Period, the detail of the analysis is removed. Rationale: The detail of the analysis will be provided in the statistical analysis plan. • In the Appendix 11, added Alternative Measures During Public Emergencies. Rationale: The Alternative Measures During Public Emergencies added to address alternative protocol actions to follow during COVID-9 pandemic. Minor administrative changes and sentence revisions made throughout the document.
Amendment 4	04 November 2019	• In the Cover page, added IND number for PF-06700841.

		• In the Schedule of Activities, Section 2 Study Objectives and Endpoints, Section 6 Study Procedures, and Section 7.6 Patient Report Outcome Measures, added a new PRO: Vitiligo Noticeability Scale (VNS). Rationale: VNS added to measure treatment effect from the patient perspective by comparing noticeability of vitiligo patches. [redacted] • In Section 1.2.3.2 Clinical Experience, added B7931019 study data and safety information from phase 2 studies. Rationale: Additional safety information was added based on emerging data. • In Section 2 Study Objectives and Endpoints, Change of extent of depigmentation in target lesion(s) was deleted from exploratory endpoints during the Extension Period. Rationale: to be consistent with the Schedule of Activities as extent of depigmentation was not collected during the Extension Period. [redacted] • In Section 7 Assessments, added Section 7. 15. If during the event adjudication, the specific documents are needed to support event adjudication by the Adjudication/Review

		Committees, additional tests or procedures that are not part of the study but that could be related to the study may be requested. Rationale: The paragraph is added to provide clarity to support safety adjudication process. • In Appendix 2, clarification was provided for Prohibited Concomitant Medications related to applicability to PF-06651600 and PF-06700841. Minor administrative changes and sentence revisions made throughout the document.
Amendment 3	02 July 2019	Changes requested from the Italian Medicines Agency (AIFA). • In the Section 1.2.5 Summary of benefits and risks, added risk-benefit assessment. • In the Section 4.2 Exclusion Criteria, removed interferences of the Sponsor, through the Sponsor medical monitor, in the clinical choices of the investigator for the eligibility of patients from criteria #3, 8, 10, and 16.
Amendment 2	14 June 2019	Changes requested from The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) for Germany. • In the Schedule of Activities and Section 6.1 Screening, added statement that subjects will be provided with an emergency ID card. • In the Schedule of Activities and Section 7 Assessments, added erythrocyte sedimentation rate (ESR) testing to be performed at local laboratory at every visit. These changes are in effect for Germany only. • In the Section 1.2.4.1 PF-06651600 Dose Rationale, added rationale for administering 10 mg PF-06651600 QD in the Dose Ranging Period not in the Extension Period.

		• In the Section 4.2 Exclusion Criteria, added exclusion criterion for subjects who have galactosemia (galactose-1-phosphate-uridylyltransferase or UDP-galactose-4-epimerase or galactokinase deficiency; Fanconi Bickel syndrome), a congenital lactase deficiency or glucose-galactose malabsorption. • In the Section 4.2 Exclusion Criteria, added exclusion criterion for subjects whose diabetes mellitus is poorly controlled. • In the Section 8 Adverse Event Reporting, added definitions of adverse reaction (AR), serious adverse reaction (SAR), and suspected unexpected serious adverse reactions (SUSAR). • In the Appendix 2 Prohibited Concomitant medications, added Rosuvastatin as a sensitive substrate to BCRP. This change is in effect for Germany only. • Minor administrative changes and sentence revisions made throughout the document.
Amendment 1	04 March 2019	• In the Schedule of Activities, Section 2 Study Objectives and Endpoints, and Section 7 Assessments, added target lesions(s) assessments. Rationale: Target lesion(s) assessments are added to provide opportunity to evaluate the change of extent of depigmentation of stable lesion and segmental lesion (if applicable) during the study to support the extrapolability of results across vitiligo types. • In the Schedule of Activities and Section 7 Assessments, details of Dermoscopy assessment are revised. Rationale: Details of Dermoscopy assessment are revised to provide a clearer guidance for the site. • In the Section 2 Study Objectives and Endpoints, added exploratory Endpoints: absolute change

		from baseline in facialVASI and VES in the Dose Ranging Period and absolute change from baseline in facialVASI, VES in the Extension Period. Rationale: The exploratory endpoints outlined above are added to provide opportunity to evaluate the efficacy of PF-06651600 compared to placebo by facial-VASI and VES during the Dose Ranging Period and to evaluate the long term efficacy of PF-06651600 and efficacy of PF-06700841 by absolute change from baseline in facial-VASI, VES. • In the Schedule of Activities, visit window is revised for Table 3, 4, and 5. Rationale: Visit Window is revised to allow greater flexibility for participant scheduling. • In the Section 1.2.3.1 Nonclinical Safety, added new non-clinical safety information. Rationale: emerging data from Rat Fertility study was added. • In the Section 1.2.3.2 Clinical Experience, emerging data was added demonstrating a drug interaction (DDI) with oral contraceptives containing ethinyl estradiol (EE). Section 4.4.1 Contraception Requirements were modified to include an additional barrier method of contraception when combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation is used. Rationale: Contraception requirements revised based on the new oral contraceptive DDI study to ensure patient safety. • Section 1.2.4 Study Rationale, Section 4 Subject Eligibility Criteria, and Section 4.4.1 Contraception Requirements, No contraception methods are required for male subjects under

		PF-06651600 or placebo in the study. CCI  • In the Section 4.4 Lifestyle Requirements, new tattoo is prohibited during the study. Rationale: New tattoo that may interfere with vitiligo assessment is prohibited during the study to ensure the consistency of clinical evaluation. • In the Section 7.4 Clinical Efficacy Assessments, updated description of static investigator global assessment (sIGA). Rationale: sIGA description was revised as a clinical efficacy measurement instrument. • In the Section 9 Data Analysis/Statistical Methods, safety adjudication committees are added. Rationale: Safety adjudication committees are added to review opportunistic infections, cardiovascular, and malignancy events to ensure patient safety and to have a consistent clinical database across the studies under the same compound PF-06651600. • In the Appendix 10 CountrySpecific Requirements, added hepatitis B testing in Korea, Japan and Taiwan. Rationale: Hepatitis B testing is added to comply with country specific requirements. • Minor administrative changes and sentence revisions made throughout the document. Rationale: Revisions made for clarity and to

		correct minor grammatical or spelling errors.
Original protocol	28 August 2018	Not applicable (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 which are critical for leukocyte activation, proliferation, survival and function.[35,36] Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of the transcription (STAT) family of transcription factors. The STATs are phosphorylated and subsequently translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.[35,36]

PF-06651600 is an orally bioavailable small molecule that inhibits, by irreversibly blocking the ATP binding site, JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family (bruton's tyrosine kinase [BTK], bone marrow-expressed kinase [BMX], inducible T-cell kinase [ITK], TEC, resting lymphocyte kinase [RLK/TXK]), with high selectivity over the other three JAK isoforms, JAK1, JAK2, and TYK2, as well as over the broader kinome. PF-06651600 is currently being investigated in patients with rheumatoid arthritis, alopecia areata, ulcerative colitis, and Crohn's disease and will be investigated in vitiligo. Considering the pathogenesis of vitiligo and mechanisms of action for PF-06651600, the hypothesis is to determine if PF-06651600 will have a clinically meaningful effect on treating active non-segmental vitiligo.

PF-06700841 is a dual TYK2/JAK1 inhibitor with a good selectivity profile over the other human kinases including JAK2. TYK2/JAK1 play critical roles in interferon gamma (IFNγ) signaling that regulate the signal transduction pathways triggered by several cytokines implicated in the pathogenesis of vitiligo.[21]

Study Objectives and Endpoints

Study Objectives and Endpoints during Dose Ranging Period

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

Secondary Objectives:	**Secondary Endpoints:**
Key Secondary Objective: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by facial-VASI at Week 24 in adult subjects with active non-segmental vitiligo.	Key Secondary Endpoint: • Proportion of subjects achieving central read facial-VASI75 (defined as at least 75% improvement in central read facial-VASI from baseline) at Week 24.
Other Secondary Objectives: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by other clinical assessments over time in adult subjects with active non-segmental vitiligo.	Other Secondary Endpoints: • Proportion of subjects achieving VASI50 (defined as at least 50% improvement in VASI from baseline) at Week 24. • Percent change from baseline in VASI, central read and site assessment of the facial-VASI, vitiligo extent score (VES), and self assessment VES (SA-VES) and absolute change from baseline in VASI at designated time points (except for Week 24 for central read facial-VASI). • Proportion of subjects achieving VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in VASI from baseline), central read and site assessment of the facial-VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in facial-VASI from baseline), and VES50/75/90/100 (defined as at least 50%/75%/90%/100% improvement in VES from baseline) at designated time points (except for Week 24 in VASI50 and central read facial-VASI75). • Change from baseline in vitiligo specific quality of life (VitiQoL) at designated time points. • Proportion of subjects achieving a static investigator global assessment (sIGA) 0 or 1, and at least 2-point improvement at Week 24.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
• To evaluate the efficacy of PF-06651600 compared to placebo by other efficacy markers in adult subjects with active non-segmental vitiligo.	• Absolute change from baseline in central read and site assessment of the facial-VASI and VES at designated time points. • Change from baseline in dermatology life quality index (DLQI)/EuroQol 5 dimension 5 level (EQ-5D-5L)/healthcare resource utilization (HCRU) at designated time points as specified in the SoA. • Facial target lesion improvement (by planimetry) of ≥50% from baseline at Week 24 (if data allow). • Proportion of subjects achieving “very much improved” or “much improved” on patient global impression of change in vitiligo (PGIC-V). • Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) on Vitiligo

	Noticeability Scale (VNS). • Change of extent of depigmentation in target lesion(s).
C C I [redacted]	[redacted]
C C I [redacted]	[redacted]
C C I [redacted]	[redacted]
• To evaluate the effect of PF-06651600 on psychological assessments over time in adult subjects with active non-segmental vitiligo.	• Change from baseline in Columbia Suicide Severity Rating Scale (C-SSRS) and hospital anxiety and depression scale (HADS) as specified in the SoA.
C C I [redacted]	[redacted]

Study Objectives and Endpoints during Extension Period

Primary Objective:	**Primary Endpoints:**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in adult subjects with active non-segmental vitiligo.	• Incidence of treatment-emergent AEs and SAEs during the Extension Period. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and liver function tests during the Extension Period.
Exploratory Objectives:	**Exploratory Endpoints:**
• To evaluate the long term efficacy of PF-06651600, efficacy of PF-06651600 and add-on narrow band ultraviolet B (nbUVB), in adult subjects with active	• Percent change from baseline in VASI during the Extension Period. • Proportion of subjects achieving VASI50/75/90/100 and central read* and site assessment of the

non-segmental vitiligo. • To evaluate the efficacy of PF-06700841 in a subset of adult subjects with active non-segmental vitiligo.	facial-VASI50/75/90/100 during the Extension Period. • Percent change from baseline in VASI, central read* and site assessment of the facial-VASI, VES, and SA-VES and absolute change from baseline in VASI, central read* and site assessment of the facial-VASI, and VES during the Extension Period. • Change from baseline in VitiQoL during the Extension Period. • Proportion of subjects achieving a sIGA 0 or 1, and at least 2-point improvement during the Extension Period. • Change from baseline in DLQI/EQ-5D-5L/HCRU in Extension Period. • Change from baseline in C-SSRS and HADS at designated time in the Extension Period as specified in the SoA. • Proportion of subjects achieving "very much improved" or "much improved" on patient global impression of change in vitiligo (PGIC-V). • Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) on Vitiligo Noticeability Scale (VNS).
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*. Central read facial-VASI may be performed and analyzed in the Extension Period as an exploratory endpoint.

Study Design and Treatments

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

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

Subjects will be screened within 28 days prior to the first dose of Investigational product (IP) to confirm that they meet the subject selection criteria for the study. Subjects will be randomized to 1 of 5 treatment groups or placebo. An induction dose of 200 mg once daily (QD) of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), an induction dose of 100 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), a dose of 50 mg QD of PF-06651600 for 24 weeks (n=60), a dose of 30 mg QD of PF-06651600 for 24 weeks (n=45), a dose of 10 mg QD of PF-06651600 for 24 weeks (n=45), and matching placebo for 24 weeks (n=60) will be investigated.

All subjects who complete the initial 24-week Dose Ranging Period may enter the Extension Period and will be allocated into 6 groups by pre-specified criteria. The pre-specified criteria will be described in the Statistical Analysis Plan for this protocol.

- Group 1: Induction dose of 60 mg QD of PF-06700841 for 4 weeks followed by maintenance dosing of 30 mg QD of PF-06700841 for 16 weeks after a 4-week drug holiday (with no IP). This arm is open label.

- Group 2: Induction dose of 200 mg QD of PF-06651600 plus standardized narrow band UVB (nbUVB) add-on therapy for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 plus standardized nbUVB add-on therapy for 20 weeks (only for subjects who provide nbUVB consent). This arm is open label.

- Group 3: Induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks. This arm is double blinded.

- Group 4: 50 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.

- Group 5: 30 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.

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

CCI [redacted]

Subjects who complete Extension Period (except for Group 6) will enter the 8-week Follow-up Period. Subjects who discontinue during the initial Dose Ranging Period will not be eligible for the Extension Period. Subjects who withdraw from the treatment will have the early termination (ET) visit and end of study (EOS) Visit.

Statistical Methods

A comprehensive overall statistical analysis plan (SAP) will be provided prior to the un-blinding of the trial.

The sample size rationale is based on the primary efficacy endpoint, percent change from baseline in central read facial vitiligo area scoring index (facial-VASI) score at Week 24.

All subjects who receive at least one dose of randomized investigational product, and have a baseline measurement will be included in the efficacy data analyses.

CCI [redacted]

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

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.

Schedule of Activities for Screening Period and Dose Ranging Period

Table 1. Schedule of Activities for Screening Period and Dose Ranging Period

Protocol Activity	Screening Period	Dose Ranging Period							
		Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (20 weeks)				
Visit Identifier	1	2	3	4	5	6	7	8	9
Visit Day[a]	Day -28 to -1	Day 1 (baseline)	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169
Week	N/A		W2	W4	W8	W12	W16	W20	W24
Visit Window	N/A		±3 Days based on Day 1 visit		±5 Days based on Day 1 visit				
Enrollment procedures									
Informed consent	X								
Inclusion/Exclusion criteria	X	X							
Demographics	X								
Medical history and Vitiligo disease history[b]	X	X							
Medical procedures									
Complete physical examination[c]	X	X							X
Targeted physical examination[d]			X	X	X	X	X	X	
Vital signs[e]	X	X	X	X	X	X	X	X	X
12-Lead ECG[f]	X	X				X			X
Height[g]		X							
Weight[h]		X							
Chest radiographs[i]	X								
Audiometry[j]	X								X
Laboratory Assessments									
Hematology	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X

Protocol Activity	Screening Period	Dose Ranging Period							
		Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (20 weeks)				
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Day[a]	**Day -28 to -1**	**Day 1 (baseline)**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**
Week	**N/A**		**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**
Visit Window	**N/A**		**±3 Days based on Day 1 visit**		**±5 Days based on Day 1 visit**				
ESR[cc]	X	X	X	X	X	X	X	X	X
Fasting lipid Panel[k]		X			X				X
Urinalysis[l]	X	X	X	X	X	X	X	X	X
Urine Myoglobin[m]	X								
Serum FSH (WONCBP only) or serum pregnancy test (WOCBP)[n]	X								
Urine pregnancy test (WOCBP)[o]		X	X	X	X	X	X	X	X
HIV testing[p]	X								
HBsAg, HBcAb, (HepB reflex testing), and HCVAb[q]	X								
Tuberculosis test[r]	X								
Viral Surveillance: EBV, CMV, HSV1, HSV2, and VZV		X							X
HbA1c	X								
CCI [redacted]									
[redacted]		[redacted]		[redacted]					[redacted]
[redacted]		[redacted]		[redacted]					[redacted]
[redacted]		[redacted]		[redacted]					[redacted]
Trial treatment									
Sunscreen dispensing[s]		X							
e-diary dispensing[t]		X							
IRT registration	X								
Randomization		X							
Provide and review dosing instructions		X	X	X	X	X	X	X	
Investigational product (PF-06651600) dispensing		X	X	X	X	X	X	X	X[u]

Protocol Activity	Screening Period	Dose Ranging Period							
		Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (20 weeks)				
Visit Identifier	1	2	3	4	5	6	7	8	9
Visit Day[a]	Day -28 to -1	Day 1 (baseline)	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169
Week	N/A		W2	W4	W8	W12	W16	W20	W24
Visit Window	N/A		±3 Days based on Day 1 visit		±5 Days based on Day 1 visit				
Investigational product (PF-06651600) administration[u]		X	→	→	→	→	→	→	X
Investigational product (PF-06651600) accountability and compliance			X	X	X	X	X	X	X
Clinical assessments									
Fitzpatrick Skin Type Assessment	X								
sIGA	X	X		X	X	X	X	X	X
VASI	X	X		X	X	X	X	X	X
Central read facial-VASI	X	X		X	X		X		X
Facial-VASI (site assessment)	X	X		X	X	X	X	X	X
BSA	X	X		X	X		X		X
VES	X	X		X	X		X		X
Photograph[v]	X	X		X	X		X		X
C-SSRS[w]	X	X		X	X		X		X
Dermoscopy[x]	X	X							X
Target Lesion(s) Assessment		X				X			X
Patient reported outcome[y]									
SA-VES	X	X		X			X		X
VitiQoL	X	X		X			X		X
DLQI	X	X		X			X		X
HADS	X	X		X					X
PHQ-8	X								
PGIC-V									X
EQ-5D-5L		X							X
HCRU		X				X			X
VNS									X
CCI [redacted]									
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]			[redacted]
[redacted]				[redacted]	[redacted]	[redacted]			[redacted]

Protocol Activity	Screening Period	Dose Ranging Period							
		Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (20 weeks)				
Visit Identifier	1	2	3	4	5	6	7	8	9
Visit Day[a]	Day -28 to -1	Day 1 (baseline)	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169
Week	N/A		W2	W4	W8	W12	W16	W20	W24
Visit Window	N/A		±3 Days based on Day 1 visit		±5 Days based on Day 1 visit				
CCI [redacted]									
[redacted]									
[redacted]									
[redacted]									
Other									
Prior and current concomitant Treatment(s)	X	→	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	X
Contraception check	X	X	X	X	X	X	X	X	X
Sun exposure (E-diary) check		X	X	X	X	X	X	X	X
Emergency ID card	X								
CCI [redacted]									
[redacted]									
CCI [redacted]									
[redacted]									
[redacted]									
[redacted]									

Abbreviations: →= ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI [redacted]; FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HbA1c = glycosylated hemoglobin A1c; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI [redacted] IL= interleukin; CCI [redacted]; PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI [redacted] SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI [redacted] VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] Day relative to start of study treatment (Day 1). Induction Phase is from Day 1 (baseline) to Week 4 Visit. Maintenance Phase is from the day after Week 4 Visit to Week 24 Visit.

[b] Medical history and vitiligo disease history includes detailed histories of conditions specified in Section 7.3.2.

[c] 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 may include visual inspection of the breasts and external genitalia.

[d] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[e] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[f] ECG should be performed before laboratory blood collection.

[g] Height will be measured without shoes.

[h] 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 (Section 7.3.2). Official reading must be located in the source documentation.

[j] Audiometry assessments may be performed at Screening Visit or within 8 weeks prior to Day 1. Evaluation for Screening must be completed for all subjects and results available prior to Day 1. At screening, in addition to audiogram, information including auditory medical history and additional examinations (ie, otoscopic exam) will be collected. At subsequent visits, audiograms will be performed; based upon results, additional audiometry assessments may be required. For details, refer to the Section 7.3.7. For subjects who terminate early from the study, efforts must be made to complete the audiogram testing.

[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] 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.

[m] Urine myoglobin will be measured at Screening and in case of CK >3 x ULN during the study.

[n] Serum pregnancy testing at screening is required for female subjects of childbearing potential. Follicle stimulating hormone (FSH) test to be performed at Screening for female subjects of non-childbearing potential 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. Note: For Japan, Korea and Taiwan, please refer to Appendix 10.

[r] Subjects can be TB screened using the Mantoux/PPD Tuberculin Skin Test or Interferon Gamma Release Assay (IGRA) test. 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 7.3.5.

[s] Sunscreen will be provided to subjects at the Baseline Visit and re-supplied during the study as applicable. Subjects will use the study provided sunscreen Day 1 through to the End of Study Visit.

[t] E-diary will be provided to subjects at the Baseline Visit.

[u] 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. IP dispensing and administration will be performed at Week 24 Visit (#9) for subjects assigned to Group 2, 3, 4, and 5 in the Extension Period.

[v] Photographs of face will be obtained at Screening and Baseline to verify BSA ≥0.25% involvement on the face. Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided. The photos may be reviewed by an independent consultant to confirm the facial-VASI at screening visit and baseline visit.

[w] Subjects who have recent or active suicidal ideation or behavior will be excluded from the study or discontinued from the study per Section 4.2.

[x] Dermoscopy will be performed per SOA. At least 2 different anatomical regions based on VES will be selected on Screening. At least two fields (possibly peripheral and central) from the largest lesion in the selected anatomical region will be examined to determine if white hair is present in less than 30% of hair in the depigmented lesion. Number of fields with less than 30% of white hair will be recorded. The same chosen lesions will be assessed per SOA. The same dermoscopy should be used throughout the study.

[y] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PHQ-8, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered.

[CCI] [redacted]

[cc] For Germany only: ESR will be performed at local laboratory.

[CC] [redacted]

Schedule of Activities for Extension Period

Table 2. Schedule of Activities for Group 1 in the Extension Period (Subjects Assigned to Receive PF-06700841; Open Label)

Protocol Activity	Extension Period							
	Drug Holiday[a] (4 weeks)	Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (16 weeks)			
Visit Identifier	10	11	12	13	14	15	16	17
Visit Day	4 weeks	198	212	226	254	282	310	338
Week	N/A	ExW4	ExW6	ExW8	ExW12	ExW16	ExW20	ExW24
Visit Window	N/A	±7 Days based on Day 1 visit (from Table 1)	±5 Days based on ExW4 visit					
Medical procedures								
Complete physical examination[b]		X						X
Targeted physical examination[c]			X	X	X	X	X	
Vital signs[d]		X	X	X	X	X	X	X
12-Lead ECG[e]		X			X			X
Audiometry								X
Laboratory Assessments								
Hematology		X	X	X	X	X	X	X
Blood chemistry		X	X	X	X	X	X	X
ESR[p]		X	X	X	X	X	X	X
Fasting lipid Panel[f]		X						X
Urinalysis[g]		X	X	X	X	X	X	X
Cystatin C (and eGFR)		X	X	X	X	X	X	X
Urine pregnancy test (WOCBP)[h]		X	X	X	X	X	X	X
CCI [redacted]								
		[redacted]		[redacted]				[redacted]
Trial treatment								
Provide and review dosing instructions for PF-06700841		X	X	X	X	X	X	
Investigational product (PF-06700841) dispensing		X	X	X	X	X	X	

Protocol Activity	Extension Period							
	Drug Holiday[a] (4 weeks)	Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (16 weeks)			
Visit Identifier	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**4 weeks**	**198**	**212**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW4**	**ExW6**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**N/A**	**±7 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExW4 visit**					
Investigational product ((PF-06700841) administration[i]		X	→	→	→	→	→	X
Investigational product ((PF-06700841) accountability and compliance			X	X	X	X	X	X
Clinical assessments								
sIGA		X		X	X	X	X	X
VASI		X		X	X	X	X	X
Central read facial-VASI[r]								
Facial-VASI (site assessment)		X		X	X	X	X	X
BSA		X		X		X		X
VES		X		X		X		X
Photograph[j]		X		X		X		X
C-SSRS[k]		X		X		X		X
Dermoscopy[l]								X
Patient reported outcome[m]								
SA-VES		X				X		X
VitiQoL		X				X		X
DLQI		X				X		X
HADS		X						X
PGIC-V								X
EQ-5D-5L								X
HCRU						X		X
VNS								X
CCI [redacted]								

Protocol Activity	Extension Period							
	Drug Holiday[a] (4 weeks)	Treatment Period Induction Phase (4 weeks)			Treatment Period Maintenance Phase (16 weeks)			
Visit Identifier	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**4 weeks**	**198**	**212**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW4**	**ExW6**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**N/A**	**±7 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExW4 visit**					
Other								
Prior and current concomitant Treatment(s)		X	→	→	→	→	→	X
Serious and non-serious adverse event monitoring		X	→	→	→	→	→	X
Contraception check		X	X	X	X	X	X	X
Sun exposure (E-diary) check		X	X	X	X	X	X	X
CCI [redacted]								
CCI [redacted]								

Abbreviations: →= ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI [redacted] FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI [redacted] IL= interleukin; CCI [redacted]; PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI [redacted] SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI [redacted] VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] Following a 4-week Drug Holiday, subjects in Group 1 (who assigned to receive PF-06700841 in the Extension Period) will receive an induction dose of PF-06700841 60 mg QD for 4 weeks followed by maintenance dosing of PF-06700841 30 mg QD for 16 weeks. This arm is open label. Induction Phase is from Extension Week 4 Visit to Extension Week 8 Visit. Maintenance Phase is from the day after Extension Week 8 Visit to Extension Week 24 Visit.

[b] 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 may include visual inspection of the breasts and external genitalia.

[c] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[d] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[e] ECG should be performed before laboratory blood collection.

[f] Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.

[g] 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.

[h] Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential.

[i] 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.

[j] Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided.

[k] Subjects who have recent or active suicidal ideation or behavior will be excluded from the study or discontinued from the study per Section 4.2.

[l] Dermoscopy will be performed per SOA. At least 2 different anatomical regions based on VES will be selected on Screening. At least two fields (possibly peripheral and central) from the largest lesion in the selected anatomical region will be examined to determine if white hair is present in less than 30% of hair in the depigmented lesion. Number of fields with less than 30% of white hair will be recorded. The same chosen lesions will be assessed per SOA. The same dermoscopy should be used throughout the study.

[m] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PHQ-8, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered.

[n] [redacted]

[o] [redacted]

[p] For Germany only: ESR will be performed at local laboratory.

[q] [redacted]

[r] Central read facial-VASI may be performed and analyzed in the Extension Period.

Table 3. Schedule of Activities for Group 2 in the Extension Period (Subjects Assigned to Receive Narrow Band UVB (nbUVB) Add-on Therapy; Open Label)

Protocol Activity	Extension Period							
	Induction Phase (4 weeks)			Maintenance Phase (20 weeks)				
Visit Identifier	**10[a]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**170 (ExD1)**	**184**	**198**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW2**	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**±5 Days based on Day 1 visit (from Table 1)**	**±5 Days based on Day 170 visit**						
Medical procedures								
Complete physical examination[b]	(X)							X
Targeted physical examination[c]		X	X	X	X	X	X	
Vital signs[d]	(X)	X	X	X	X	X	X	X
12-Lead ECG[e]	(X)				X			X
Audiometry								X
Laboratory Assessments								
Hematology	(X)	X	X	X	X	X	X	X
Blood chemistry	(X)	X	X	X	X	X	X	X
ESR[q]	(X)	X	X	X	X	X	X	X
Fasting lipid Panel[f]	(X)			X				X
Urinalysis[g]	(X)	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP)[h]	(X)	X	X	X	X	X	X	X
CCI [redacted]								
Trial treatment								
Provide and review dosing instructions	(X)	X	X	X	X	X	X	
Investigational product (PF-06651600) dispensing	(X)	X	X	X	X	X	X	
Investigational product (PF-06651600) administration[i]	(X)	→	→	→	→	→	→	X

Protocol Activity	Extension Period							
	Induction Phase (4 weeks)			Maintenance Phase (20 weeks)				
Visit Identifier	**10[a]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**170 (ExD1)**	**184**	**198**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW2**	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**±5 Days based on Day 1 visit (from Table 1)**	**±5 Days based on Day 170 visit**						
Investigational product (PF-06651600) accountability and compliance		X	X	X	X	X	X	X
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical assessments								
sIGA	(X)		X	X	X	X	X	X
VASI	(X)		X	X	X	X	X	X
Central read facial-VASI[s]	(X)		X	X		X		X
Facial-VASI (site assessment)	(X)		X	X	X	X	X	X
BSA	(X)		X	X		X		X
VES	(X)		X	X		X		X
Photograph[k]	(X)		X	X		X		X
C-SSRS[l]	(X)		X	X		X		X
Dermoscopy[m]								X
Patient reported outcome[n]								
SA-VES	(X)		X			X		X
VitiQoL	(X)		X			X		X
DLQI	(X)		X			X		X
HADS	(X)		X					X
PGIC-V								X
EQ-5D-5L								X
HCRU					X			X
VNS								X
CCI [redacted]								
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]			[redacted]
[redacted]			[redacted]	[redacted]	[redacted]			[redacted]
[redacted]								
[redacted]	[redacted]							[redacted]

Protocol Activity	Extension Period							
	Induction Phase (4 weeks)			Maintenance Phase (20 weeks)				
Visit Identifier	**10[a]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**170 (ExD1)**	**184**	**198**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW2**	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**±5 Days based on Day 1 visit (from Table 1)**	**±5 Days based on Day 170 visit**						
CCI [redacted]	[redacted]							[redacted]
Other						X		
Prior and current concomitant Treatment(s)	(X)	→	→	→	→	→	→	X
Serious and non-serious adverse event monitoring	(X)	→	→	→	→	→	→	X
Contraception check	(X)	X	X	X	X	X	X	X
CCI [redacted]								[redacted]
CCI [redacted]								[redacted]

Abbreviations: →= ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI [redacted] FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI [redacted] IL= interleukin; CCI [redacted] PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI [redacted] SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI [redacted] VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[redacted]

[b] 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 may include visual inspection of the breasts and external genitalia.

[c] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[d] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[e] ECG should be performed before laboratory blood collection.

[f] Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.

[g] 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.

[h] Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential.

[i] 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.

[redacted]

[l] Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided.

[l] Subjects who have recent or active suicidal ideation or behavior will be excluded from the study or discontinued from the study per Section 4.2.

[m] Dermoscopy will be performed per SOA. At least 2 different anatomical regions based on VES will be selected on Screening. At least two fields (possibly peripheral and central) from the largest lesion in the selected anatomical region will be examined to determine if white hair is present in less than 30% of hair in the depigmented lesion. Number of fields with less than 30% of white hair will be recorded. The same chosen lesions will be assessed per SOA. The same dermoscopy should be used throughout the study.

[n] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered.

[redacted]

[q] For Germany only: ESR will be performed at local laboratory.

[redacted]

[s] Central read facial-VASI may be performed and analyzed in the Extension Period.

Table 4. Schedule of Activities for Groups 3, 4, and 5 in the Extension Period (Subjects Receive All Other IP Assignments [Except for nbUVB Add-on Therapy or PF-06700841]; Blinded Arms)

Protocol Activity	Extension Period							
	Induction Phase (4 weeks)			Maintenance Phase (20 weeks)				
Visit Identifier	**10 (=9)**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**170 (=169) (ExD1[a])**	**184**	**198**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW2**	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**±5 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExD1 visit**						
Medical procedures								
Complete physical examination[b]	(X)							X
Targeted physical examination[c]		X	X	X	X	X	X	
Vital signs[d]	(X)	X	X	X	X	X	X	X
12-Lead ECG[e]	(X)				X			X
Audiometry								X
Laboratory Assessments								
Hematology	(X)	X	X	X	X	X	X	X
Blood chemistry	(X)	X	X	X	X	X	X	X
ESR[o]	(X)	X	X	X	X	X	X	X
Fasting lipid Panel[f]	(X)			X				X
Urinalysis[g]	(X)	X	X	X	X	X	X	X
Urine pregnancy test (WOCBP)[h]	(X)	X	X	X	X	X	X	X
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trial treatment								
Provide and review dosing instructions	(X)	X	X	X	X	X	X	
Investigational product (PF-06651600) dispensing	(X)	X	X	X	X	X	X	
Investigational product (PF-06651600) administration[i]	(X)	→	→	→	→	→	→	X
Investigational product (PF-06651600) accountability and compliance		X	X	X	X	X	X	X
Clinical assessments								
sIGA	(X)		X	X	X	X	X	X
VASI	(X)		X	X	X	X	X	X

Protocol Activity	Extension Period							
	Induction Phase (4 weeks)			Maintenance Phase (20 weeks)				
Visit Identifier	**10 (=9)**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Visit Day	**170 (=169) (ExD1[a])**	**184**	**198**	**226**	**254**	**282**	**310**	**338**
Week	**N/A**	**ExW2**	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**ExW24**
Visit Window	**±5 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExD1 visit**						
Central read facial-VASI[q]								
Facial-VASI (site assessment)	(X)		X	X	X	X	X	X
BSA	(X)		X	X		X		X
VES	(X)		X	X		X		X
Photograph[j]	(X)		X	X		X		X
C-SSRS[k]	(X)		X	X		X		X
Dermoscopy[l]								X
Patient reported outcome[m]								
SA-VES	(X)		X			X		X
VitiQoL	(X)		X			X		X
DLQI	(X)		X			X		X
HADS	(X)		X					X
PGIC-V								X
EQ-5D-5L								X
HCRU					X			X
VNS								X
CCI								
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
Sun exposure (E-diary) check	(X)	X	X	X	X	X	X	X

Abbreviations: → = ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI [redacted] FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI [redacted] IL= interleukin; CCI [redacted] PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI [redacted] SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI [redacted] VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] For subjects in Groups 3, 4, and 5 (who assigned to receive all other treatments CCI [redacted] in the Extension Period), all procedures and evaluations on the Extension Day 1 Visit (#10) will be combined with Week 24 Visit (#9) (in Table 1) as though they are a single visit. ( ) indicates that procedures and evaluations are performed at Visit 9 and will not be performed at Visit 10. These arms are blind. Induction Phase is from Extension Day 1 Visit to Extension Week 4 Visit. Maintenance Phase is from the day after Extension Week 4 Visit to Extension Week 24 Visit. Note: IP dispensing and administration will be performed at Week 24 Visit (#9) (in Table 1).

[b] 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 may include visual inspection of the breasts and external genitalia.

[c] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[d] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[e] ECG should be performed before laboratory blood collection.

[f] Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.

[g] 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.

[h] Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential.

[i] 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.

[j] Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided.

[k] Subjects who have recent or active suicidal ideation or behavior will be excluded from the study or discontinued from the study per Section 4.2.

[l] Dermoscopy will be performed per SOA. At least 2 different anatomical regions based on VES will be selected on Screening. At least two fields (possibly peripheral and central) from the largest lesion in the selected anatomical region will be examined to determine if white hair is present in less than 30% of hair in the depigmented lesion. Number of fields with less than 30% of white hair will be recorded. The same chosen lesions will be assessed per SOA. The same dermoscopy should be used throughout the study.

[m] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered.

[redacted]

[o] For Germany only: ESR will be performed at local laboratory.

[redacted]

[q] Central read facial-VASI may be performed and analyzed in the Extension Period.

Table 5. Schedule of Activities for Group 6 in the Extension Period (Observations only; No IP; Open Arm)

Protocol Activity	Extension Period					
	Observation (24 weeks)[a]					
Visit Identifier	**10**	**11**	**12**	**13**	**14**	**15**
Visit Day	**198**	**226**	**254**	**282**	**310**	**338**
Week	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**EOS**
Visit Window	**±7 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExW4 visit**				
Medical procedures						
Complete physical examination[b]						X
Targeted physical examination[c]	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X
Laboratory Assessments						
Hematology	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X
ESR[j]	X	X	X	X	X	X
Fasting lipid Panel[e]						X
Urinalysis[f]	X	X	X	X	X	X
Urine pregnancy test (WOCBP)[g]	X	X	X	X	X	X
CCI [redacted]						
[redacted]						
[redacted]						
Clinical assessments						
sIGA	X	X	X	X	X	X
VASI	X	X	X	X	X	X
Central read facial-VASI[l]	X	X		X		X
Facial-VASI (site assessment)	X	X	X	X	X	X
BSA	X	X		X		X
VES	X	X		X		X
Photograph[h]	X	X		X		X
C-SSRS						X
Patient reported outcome[i]						
SA-VES						X
VitiQoL						X
DLQI						X
HADS						X
VNS						X
Other						
Prior and current concomitant Treatment(s)	X	X	X	X	X	X

Protocol Activity	Extension Period					
	Observation (24 weeks)[a]					
Visit Identifier	**10**	**11**	**12**	**13**	**14**	**15**
Visit Day	**198**	**226**	**254**	**282**	**310**	**338**
Week	**ExW4**	**ExW8**	**ExW12**	**ExW16**	**ExW20**	**EOS**
Visit Window	**±7 Days based on Day 1 visit (from Table 1)**	**±5 Days based on ExW4 visit**				
Serious and non-serious adverse event monitoring	X	X	X	X	X	X
Contraception check	X	X	X	X	X	X
Sun exposure (E-diary) check	X	X	X	X	X	X

Abbreviations: → = ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI [redacted] FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI [redacted] IL= interleukin; CCI [redacted] PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI [redacted] SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI [redacted] VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] For subjects in Group 6, no IP will be assigned. This 24-week arm is open. Visits will be conducted every 4 weeks until EOS or until 30% or greater depigmentation from baseline VASI occurs, whichever is shorter. No follow up visits will be performed for subjects in Group 6.

[b] 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 may include visual inspection of the breasts and external genitalia.

[c] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[d] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[e] Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.

[f] 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.

[g] Urine pregnancy test must be performed for female subjects of childbearing potential.

[h] Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided.

[i] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, and VNS, at those visits where they are to be administered.

j For Germany only: ESR will be performed at local laboratory.

[redacted]

l Central read facial-VASI may be performed and analyzed in the Extension Period.

Schedule of Activities for Follow-Up Period and Early Termination Visit

Table 6. Schedule of Activities for Follow-Up Period and Early Termination Visit

Protocol Activity	Follow-Up Period		Early Termination Visit[a]
Visit Identifier	**18**	**19**	
Week	**FU1[b]**	**EOS**	**ET**
Visit Window	**±7 Days based on ExW24 visit (from applicable Table 2, Table 3 or Table 4)[b]**		
Medical procedures			
Complete physical examination[c]		X	X
Targeted physical examination[d]	X		
Vital signs[e]	X	X	X
12-Lead ECG[f]			X
Audiometry[g]			X
Laboratory Assessments			
Hematology	X	X	X
Blood chemistry	X	X	X
ESR[o]	X	X	X
Fasting lipid Panel[h]		X	X
Urinalysis[i]	X	X	X
Urine pregnancy test (WOCBP)[j]	X	X	X
CCI [redacted]			
Trial treatment			
Investigational product accountability and compliance			X (if applicable)
Clinical assessments			
sIGA	X	X	X
VASI	X	X	X
Central read facial-VASI[q]	X	X	X
Facial-VASI (site assessment)	X	X	X
BSA	X	X	X
VES	X	X	X
Photograph[k]	X	X	X
C-SSRS	X	X	X
Patient reported outcome[l]			
SA-VES		X	X
VitiQoL		X	X

Protocol Activity	Follow-Up Period		Early Termination Visit[a]
Visit Identifier	**18**	**19**	
Week	**FU1[b]**	**EOS**	**ET**
Visit Window	**±7 Days based on ExW24 visit (from applicable Table 2, Table 3 or Table 4)[b]**		
DLQI		X	X
HADS		X	X
PGIC-V			X
EQ-5D-5L			X
HCRU			X
VNS			X
CCI			
Other			
Prior and current concomitant Treatment(s)	X	X	X
Serious and non-serious adverse event monitoring	X	X	X
Contraception check	X	X	X
CCI			
CCI			

Abbreviations: → = ongoing/continuous event; AT = Active Treatment; BSA = body surface area; C-SSRS = Columbia suicide severity rating scale; CMV = Cytomegalovirus; CXCL10 = C-X-C motif chemokine 10; DLQI = dermatology life quality index; EBV = Epstein-Barr virus; ECG = electrocardiogram; EOT = End of Treatment; EOS = End of Study; EQ-5D-5L = EuroQol 5 dimension 5 level; ESR = erythrocyte sedimentation rate; ET = Early Termination; CCI FSH = follicle stimulating hormone; HADS = hospital and anxiety depression scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCRU = Healthcare Resource Utilization; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; CCI ; IL= interleukin; CCI PQIC-V = Patient Global Impression of Change – Vitiligo; PHQ-8 = patient health questionnaire – 8 items; CCI SE-VES = self-assessment vitiligo extent score; sIGA = static Investigator Global Assessment; CCI VASI = vitiligo area scoring index; VES = vitiligo extent score; VitiQoL = vitiligo quality of life; VNS = Vitiligo Noticeability Scale; VZV = varicella zoster virus; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] The procedures scheduled for Early Termination Visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter.

[b] Follow-up Visit 1 will occur 4 weeks after the Extension Week 24 (ExW24). End of Study Visit will occur 4 weeks after the FU Visit 1 or Early Termination (ET) Visit. For early terminated subjects, End of Study (EOS) Visit will occur 4 weeks (with a visit window of +7 days based on the ET Visit) after the ET Visit and no FU1 Visit will be performed.

[c] 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 may include visual inspection of the breasts and external genitalia.

[d] Targeted physical examination consists of skin, heart, lungs, abdomen, neurologic function, and examination of body systems where there are symptom complaints by the subject.

[e] Vital signs should be performed before laboratory blood collection as specified in Section 7.3.1 and will be measured after 5 minutes of rest.

[f] ECG should be performed before laboratory blood collection.

[g] For subjects who terminate early from the study, efforts must be made to complete the audiometry testing and obtain the results.

[h] Fasting lipid profile includes total cholesterol, triglycerides, HDL, and LDL. A minimum of 8-hour fasting is required for fasting lipid profile evaluation.

[i] 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.

[j] Urine pregnancy test must be performed for female subjects of childbearing potential.

[k] Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained. Refer to Photograph Instruction Section 7.7 and a separate Photography Instructions will be provided.

[l] Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered.

[m] [redacted]

[o] For Germany only: ESR will be performed at local laboratory.

[p] [redacted]

[q] Central read facial-VASI may be performed and analyzed.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06651600 is an orally bioavailable small molecule that inhibits, by irreversibly blocking the ATP binding site, JAK3 and the TEC kinase family (BTK, BMX, ITK, TEC, RLK/TXK), with high selectivity over the other three JAK isoforms, JAK1, JAK2, and TYK2, as well as over the broader kinome. PF-06651600 is currently being investigated in patients with rheumatoid arthritis, alopecia areata, ulcerative colitis, and Crohn's disease and will be investigated in vitiligo.

PF-06700841 is a dual inhibitor of human tyrosine-protein kinase 2 (TYK2) and Janus kinase 1 (JAK1) that is currently being investigated in patients with psoriasis, alopecia areata, ulcerative colitis, and Crohn's disease and will be investigated in vitiligo.

1.2. Background and 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 which are critical for leukocyte activation, proliferation, survival and function.[35,36] Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family of transcription factors. The STATs are phosphorylated and subsequently translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.[35,36]

PF-06651600 potently inhibits signaling of the common-γ chain receptors for IL-2, IL-15, and IL-17, which have been implicated in the pathogenic pathways of vitiligo.[2,13] Considering the pathogenesis of vitiligo and mechanisms of action for PF-06651600, the hypothesis is to determine if PF-06651600 will have a clinically meaningful effect on treating active non-segmental vitiligo.

PF-06700841 is a dual TYK2/JAK1 inhibitor with a good selectivity profile over the other human kinases including JAK2. TYK2/JAK1 play critical roles in IFNγ signaling that regulate the signal transduction pathways triggered by several cytokines implicated in the pathogenesis of vitiligo.[21]

1.2.1. Study Background

Vitiligo is an acquired hypopigmented disorder with or without autoimmune comorbidities including thyroid disease, alopecia areata, psoriasis, inflammatory bowel disease, type 1 diabetes mellitus and pernicious anemia.[29] The worldwide prevalence of vitiligo ranges between 0.5% and 2.0%.[19] Lesions are depigmented completely at the initiation phase and pigmented orifices of hair follicles are seen at the recovering phase. Differential diagnoses include Vogt-Koyanagi-Harada disease, halo nevus/nevi, malignancy-induced hypopigmentation (melanoma and mycosis fungoides), postinflammatory hypopigmentation, pityriasis alba (a minor manifestation of atopic dermatitis), senile leukoderma (age-related

depigmentation), chemical/drug-induced leukoderma, ataxia telangiectasia, tuberous sclerosis, and melasma.[33] Vitiligo can be classified into two forms based on distribution patterns: non-segmental vitiligo (wide distribution; also known as generalized vitiligo) and segmental vitiligo (confined to the dermatome).[6,33] Vitiligo also can be classified into two forms based on disease activities: active vitiligo (confetti-like lesions, trichrome lesions and Koebner phenomenon) and stable vitiligo (more than 30% of white hair as determined by dermoscopy).[1,16] Since vitiligo has been given a diagnosis code (L80) by the World Health Organization, may result from autoimmunity, has numerous systemic associations, and adversely affects quality of life with significant economic burden, it is considered a serious medical disease.[7]

The trifecta of vitiligo pathogenesis can be oxidative stress causing melanocyte damage, genetics affecting melanocyte growth and differentiation, and autoimmunity involving autoreactive cytotoxic T cells,[26] although, the complex pathophysiology of vitiligo is not fully understood. Stressed melanocytes may initiate the activated innate immunity via natural killer cells and nearby dendritic cells, followed by the activation of adaptive immunity.[26] The presence of CD8+ T cells in close apposition to melanocytes suggests that the pathogenesis of vitiligo is T cell mediated although antibody-mediated pathogenesis is also proposed.[33] Recent review proposes the hypothesis that CD8+ T cells produce IFN γ, which activate the release of CXCL9/10/11 from keratinocytes, which in turn activate the function of CD8+ T cells via the activation of CXCR3.[26] Cytokines involved in vitiligo include IFNγ, IL-2, IL-17, IL-15 and IL-4. Of note, IL-2 and IL-15 are suggested to activate CD49a+/CD8+ resident memory T cells in vitiligo skin and to induce perforin and granzyme B in those T cells, which induce melanocyte apoptosis.[2]

There are currently no approved treatments specifically to treat active non-segmental vitiligo. Current treatment options, which are limited and may be inefficacious, include topical corticosteroids, topical vitamin D3, topical calcineurin inhibitors, systemic corticosteroids (to treat rapidly progressive active lesions), phototherapy, surgical treatments (to treat small and stable lesions) and camouflage.[6,26,29] Recent case reports have suggested potential utility of JAK inhibitors in treating vitiligo. Tofacitinib a JAK inhibitor, appears to have a repigmentation effect on vitiligo, noting that concomitant phototherapy may be necessary.[3,8,18,20] Ruxolitinib, a JAK1/2 inhibitor, also seems to have a similar effect.[10,17,28] Considering the pathogenesis of vitiligo and mechanisms of action for PF-06651600 and PF-06700841, the hypothesis is to determine if PF-06651600 and PF-06700841 will have a clinically meaningful effect on treating active non-segmental vitiligo.

1.2.2. Non-Clinical Pharmacokinetics and Metabolism

1.2.2.1. 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.

Further details of the non-clinical pharmacokinetics and metabolism of PF-06651600 are provided in the current Investigator's Brochure (IB).

1.2.2.2. 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_{50}=1.1 µM), multidrug and toxin extrusion 1 (MATE1) (IC_{50}=7.7 µM) and MATE2K (IC_{50}=17 µM) in vitro. The respective unbound I_{max}/IC_{50} ratios are 0.65, 0.09, and 0.04 for a predicted 60 mg clinical dose of PF-06700841 (unbound C_{max}=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_{max}/AUC ratios 1.19/1.20).

Further details of the non-clinical PK and metabolism of PF-06700841 are provided in the current IB.

1.2.3. Safety Data

1.2.3.1. Non-Clinical Safety

1.2.3.1.1. Non-Clinical Safety of PF-06651600

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Details of the nonclinical safety program are provided in the current Investigator's Brochure.

1.2.3.1.2. Non-Clinical Safety of PF-06700841

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Further details of the non-clinical safety of PF-06700841 are provided in the current IB.

1.2.3.2. Clinical Experience

1.2.3.2.1. Clinical Experience with PF-06651600

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Safety Results

SAD Period: during the SAD period, 31 subjects had a total of 42 treatment-emergent adverse events (TEAE)s, 30 of which were considered to be treatment-related. There were no deaths, severe adverse events (AE)s, temporary discontinuations, or dose reductions due to AEs reported in this period. Two (2) subjects reported treatment-emergent serious adverse events (SAEs) during the SAD period (1 subject each in the PF-06651600 200 mg [furuncle]) and PF-06651600 400 mg [pilonidal cyst] treatment groups). Four (4) subjects discontinued from the study during the SAD period (1 subject each in the placebo [erythema] and the PF-06651600 100 mg [rash macro papular], PF-06651600 200 mg [furuncle], and PF-06651600 400 mg [pilonidal cyst] treatment groups) due to AEs.

The system organ classes (SOCs) with the greatest number of subjects reporting AEs in the SAD period were infections and infestations (8 subjects); nervous system disorders (7 subjects); gastrointestinal (GI) disorders (5 subjects); musculoskeletal and connective tissue disorders (5 subjects); and respiratory, thoracic and mediastinal disorders (5 subjects). Most TEAEs reported in the SOCs of GI disorders, musculoskeletal and connective tissue disorders, and nervous system disorders (5 subjects in each SOC) were treatment-related.

There were generally few TEAEs in the SAD period, most of which occurred in a single subject, with the exception of headache and nasopharyngitis (experienced by 5 subjects each) and oropharyngeal pain (experienced by 4 subjects). Most of the TEAEs were mild in severity except for the following AEs that were moderate in severity: 1 AE each in the PF-06651600 5 mg (oropharyngeal pain), 20 mg (musculoskeletal pain), and 200 mg (subcutaneous abscess) treatment groups; 2 AEs in the placebo group (dry skin and limb injury); 3 AEs in the PF-06651600 400 mg treatment group (nasopharyngitis, pilonidal cyst, and headache), and 5 AEs in the PF-06651600 100 mg treatment group (abdominal pain, arthralgia, rash maculopapular, and 2 AEs of headache).

MAD Period: during the MAD period, 35 subjects had a total of 90 TEAEs, 75 of which were considered to be treatment-related. The treatment groups with the most AEs were the PF-06651600 400 mg QD (39 AEs in 13 subjects), 200 mg BID (16 AEs in 5 subjects), and 100 mg BID treatment groups (14 AEs in 4 subjects). There were no deaths, temporary discontinuations, or dose reductions due to AEs reported in this period. One (1) subject who received PF-06651600 400 mg QD during the MAD period reported an SAE (varicella). Two (2) subjects experienced severe AEs during the MAD period (1 subject each in the PF-06651600 400 mg QD [varicella] and PF-06651600 200 mg BID [rash macro papular] treatment groups. Two (2) subjects discontinued from the study during the MAD period (1 subject each in the PF-06651600 400 mg QD [herpes zoster] and PF-06651600 200 mg BID [rash macro-papular] treatment groups) due to AEs.

The SOCs with the greatest number of subjects reporting AEs in the MAD period were skin and subcutaneous tissue disorders (21 subjects); GI disorders (18 subjects); nervous system disorders (12 subjects); musculoskeletal and connective tissue disorders (6 subjects); and respiratory, thoracic, and mediastinal disorders (5 subjects). Most TEAEs reported in the SOCs of skin and subcutaneous tissue disorders (20 subjects), GI disorders (17 subjects), and

nervous system disorders (12 subjects) were treatment-related. The most frequently reported TEAEs across all treatment groups were diarrhea, headache, and erythema, which were experienced by 8, 7, and 6 subjects, respectively.

Most of the TEAEs were mild in severity except for the following AEs that were moderate in severity: 1 AE in the PF-06651600 50 mg QD treatment group (dysphagia); 2 AEs in the placebo group (aphthous ulcer and headache); 2 AEs in the PF-06651600 100 mg BID treatment group (headache and rash maculopapular); 3 AEs in the PF-06651600 400 mg QD treatment group (vomiting, pyrexia, and herpes zoster); and 5 AEs in the PF-06651600 200 mg BID treatment group (pyrexia, presyncope, erythema, rash pruritic, and rash maculopapular). In addition, there were 2 AEs of severe intensity: varicella in the PF-06651600 400 mg QD treatment group and rash maculopapular in the PF-06651600 200 mg BID treatment group.

SAD and MAD Periods: none of the observations in vital sign measurements; electrocardiograms (ECGs); physical examination findings; clinical safety laboratory measurements; changes from baseline in urine volume, electrolytes, and urine osmolality, 24-hour urine creatinine clearance or telemetry were found to be clinically significant in either the SAD or MAD period. The completed concentration-QT analysis of the Phase 1 data showed no evidence of QT prolongation.

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1.2.3.2.1.5. Phase 2 Studies Safety and Efficacy Data

PF-06651600 is currently being investigated in patients with rheumatoid arthritis (RA) (B7981006), alopecia areata (B7931005), ulcerative colitis (B7981005), and Crohn's disease (B7981007). B7931005, B7981005, and B7981007 are ongoing and blinded.

B7981006 study is a completed Phase 2a, 8-week, randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the efficacy and safety profile of PF-06651600 in seropositive subjects with moderate to severe active RA with an inadequate response to methotrexate (MTX) (up to approximately 50% of subjects may have also had an inadequate response to 1 anti-TNFα biologic disease-modifying antirheumatic drug [DMARD]). PF-06651600 was determined to be generally safe and well tolerated in this study. There were no deaths or SAEs. TEAEs were numerically higher in subjects receiving PF-06651600 compared to those receiving placebo. PF-06651600 met the primary endpoint with a mean change from baseline in Simplified Disease Activity Index at Week 8 with a placebo-adjusted difference of -9.25 (95% CI: -14.75, -3.79) ($p < 0.001$).

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

1.2.3.2.1.6. Clinical Pharmacokinetics Experience with PF-06651600

PF-06651600 was absorbed rapidly following single doses of 5 mg to 200 mg with median T_{max} values ≤0.75 hours, and more slowly at the higher doses with a median T_{max} of 1.0 and 1.5 hours for the 400 mg and 800 mg doses, respectively. Following attainment of C_{max}, the disposition of PF-06651600 generally showed a monophasic decline at the lower doses of 5 to 200 mg (mean t½ of 1.1 to 1.8 hours) while a biphasic decline observed at doses of 400 to 800 mg (mean t½ of 2.2 to 2.5 hours). An apparent trend toward longer t½ values at higher doses (400 and 800 mg) is probably due to concentrations remaining above the quantifiable limit for a longer period of time at the higher doses and defining a later terminal phase. In general, PF-06651600 AUC from 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.

On Day 14 of multiple dose administration, PF-06651600 was absorbed rapidly with median T_{max} values of 1 hour or less across the entire range of doses, from a total daily dose of 50 mg (50 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, the disposition of PF-06651600 was consistent with that observed following single dose administration, showing a monophasic decline for the lowest doses and a biphasic decline following the 200 mg BID and 400 mg QD dosing regimens and a mean terminal t½ of approximately 1.3 to 2.3 hours. In general, plasma PF-06651600 AUC from time zero to time tau (tau = 12 hours for BID; 24 hours for QD), the dosing interval (AUC_{tau}) and C_{max} increased with dose across the 50 mg to 400 mg total daily dose range based on visual

comparison of individual and dose normalized geometric mean C_{max} and AUC_{tau} values. The geometric mean value for the accumulation ratio (R_{ac}) ranged from 1.0 to 1.8 for the QD dosing and was 1.7 for the 100 mg BID dosing. This ratio compares AUC_{tau} for multiple dose administration to AUC_{tau} for single dose administration, and assesses the magnitude of accumulation with multiple dose administration. Similar R_{ac} ratios were observed for C_{max} ($R_{ac}C_{max}$), which ranged from 0.9 to 1.4 for QD dosing and was 1.0 for 100 mg BID dosing. The steady state accumulation ratio (R_{ss}) compares AUC_{tau} for multiple dose administration to AUC_{inf} for single dose administration, and assesses the linearity in PK exposure from a single dose to steady state. Geometric mean R_{ss} values were consistently ≥1, ranging from 1.0 to 1.8, suggesting that there may be a greater than dose proportional increase in PF-06651600 exposure with multiple dose administration. However, based on R_{ac} and $R_{ac}C_{max}$, the increase in exposure after 14 days of multiple dosing is less than 2-fold for any of the dosing regimens studied. Steady state generally appears to have been reached by Day 4 for the QD regimens and Day 6 for the BID regimens based on similar median trough (predose) concentrations on Days 6, 8, 10, 12 and 14.

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 amount of drug excreted from time zero to time tau, the dosing interval [Ae_{tau}]% of 4.1% to 7.0%). Renal clearance ranged from 42.9 mL/min to 63.1 mL/min.

The relative bioavailability (B7981003) of 50 mg PF-06651600 tablets was compared to 50 mg oral suspension. The ratio (90% confidence interval [CI]) of adjusted geometric mean was 93.4% (87.8, 100) for AUC_{inf} and 90.4% (72.2, 113) for C_{max} under fasted conditions. When the 50 mg tablets were administered under fed conditions, T_{max} was slightly delayed with a median value of 1.0 hours, compared to a median T_{max} 0.5 hours under fasted conditions. For the 50 mg tablets fed vs. fasted, the ratio of adjusted geometric means for AUC_{inf} and C_{max} was 102% (95.2, 109) and 61.5% (48.5, 77.8), respectively.

On Day 1 following the first morning oral dose of PF-06651600 200 mg under fasted conditions to healthy Japanese, PF-06651600 absorption was rapid with a median T_{max} of 0.525 hours and a range of 0.500-1.00 hours. Overall, exposures as measured by AUC_{tau} based on geometric mean were 3779 ng•hr/mL and for C_{max} of 1803 ng/mL on Day 1 after a single dose. Mean $t_{½}$ was 1.69 hours and it was calculated based on a 24–hour sampling.

Trough (predose) concentrations on Days 4, 6, 8 and 10 for all subjects were below the lower limit of quantification (LLOQ) (<1.00 ng/mL).

Following multiple oral dosing on Day 10, AUC_{tau} increased slightly while C_{max} was similar to Day 1. The geometric mean values for AUC_{tau} and C_{max} were 4983 ng•hr/mL and 1790 ng/mL, respectively. Median T_{max} was similar to Day 1 with a value of 0.500 hours with no range for Day 10. Following the attainment of C_{max}, concentrations appeared to decline in monophasic fashion. A short mean $t_{½}$ was observed with an estimate of 1.8 hours. Based on AUC_{tau} calculation, mean apparent total body clearance of the drug from plasma (CL/F) was 40.1 L/hr and mean apparent volume of distribution during terminal phase after non-intravenous administration (V_z/F) was 103 L.

Plasma PF–06651600 accumulation was 1.3–fold for AUC_{tau} (observed R_{ac}) and 0.99–fold for C_{max} (observed accumulation ratio for C_{max} [$R_{ac}C_{max}$]). Geometric mean R_{ss} was 1.3 (close to 1), suggesting linear increases in PF-06651600 exposure with multiple-dose administration.

Variability in plasma PF–06651600 exposure on Day 1 and Day 10 based on geometric percent coefficient of variation (%CV), ranged from 35% to 43% for C_{max} and from 23% to 25% for AUC_{tau}.

Urinary recovery of PF-06651600 was low, with <7% of the dose recovered unchanged in urine on Day 10 (geometric mean percent of dose recovered unchanged in urine up to 24 hours [Ae_{tau}%] of 6.89%). Renal clearance was approximately 46.1 mL/min.

1.2.3.2.2. Clinical Experience with PF-06700841

1.2.3.2.2.1. First-in-Human (B7931001) Safety Data

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 (PsO), with a relative bioavailability and food effect assessment of a tablet formulation of PF-06700841 in healthy adult subjects. In the completed first-in-human study (B7931001), 41 healthy volunteers were exposed to single doses and 26 of the 41 subjects received multiple daily doses of PF-06700841 over 10 days; a small cohort of plaque PsO patients (n=21) were treated once daily with PF-06700841 for 28 days at 30 mg and 100 mg doses.

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).PF-06700841 was generally safe and well tolerated in the Phase 1 clinical study B7931001.

The most commonly reported all causality TEAEs across active subjects in both SAD and MAD cohorts were increased blood creatinine, and decreased neutrophil count. In the SAD period, 1 subject in the PF-06700841 100 mg group had serum creatinine (Scr) values meeting the criteria for high levels (>1.3 X ULN). In the MAD period, 4 subjects (1, 2, and 1 subjects in the PF-06700841 10 mg QD, 100 mg QD, and 50 mg BID groups, respectively) had Scr values meeting the criteria for high levels. No subjects in the psoriasis period had SCr values meeting the criteria for high levels. In the SAD period, 3 subjects (1 subject each in the PF-06700841 1 mg, 200 mg, and placebo group) had abnormal low neutrophil counts (<0.8 X LLN). In the MAD period, 14 subjects (1, 3, 3, 5, and 2 subjects in the PF-06700841 10 mg QD, 100 mg QD, 50 mg BID, 175 mg QD, and placebo group, respectively) had abnormal low neutrophil counts. In the psoriasis period, 6 subjects (1 and 5 subjects in the PF-06700841 30 mg and 100 mg QD groups, respectively) had abnormal low neutrophil counts. 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^3 during the study.

The most commonly reported all causality TEAEs across active subjects in the PsO cohorts treated with either 30 mg or 100 mg PF-06700841 were blood creatinine increased and neutrophil count decreased.

An AE of herpes zoster occurred in a single subject with PsO after completing 28-day treatment with PF-06700841 at the 100 mg QD dose level. The subject had a 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 reported AEs were nausea, contusion, and headache, each of which was experienced by 1 subject. All TEAEs were mild in severity.

Oral administration of PF-06700841 at multiple doses of 100 mg QD was well-tolerated and generally safe in healthy Japanese subjects investigated in study B7931009. There were no deaths, SAEs, severe AEs, discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs during this study.

Overall, 3 TEAEs were reported by 1 subject following placebo treatment, including palpitations, abdominal pain and insomnia. Among these AEs, palpitations and insomnia were considered treatment-related. Seven (7) TEAEs were reported by 3 subjects following oral administration of PF-06700841 100 mg, including flatulence, fatigue, viral upper respiratory tract infection, headache, somnolence, nocturia and haematoma. Among these AEs; flatulence, headache, somnolence and nocturia were considered treatment-related by the investigator. One (1) AE of abdominal pain in the placebo treatment group was moderate and the others were considered mild in severity.

There were no clinically significant findings observed in laboratory parameters, vital signs, ECG parameters, and physical examinations.

Safety data generated in study B7931001 supported PF-06700841's further clinical development and advancement to the Phase 2 study B7981019, in patients with active vitiligo.

Further details on the clinical safety information with PF-06700841 are provided in the IB.

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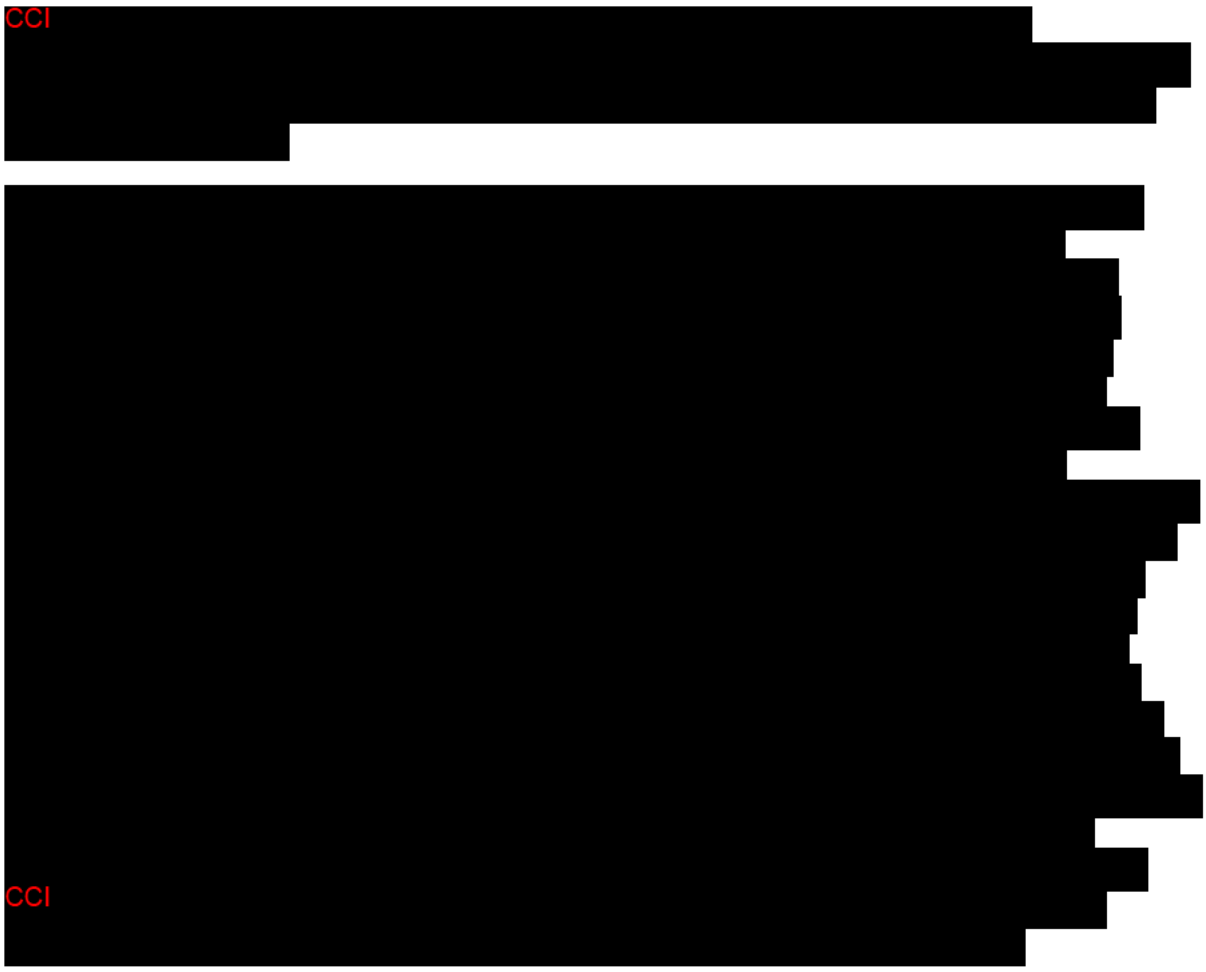

1.2.3.2.2.3. Safety Data from Phase 2 Studies

In addition to this study, PF-06700841 is currently under assessment in 5 ongoing Phase 2 studies in alopecia areata (B7931005), ulcerative colitis (B7981005), Crohn's disease (B7981007), systemic lupus erythematosus (B7931028) and psoriatic arthritis (B7931030), and 1 planned Phase 2 study in hidradenitis suppurativa (C2501007). The topical development program consists of 2 ongoing Phase 2 studies in atopic dermatitis (B7931022) and psoriasis (B7931023).

All Phase 2b studies are ongoing and blinded.

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

1.2.3.2.2.4. Clinical Pharmacokinetics Experience with PF-06700841

Following single oral PF-06700841 doses, peak plasma concentrations generally occurred at or before 1 hour for doses of 1 mg-200 mg. In general, both AUC_{inf} and C_{max} appeared to increase proportionally with dose from 1 mg-100 mg; there appeared to be a trend toward more than proportional increase from 100 mg-200 mg. However, there was considerable overlap between the dose-normalized parameter values for individual subjects across the

entire dose range. Mean $t_{½}$ was 3.8-7.5 hours with a trend towards longer $t_{½}$ at the higher doses, probably due to concentrations remaining above the lower limit of quantification (LLOQ) for a longer time as the dose increased. The mean CL/F was 10.9-28.3 L/hr and the mean V_z/F was 102.4-210.5 L. Variability in PF-06700841 exposure based on geometric %CV ranged from 31%-65% for AUC_{inf} and 21%-92% for C_{max}.

On Day 10 of multiple-dose administration, PF-06700841 was absorbed rapidly with median T_{max} at or before 1.5 hours postdose across the entire range of doses from a total daily dose of 10 mg up to 175 mg. Plasma C_{max} and AUC_{tau} both appeared to increase proportionally with dose from 10 mg QD to 100 mg QD with a trend towards greater than proportional increase from 100 mg to 175 mg QD. As would be expected, dose normalized C_{max} for 50 mg BID is slightly higher than that for 100 mg QD while dose normalized AUC_{tau} is consistent between the two dosing regimens. Mean terminal $t_{½}$ ranged from 4.9 to 10.7 hours. Steady state generally appeared to have been reached by Day 8 of QD or BID dosing. Urinary recovery of PF-06700841 was low, with less than 16% of the dose recovered unchanged.

Following multiple-dose administration in subjects with PsO, PF-06700841 was absorbed rapidly with median T_{max} of 1 to 2 hours post dose. Mean terminal $t_{½}$ was 16 hours in the 30 mg group and 6 hours in the 100 mg group. The mean $t_{½}$ value in the 30 mg group included a reported $t_{½}$ value of 87.5 hours for one subject with an anomalous data point at 216 hours postdose. All other subjects in the dose group had concentrations below the LLOQ after 24 hours and $t_{½}$ values of 6.48 hours or less. The subject in the 30 mg group with the highest C_{max} and AUC_{tau} values was not the same subject with the anomalous 87.5 hour $t_{½}$ value. CL/F and Vz/F were 30.30 L/hr and 245.4 L for the 30 mg dose, respectively, and were 13.04 L/hr and 109.6 L for the 100 mg dose, respectively. Variability in PF-06700841 exposure based on geometric %CV ranged from 43% to 103% for AUC_{tau} and 13% to 43% for C_{max}.

Relative BA of 100 mg PF-06700841 tablets compared to 100 mg oral suspension was 96.18% for AUC_{inf} and 94.28% for C_{max}. Both of the 90% CIs for the ratio were within the 80%-125% equivalence interval. When the 100 mg tablets were administered under fed conditions, T_{max} was delayed with a median value of 4.0 hours, compared to 0.5 hours under fasted conditions. For 100 mg tablets fed versus fasted, the ratio (90% CI) of adjusted geometric means for AUC_{inf} and C_{max} was 82.33% (73.45%, 92.29%) and 64.25% (55.98%, 73.75%), respectively.

Following single oral dose of PF-06700841 100 mg under fasted conditions in Japanese subjects, absorption was rapid with a median T_{max} of 1 hour and a range of 0.5-2 hours on Day 1. Geometric mean AUC_{inf} was 8725 ng•hr/mL and C_{max} was 1035 ng/mL. Mean terminal $t_{½}$ was 5.7 hours based on a 24-hour sampling.

On Day 10 following multiple oral dosing, median T_{max} was 0.76 hours with a range of 0.5-4.0 hours. Both AUC_{tau} and C_{max} increased slightly compared to Day 1, with geometric mean values of 9888 ng•hr/mL and 1114 ng/mL, respectively. Mean terminal $t_{½}$ was 8.9 hours. Steady-state generally appeared to have been achieved by Day 6. Urinary recovery of PF-06700841 was low, with less than 16% of the dose recovered unchanged.

1.2.4. Study Rationale

This is a Phase 2b, randomized, double-blind, multicenter, multiple-arm, placebo-controlled study to evaluate the safety, tolerability, efficacy, CCI of PF-06651600 in subjects with active non-segmental vitiligo. In addition this study will provide opportunities for subjects to receive additional study treatment with or without narrow band UVB add-on therapy or PF-06400841 in the Extension Period.

The total sample size for the study is computed to be approximately 330 randomized to expect approximately260 completers. The null hypothesis to be tested for PF-06651600 is to assess if the difference between PF-06651600 and placebo is less than or equal to 0% in percent change from baseline in central read facial-VASI score versus (vs) the alternative hypothesis that the difference between PF-06651600 and placebo is greater than 0%.

The 24-week double blind dosing ranging treatment period will assess the efficacy and safety of PF-06651600 in patients with active non-segmental vitiligo. The potential benefit of an induction dose regimen is based on the hypothesis that maximal inhibition of the relevant immunomodulatory pathways at initiation of treatment can provide a high pharmacological stimulus to an accelerated response, which can be maintained by the follow-on lower maintenance dose. The 200 mg chosen as the highest induction dose is expected to produce a >70% inhibition of IL-15 and IL-21 signaling. The inclusion of the 100 mg induction dose allows for selection of the induction dose that best optimizes benefit/risk ratio. Doses of 10 mg QD, 30 mg QD, and 50 mg QD will be evaluated as fixed dose regimens for the 24 weeks Dose Ranging Period. The current non-clinical toxicology packages support treatment duration ≥6 months for the maintenance doses.

This study includes an extension period to evaluate additional safety and tolerability of PF-06651600 with or without narrow band UVB (nbUVB) add-on therapy. The average improvement rate on administration of nbUVB was 32% for various durations (8-24 weeks), as measured by the mean percent change of VASI improvement from baseline.[39-46] Subjects who have <10% improvement in percent change in VASI at Extension Week 12 from the baseline value at Dose Ranging Period Week 24 will be discontinued from the treatment. The Extension Period will also evaluate the safety, efficacy and tolerability of PF-06700841 in subjects with vitiligo after a 4-week Drug Holiday with no IP. The Drug Holiday will provide a wash out period for subjects between Dose Ranging Period and Extension Period. There will be 6 arms in the Extension Period. The PF-06651600 with nbUVB add-on therapy and the PF-06700841 arms will be open label. The other three arms will be blinded. The observation only arm will be open. Subjects who complete the initial 24 weeks of the protocol may enter the Extension Period. Subjects who discontinue prior to Week 24 Visit will not be eligible for the Extension Period.

The Vitiligo Area Scoring Index (VASI) is a validated quantitative scale, initially developed to measure the response of vitiligo to nbUVB treatment, but has since been used to evaluate various therapies for vitiligo. Clinical evaluations of vitiligo in this study will include VASI, central read and site assessment of facial-VASI, static Investigator Global Assessment (sIGA), Body Surface Area (BSA) involvement, Vitiligo Extent Score (VES), and dermoscopy. Photographs will be taken to verify eligibility (inclusion criterion #5c) and evaluate the central read facial-VASI.

PF-06651600 and PF-06700841 efficacy will also be evaluated via patient reported outcomes (PROs): Self-Assessment VES (SA-VES), Vitiligo Specific Quality of Life (VitiQoL), Dermatology Life Quality Index (DLQL), Hospital Anxiety and Depression Scale (HADS), Patient Global Impression of Change Vitiligo (PGIC-V), EQ-5D-5L, Healthcare Resource Utilization (HCRU) and Vitiligo Noticeability Scale (VNS).

Emerging data is added demonstrating a DDI with oral contraceptives containing ethinyl estradiol (EE). An additional barrier method of contraception is added when hormonal contraceptives containing EE is used by female subjects.

The risk of drug exposure to a sexual partner through ejaculate, vaginal secretion, or saliva from a subject on maximum oral doses of PF-06651600 at C_{max} is below pharmacologically relevant levels, and unlikely to present a significant risk of adverse effects on embryofetal development. No contraception methods are required for male participants under PF-06651600 in this study, CCI [redacted]

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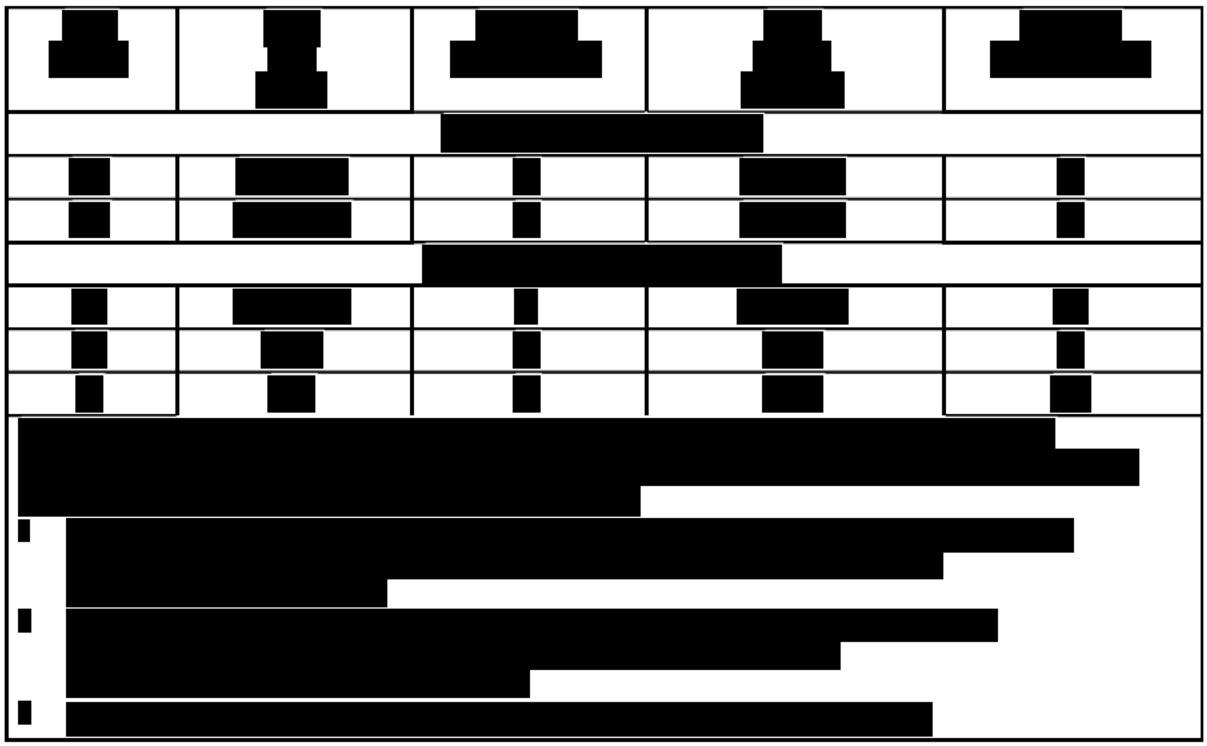

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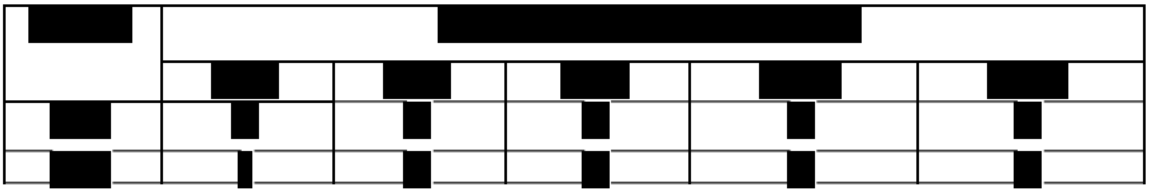

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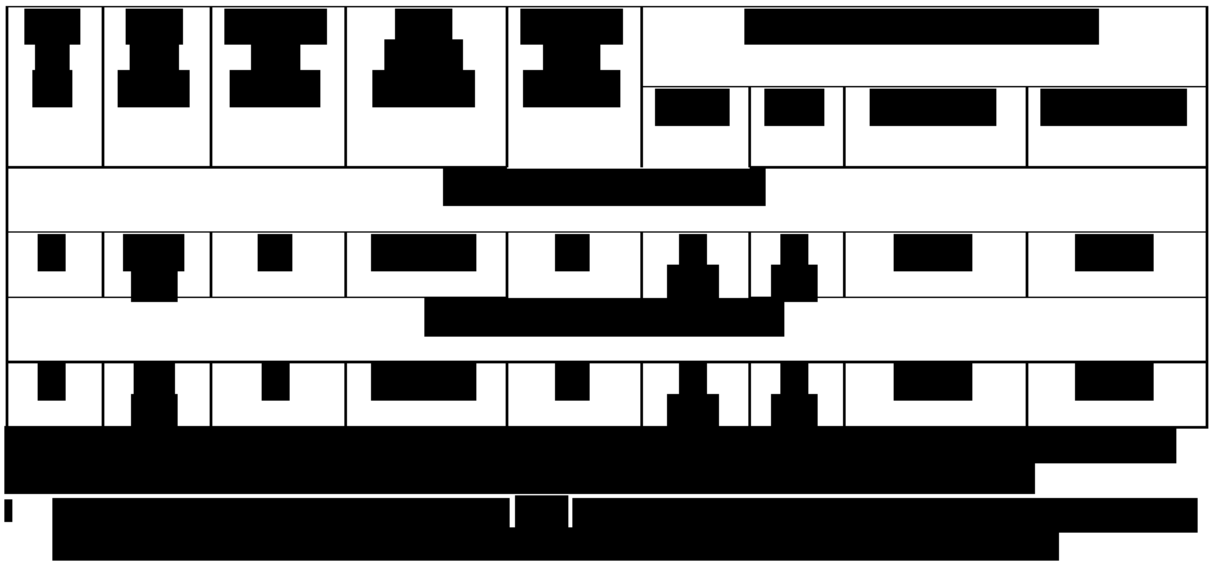

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1.2.5. Summary of Benefits and Risks

There are currently no approved treatments specifically to treat active non-segmental vitiligo. Recent case reports have suggested potential utility of JAK inhibitors in treating vitiligo as detailed in Section 1.2.1.

Both PF-06651600 and PF-06700841 inhibit signal transduction pathways triggered by several cytokines implicated in the pathogenesis of vitiligo. Considering the mechanisms of action for PF-06651600 and PF-06700841 and the vitiligo pathogenesis, both IPs are expected to have a clinically meaningful effect for the treatment of active non-segmental vitiligo.

The dose rationales for PF-06651600 and PF-06700841 are detailed in Sections 1.2.4.1 and 1.2.4.2, respectively.

PF-06651600 and PF-06700841 are generally safe and well tolerated as supported by the totality of safety data to date. 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 QD. The safety profile observed during the Phase 1 program for PF-06700841 appears to be acceptable at dosages up to 175 mg administered orally QD.

In the ongoing Phase 2a proof-of-concept Study B7931005 in adult patients with alopecia areata (AA), preliminary data showed that both PF-06651600 and PF-06700841 met its primary endpoint of improvement in severity of alopecia tool (SALT) 30 score relative to placebo at Week 24. PF-06651600 and PF-06700841 appeared generally safe and well tolerated as suggested by adverse event (AE) number and profile. Both PF-06651600 and PF-06700841 had a favorable benefit: risk profile and provided meaningful clinical benefit in AA, another dermatological disease with similar underlying pathogenesis and psychological burden as vitiligo.[47,48]

In the Study B7981019, events requiring review, including opportunistic infections, cardiovascular, and malignancy events will be externally evaluated using the same adjudication committee as in the ongoing Phase 2b AA Study B7981015 as detailed in Section 9.9.

Based on the current clinical and nonclinical experience with PF-06651600, PF-06700841, and other information from other JAK inhibitors (eg, Xeljanz® (tofacitinib), Jakafi® (ruxolitinib), baricitinib, GLPG0634, and VX-509), the potential risks for PF-06651600 and PF-06700841 include: (1) viral reactivation; (2) serious infection and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) change in neutrophil counts; (6) decreased platelet count; (7) alterations in the lipid profile; (8) dermatologic effects (rash/acne); (9) interaction with other medicinal products and other forms of interaction; (10) fertility, pregnancy, and lactation.

In conclusion, the results of the nonclinical studies together with the clinical experience obtained to date with PF-06651600 and PF-06700841 support the investigation of these IPs for the treatment of subjects with active non-segmental vitiligo. Subjects may experience improvements during the study treatment. Subjects that are randomized to placebo may also benefit from the overall health assessment that are conducted while participating in the Study B7981019 and may experience improvement after subjects are allocated with active therapy during the Extension Period of this study. Subjects will also contribute to the process of developing novel drugs for the treatment of vitiligo. Considering the measures to minimize risk to subjects, the potential risks that are identified in association with PF-06651600 and PF-06700841 are justified by the anticipated benefits that may be afforded to subjects.

Additional information for these two compounds may be found in the two single reference safety documents (SRSDs), which are the respective IBs for PF-06651600 and PF-06700841.

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2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints during Dose Ranging Period

Primary Objectives:	**Primary Endpoints:**
• To evaluate the efficacy of PF-06651600 dose/dosing regimens at Week 24 in adult subjects with active non-segmental vitiligo.	• Percent change from baseline in central read facial-vitiligo area scoring index (facial-VASI) at Week 24.
• To evaluate the safety and tolerability of PF-06651600 over time in adult subjects with active non-segmental vitiligo.	• Incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs) up to Week 24. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and liver function tests (LFTs) up to Week 24.
Secondary Objectives:	**Secondary Endpoints:**
Key Secondary Objective: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by facial-VASI at Week 24 in adult subjects with active non-segmental vitiligo.	**Key Secondary Endpoint:** • Proportion of subjects achieving central read facial-VASI 75 (defined as at least 75% improvement in central read facial-VASI from baseline) at Week 24.
Other Secondary Objectives: • To evaluate the efficacy of PF-06651600 compared to placebo as measured by other clinical assessments over time in adult subjects with active non-segmental vitiligo.	**Other Secondary Endpoints:** • Proportion of subjects achieving VASI50 (defined as at least 50% improvement in VASI from baseline) at Week 24. • Percent change from baseline in VASI, central read and site assessment of the facial-VASI, vitiligo extent score (VES), and self assessment -VES (SA-VES) and absolute change from baseline in VASI at designated time points (except for Week 24 for central read facial-VASI). • Proportion of subjects achieving VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in VASI from baseline), central read and site assessment of the facial-VASI50/75/90/100 (defined as at least 50%/75%/90% or 100% improvement in facial VASI from baseline), and VES50/75/90/100 (defined as at least 50%/75%/90%/100% improvement in VES from baseline) at designated time points (except for Week 24 in VASI50 and central read facial-VASI75). • Change from baseline in vitiligo specific quality of life (VitiQoL) at designated time points. • Proportion of subjects achieving a static investigator global assessment (sIGA) 0 or 1, and at least 2-point improvement at Week 24.

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

2.2. Study Objectives and Endpoints during Extension Period

Primary Objective:	**Primary Endpoints:**
• To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in adult subjects with active non-segmental vitiligo.	• Incidence of treatment-emergent AEs and SAEs during the Extension Period. • Incidence of specific clinical laboratory abnormalities including but not limited to anemia, neutropenia, thrombocytopenia, lymphopenia, changes in lipid profile, and liver function tests during the Extension Period.
Exploratory Objectives:	**Exploratory Endpoints:**
• To evaluate the long term efficacy of PF-06651600, efficacy of PF-06651600 and add-on nbUVB, in adult subjects with active non-segmental vitiligo. • To evaluate the efficacy of PF-06700841 in a subset of adult subjects with active non-segmental vitiligo.	• Percent change from baseline in VASI during the Extension Period. • Proportion of subjects achieving VASI50/75/90/100 and central read* and site assessment of the facial-VASI50/75/90/100 during the Extension Period. • Percent change from baseline in VASI, central read* and site assessment of the facial-VASI, VES, and SA-VES and absolute change from baseline in VASI, central read* and site assessment of the facial-VASI, and VES during the Extension period. • Change from baseline in VitiQoL during the Extension Period. [redacted] • Change from baseline in DLQI/EQ-5D-5L/HCRU in Extension Period. • Change from baseline in C-SSRS and HADS at designated time in the Extension Period as specified in the SoA. • Proportion of subjects achieving "very much improved" or "much improved" on patient global impression of change in vitiligo (PGIC-V). • Proportion of subjects achieving a score of 4 (a lot less noticeable) or 5 (no longer noticeable) on Vitiligo Noticeability Scale (VNS).
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*. Central read facial-VASI may be performed and analyzed in the Extension Period as an exploratory endpoint.

3. STUDY DESIGN

Study Design Schematic

Figure 2. Study Design Schema for Screening Period and Dose Ranging Period

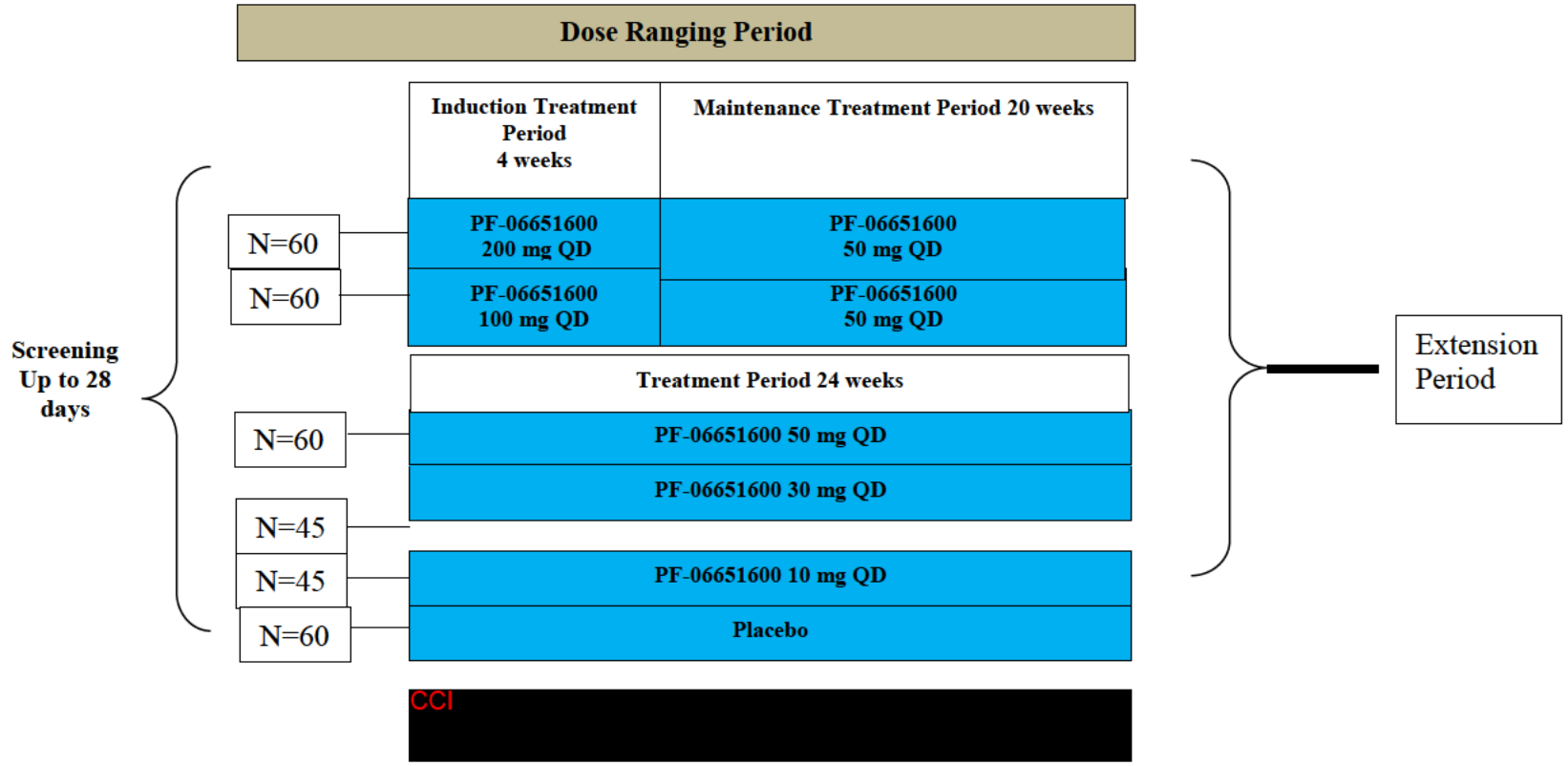
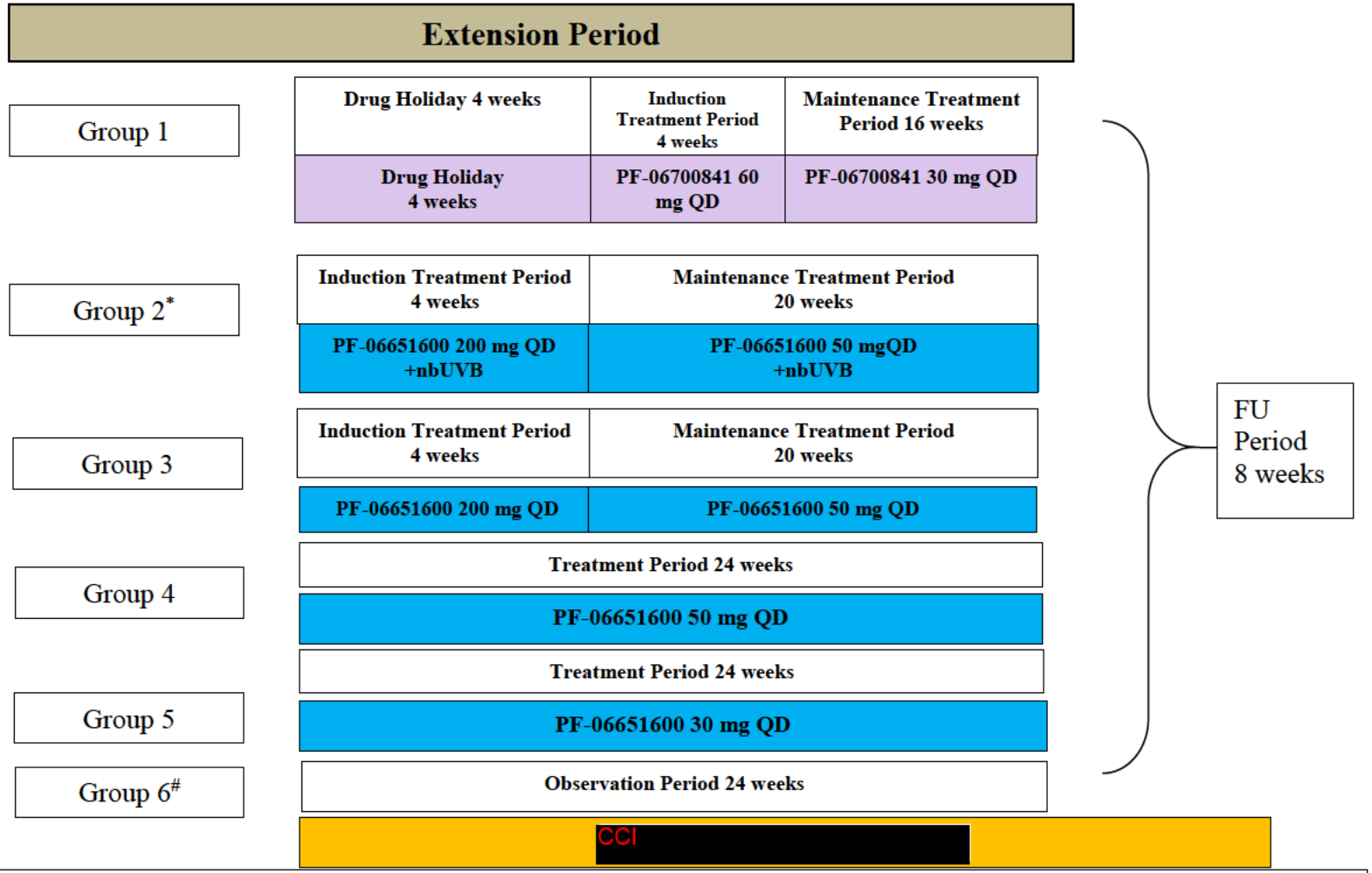


Figure 3. Study Design Schema for Extension Period and Follow-up Period



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

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

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

Subjects will be screened within 28 days prior to the first dose of Investigational product (IP) to confirm that they meet the subject selection criteria for the study. Subjects will be randomized to 1 of 5 treatment groups or placebo in the ratio of 4:4:4:3:3:4. An induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), an induction dose of 100 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), a dose of 50 mg QD of PF-06651600 for 24 weeks (n=60), a dose of 30 mg QD of PF-06651600 for 24 weeks (n=45), a dose of 10 mg QD of PF-06651600 for 24 weeks (n=45), and matching placebo for 24 weeks (n=60) will be investigated during the 24 week Dose Ranging Period.

All subjects who complete the initial 24-week Dose Ranging Period may enter the Extension Period and will be allocated into 6 groups by pre-specified criteria. The pre-specified criteria will be described in the Statistical Analysis Plan for this protocol.

- Group 1: Induction dose of 60 mg QD of PF-06700841 for 4 weeks followed by maintenance dosing of 30 mg QD of PF-06700841 for 16 weeks after a 4-week drug holiday (with no IP). This arm is open label.

- Group 2: Induction dose of 200 mg QD of PF-06651600 plus standardized narrow band UVB (nbUVB) add-on therapy for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 plus standardized nbUVB add-on therapy for 20 weeks (only for subjects who provide nbUVB consent). Subjects who have <10% improvement in percent change in VASI at Extension Week 12 from the baseline value at Dose Ranging Period Week 24 will be discontinued from the treatment and enter Follow-up Period. This arm is open label.

- Group 3: Induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks. This arm is double blinded.

- Group 4: 50 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.

- Group 5: 30 mg QD of PF-06651600 for 24 weeks. This arm is double blinded.

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

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

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 18-65 years of age, inclusive, at time of informed consent.

4. Female subjects of childbearing potential and at risk for pregnancy must agree to use one 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.

   Note: For all subjects assigned to Group 1 in the Extension Period, please refer to Section 4.4.1.

5. Must meet the following active non-segmental vitiligo criteria **at the Screening Visit and the Baseline Visit:**

   a. Have a clinical diagnosis of non-segmental vitiligo for at least 3 months; and

   b. Body surface area (BSA) involvement 4% - 50% **excluding** involvements at palms of the hands, dorsal aspect of fingers and thumbs including metacarpophalangeal joints, soles of the feet, or dorsal aspect of the feet; and

   c. BSA ≥0.25% involvement on the face excluding involvement at vermilion (confirmed by photographs at Screening Visit); and

   d. Subjects should have at least one active lesion defined as one of the following:

      (i) New/extending lesion(s) in the past 3 months (confirmed by photographs or medical record);

      (ii) Confetti-like lesion(s);

      (iii) Trichrome lesion(s);

(iv) Koebner phenomenon/ phenomena [excluding Type 1 (history based isomorphic reaction)];

e. Coexistence of halo nevus/nevi (also known as Sutton nevus/ nevi) is permitted.

6. If receiving concomitant medications for any reason other than vitiligo, 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 5.8.2).

7. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources other than provided/requested by the study team during the study (Section 4.4 Lifestyle Requirements).

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 that meets any of the following criteria:

   - Suicidal ideation associated with actual intent and a method or plan in the past year: “Yes” answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) (Section 7.5).

   - Previous history of suicidal behaviors in the past 5 years: “Yes” answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.

   - Any lifetime history of serious or recurrent suicidal behavior.

   - Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) (Section 7.6.5) total score ≥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, exclusion is required.

4. Subjects considered in imminent need for surgery (for example in the next 6 months) or with elective surgery scheduled to occur during the study.

5. Subjects that have other types of vitiligo (including but not limited to segmental vitiligo). Note: Mixed vitiligo is permitted.

6. Currently have active forms of other hypopigmentation (including but not limited to Vogt-Koyanagi-Harada disease, malignancy-induced hypopigmentation [melanoma and mycosis fungoides], post-inflammatory hypopigmentation, pityriasis alba [minor manifestation of atopic dermatitis], senile leukoderma [age-related depigmentation], chemical/drug-induced leukoderma, ataxia telangiectasia, tuberous sclerosis, melasma, and congenital hypopigmentation disorders including piebaldism, Waardenburg syndrome, hypomelanosis of Ito, incontinentia pigmenti, dyschromatosis symmetrica hereditaria, xeroderma pigmentosum, and nevus depigmentosus). Note: Coexistence of halo nevus/nevi (also known as Sutton nevus/nevi) is permitted.

7. Currently have active forms of inflammatory skin disease(s) or evidence of skin conditions (including but not limited to morphea, discoid lupus, leprosy, syphilis, psoriasis, seborrheic dermatitis) at the time of the Screening or Day 1 Visit that in the opinion of the investigator would interfere with evaluation of vitiligo or response to treatment.

8. Have received any of the following treatment regiments specified in the timeframes outlined below:

   <u>At any time:</u>

   - Use of permanent depigmentation treatment for vitiligo and/or other types of pigmentation disorders (eg, monobenzone or phenol).

   <u>Within 6 months of Day 1:</u>

   - Any cell-depleting agents including but not limited to rituximab: within 6 months of Day 1, or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer.

   <u>Within 12 weeks of Day 1:</u>

   - Use of oral JAK inhibitors.

- Other biologics: within 12 weeks of Day 1 or 5 half-lives (if known), whichever is longer.

Within 8 weeks of Day 1:

- Systemic treatments that could affect vitiligo within 8 weeks of Day 1 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 Day 1 or within 5 half-lives (if known), whichever is longer.

- Intralesional steroid injection within 8 weeks of Day 1 or within 5 half-lives (if known), whichever is longer.

- Participation in other studies involving investigational drug(s) within 8 weeks of Day 1 or within 5 half-lives (if known), whichever is longer and/or during study participation.

Note: Any investigational or experimental therapy taken or procedure performed for vitiligo and other diseases including but not limited to rheumatoid arthritis, psoriasis, alopecia areata, thyroid disease, allergic rhinitis, or atopic dermatitis within the previous 1 year should be carefully evaluated. 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 Day 1:

- Live or attenuated live vaccine.

Within 4 weeks of Day 1:

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

Within 2 weeks of Day 1:

- Topical treatments (including JAK inhibitors) that could affect vitiligo (eg, corticosteroids, vitamin D3, and calcineurin inhibitor).

Within 1 week of Day 1:

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

9. Pregnant female subjects; breastfeeding female subjects; and female subjects of childbearing potential who are unwilling or unable to use one 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.

10. 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; history of severe allergic or anaphylactoid reaction to kinase inhibitors; or in the opinion of the investigator, the subject is inappropriate for entry into this study, or unwilling/unable to comply with Section 6 Study Procedures and Section 4.4 Lifestyle Requirements.

11. Have hearing loss with progression over the previous 5 years, sudden hearing loss, or middle or inner ear disease such as otitis media, cholesteatoma, Meniere's disease, labyrinthitis, or other auditory condition that is considered current, fluctuating or progressive.

12. 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.

13. 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.

14. 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.

15. 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.

16. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study or protocol adherence in the study.

17. ANY of the following conditions at screening:

    a. 12-lead electrocardiogram (ECG) that demonstrates:

        - Clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (eg, cardiomyopathy, Wolff-Parkinson-White syndrome);

        - Confirmed QTcF prolongation (>450 milliseconds).

    b. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes;

    c. Use of concomitant medications that prolong the QT interval.

18. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

19. 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.

20. 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.

21. Have undergone significant trauma or major surgery within 1 month of the first dose of IP.

22. Require treatment with prohibited concomitant medication(s) (Section 5.8.3 and Appendix 2) or have received a prohibited concomitant medication within 7 days or 5 half-lives (whichever is longer) prior to Day 1.

23. History of human immunodeficiency virus (HIV) or positive HIV serology at screening.

24. 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. Note: For Japan, Korea and Taiwan, please refer to Appendix 10.

25. 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 strongly 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 7.3.5 for requirements for Mantoux/PPD tuberculin skin testing. The following are acceptable IGRA assays: QuantiFERON® - TB Gold test (QFT-G), QuantiFERON® - TB Gold In-Tube test (QFT-GIT) and T-SPOT®.

        - 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 who determines that the risk of infection is low (ie, subject would be acceptable for immunosuppressant treatment without additional action).

        - Subjects who test positive for IGRA test (including borderline T-SPOT result), 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 (or performed and documented within 3 months prior to Day 1) with changes suggestive of active TB infection.

    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.

26. Have galactosemia (galactose-1-phosphate-uridylyltransferase or UDP-galactose-4-epimerase or galactokinase deficiency; Fanconi Bickel syndrome), a congenital lactase deficiency or glucose-galactose malabsorption.

27. Donation of blood in excess of 500 mL within 8 weeks prior to Day 1.

28. **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 <60 ml/min/1.73m^2 based on the age appropriate calculation;
- Enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
- Total bilirubin ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is≤ ULN;
- Creatine kinase (CK) >3 times the ULN and positive urine myoglobin;
- Glycosylated hemoglobin A1c (HbA1c) >10%; Subjects whose diabetes mellitus is poorly controlled should be excluded;
- 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 plans to enroll a total of approximately 330 subjects (expected to provide approximately 260 completers). Eligible subjects will be randomly assigned to a treatment group through the interactive response technology (IRT) system stratified by subject skin type, and geographical locations.

Subjects will be randomized to 1 of 5 active treatment groups or placebo in the ratio of 4:4:4:3:3:4 approximately. An induction dose of 200 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), an induction dose of 100 mg QD of PF-06651600 for 4 weeks followed by maintenance dosing of 50 mg QD of PF-06651600 for 20 weeks (n=60), a dose of 50 mg QD of PF-06651600 for 24 weeks (n=60), a dose of 30 mg QD of PF-06651600 for 24 weeks (n=45), a dose of 10 mg QD of PF-06651600 for 24 weeks (n=45), and matching placebo for 24 weeks (n=60) will be investigated during the 24 week Dose Ranging Period.

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

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 IP 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 and Appendix 2).
- Agree to use appropriate contraception methods (Section 4.4.1).
- During the Dose Ranging Period, encouraged to be exposed to the natural sun without sunscreen (including makeup with sun protection factor [SPF]) for no more than 15 minutes daily.
- During the Extension Period, encouraged to be exposed to the natural sun without sunscreen (including makeup with SPF) for no more than 15 minutes daily. Subjects allocated to nbUVB phototherapy should not be exposed to the natural sun without sunscreen.
- Agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources other than provided/requested by the study team during the study.

- Agree to use the sunscreen (provided by the sponsor) during the study conduct.
- New tattoo that may interfere with vitiligo assessment will be prohibited during the study conduct.
- For subjects who undergo color application (camouflage), or other procedures to their body surface/eyebrow/eyelash that may interfere with vitiligo assessment, the procedures should be avoided at least one week prior to the scheduled clinical assessment visits. This will facilitate the consistency of vitiligo clinical assessment.
- Agree not to use makeup prior to the scheduled clinical assessment visits to facilitate the accuracy and consistency of vitiligo 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 in the Extension Period). PF-06700841 has been associated with demonstrated teratogenicity/fetotoxicity in animals (more details in IB).

For PF-06651600 or placebo:

No contraception methods are required for male subjects under PF-06651600 or placebo in the study.

Female subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 1 method of highly effective contraception (as defined below) throughout the study and for at least 28 days after the last dose of investigational product.

For PF-06700841:

The risk of drug exposure to a sexual partner through ejaculate, vaginal secretion, or saliva from a subject on maximum oral doses of PF-06700841 at C_{max} is below pharmacologically relevant levels, and unlikely to present a significant risk of adverse effects on embryofetal development. However, all sexually active male subjects in Group 1 who are assigned to receive PF-06700841 during the Extension Period 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.

In addition to male condom use, a highly effective method of contraception (as defined below) should be used in women of child bearing potential (WOCBP) partners of male participants to prevent any potential for fertilization by sperm throughout the study and for at least 28 days after the last dose of investigational product.

Female subjects in Group 1 who are assigned to receive PF-06700841 during the Extension Period and in the opinion of the investigator are sexually active and at risk for pregnancy with their partner(s) must agree to use 1 method of highly effective contraception (as defined below) throughout the Extension Period and for at least 28 days after the last dose of PF-06700841.

In addition to a highly effective method of contraception use, male partner(s) of female participants in Group 1 must agree to use 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. If the female subject under PF-06700841 chooses sexual abstinence, male condom use is not applicable.

The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected appropriate method(s) 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 appropriate method(s) 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 :

1. Oral, injectable, or implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion or bilateral tubal ligation.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation used in combination with a barrier method.

Acceptable barrier methods include:

- Male or female condom with or without spermicide.
- Cervical cap, diaphragm, or sponge with spermicide.

Male condom and female condoms should not be used together (due to risk of failure with friction).

7. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Additionally, contraceptive use should be consistent with local regulations or guidance regarding the use of contraceptive methods for those participating in clinical trials.

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 (PF-06700841 for Extension Period only). Phototherapy will be used for subjects who will be allocated to nbUVB add-on therapy during Extension Period.

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will occur 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 double blind (sponsor, subject and investigator blinded) during the Dose Ranging Period. During the Extension Period, the group 1 (PF-06700841 arm) and group 2 (PF-06651600 with nbUVB arm) will be open label while the other 3 arms (group 3, 4 and 5) will be double blind. Group 6 is for observation only. No IP will be administered.

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. However, discussion with a member of the study team in advance of unblinding is not required. 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 possible 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 study site, 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 source document. If compliance is <80% or >120%, 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 tablets and matching placebos will be provided as tablets for oral administration. PF-06700841 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. The PF-06651600 10 mg and 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 will be supplied in bottles and labeled according to local regulatory requirements. Subjects will receive blinded labeled supplies for PF-06651600 throughout the study including the Extension Period. PF-06700841 supplies will be 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. PF-06700841 tablets 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 once daily; Subjects should swallow the tablets with ambient temperature water to a total volume of approximately 240 mL (2.4 DL or 1 cup); 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 (from the containers being returned to the site [ie, dispensed at the previous study visit]).

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 or 7 days between visits 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 IPs must be returned to the investigator by the subject at every applicable 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 IP) will be documented as prior medications. Medications taken after the first dose of IP 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. Narrow Band Ultraviolet B Light (nbUVB)

The use of narrow band ultraviolet b light (nbUVB) phototherapy may be an important component in the Extension Period to enhance melanocyte growth and differentiation. In the Extension Period, subjects who have signed a consent form for the nbUVB will have a chance to receive an induction dose of 200 mg QD plus standardized nbUVB add-on therapy for 4 weeks followed by maintenance dosing of 50 mg QD plus standardized nbUVB add-on therapy for 20 weeks. This arm will be an unblinded arm since the other 4 arms in the Extension Period will not use nbUVB. Sun exposure is prohibited during nbUVB phototherapy.

The administration of nbUVB phototherapy will follow the Vitiligo Working Group phototherapy recommendations (Appendix 3)[23] except that nbUVB phototherapy will be conducted **twice a week** during the study instead of three times a week.

Subjects who have <10% improvement in percent change in VASI at Extension Week 12 from baseline at Week 24 Dose Ranging Period will be discontinued from the treatment and enter Follow-up Period.

5.8.2. 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 throughout the study, unless otherwise noted below.

Subjects will be provided a sunscreen at the Baseline Visit. Subjects will use the sunscreen Day 1 through to the End of Study Visit as needed. If a subject has a history of intolerability or currently does not tolerate the sunscreen or if the product is unavailable, the investigator should contact the Pfizer clinician or designee for approval to use an alternative topical sunscreen; The approved alternative sunscreen should be documented in study records.

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.

5.8.3. 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 drug**. Treatment with simvastatin-containing products should not be initiated during participation in this study.

All medications and treatments that could affect vitiligo 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 other than provided/requested by the study team 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 vitiligo 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 5.8.4.

5.8.4. 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 IP, 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® (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.

5.8.5. Rescue Medication

Since currently there are no approved treatments in vitiligo (other than phototherapy), no rescue therapy will be mandated by the sponsor. Subjects requiring rescue medication during the Dose Ranging Period or Extension Period will be discontinued from IP (PF-06651600 or PF-06700841 or placebo) and will enter the Follow-up Period. Subjects requiring rescue medication during the Follow-up Period should also complete the Follow-up Period.

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. Visit windows are based on Day 1 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-investigational products are permitted).

Due to possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit within the 28 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).

Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified as following: SA-VES, VitiQoL, DLQI, HADS, PHQ-8, PGIC-V, EQ-5D-5L, HCRU, and VNS, at those visits where they are to be administered except for Screening Visit and Baseline Visit.

Sunscreen will be provided to subjects at the Baseline Visit and re-supplied during the study as applicable. Subjects will use the study provided sunscreen Day 1 through to the EOS visit.

Refer to Appendix 5 for guidelines on subject safety monitoring and discontinuation.

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6.1. Screening

Subjects will have up to 28 days of a screening period to 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 4-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**.

Subjects will be provided with an emergency ID card.

For screening procedures, see Schedule of Activities and Section 7.

6.2. Dose Ranging Period

For treatment period procedures, see Schedule of Activities Table 1 and Section 7.

6.3. Extension Period

For subjects in Group 1 (who are assigned to receive PF-06700841 in the Extension Period) procedures, see Schedule of Activities Table 2 and Section 7.

For subjects in Group 2 **(**who are assigned to receive narrow band UVB (nbUVB) add-on therapy in the Extension Period procedures, see Schedule of Activities Table 3 and Section 7.

For subjects in Groups 3, 4, and 5 (who receive all other assignments [except for nbUVB add-on therapy or PF-06700841] in the Extension Period) procedures, see Schedule of Activities Table 4 and Section 7.

For subjects in Group 6 (observation only) procedures, see Schedule of Activities Table 5 and Section 7.

6.4. Follow-up Period including End of Study

Follow-up Visit 1 will occur 4 weeks after the Extension Week 24 (ExW24). End of Study Visit will occur 4 weeks after the FU Visit 1 or Early Termination (ET) Visit. For early terminated subjects, End of Study (EOS) Visit will occur 4 weeks (with a visit window of +7 days based on the ET Visit) after the Early Termination (ET) Visit and no FU1 Visit will be performed.

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.

For follow-up and end of study procedures, see Schedule of Activities Table 6 and Section 7.

6.5. 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 Dose Ranging Period or Extension Period (except for Group 6) will enter into the Follow-up Period **with their End of Study Visit occurring 4 weeks after the ET 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. Subjects in Group 6 who requested to discontinue study from the Extension Period will have the End of Study Visit occurring 4 weeks after the last visit. No follow up visit will be performed.

See Appendix 5 for guidelines on subject safety monitoring and discontinuation. The ET Visit only applies to subjects who are randomized, received at least one dose of IP, 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 Period will enter the Follow-up Period with their EOS **visit occurring 4 weeks after the ET Visit** and 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 before the subject may receive the study treatment. In the absence of regular menstrual bleeding, the study candidate should have used 1 form of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at every applicable 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 [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

CCI [redacted]

CCI [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. Note: For Japan, please refer to Appendix 10.

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 vitiligo disease history includes collection of details of vitiligo at Screening: background, vitiligo history, vitiligo diagnosis, the use of topical treatments, systemic treatments and other treatments for vitiligo (up to 2 years, if possible). Medical history, in addition to vitiligo history, including history of drug (up to 2 years, if possible), alcohol, tobacco use, auditory, skin rash, skin infection, and any dermal abnormalities that may predispose to infection will be collected at Screening and Baseline (if applicable). Smoking status and average weekly alcohol consumption (units/week) will 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 Baseline Visit.

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 may 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, neurologic function, and abdomen and examination of body systems where there are symptom complaints by the subject.

Subjects with clinically meaningful changes from baseline in neurologic signs or symptoms should be referred to a neurologist to undergo a formal neurologic evaluation.

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. Tuberculosis Testing

Subjects could be screened for TB using either test listed below.

7.3.5.1. 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®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® 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 IGRA test (including borderline T-SPOT result), 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.

7.3.5.2. 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.

7.3.6. Special Safety Assessment

7.3.6.1. Dermatological Events

All subjects will have dermatological full body exam (s) per SOA. Skin lesions will be evaluated and managed as defined in the National Cancer Institute Common Toxicity Criteria for Adverse Events v 4.0) (Appendix 4).

7.3.6.1.1. 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.

7.3.6.1.2. 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 7.3.6.1.1.

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 cytomegalovirus (CMV), EBV, herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), and varicella zoster virus (VZV), if applicable.

Subjects reporting potential drug-related rash should assess itch on a 10-point numeric rating scale (NRS) provided by Pfizer where 0 is no itching and 10 is worst possible itching (Appendix 8). The investigator will enter this assessment into the data collection tool.

Investigators will complete a questionnaire (provided by the study team) 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 investigator.

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

7.3.6.2. 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.[12]

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.[4,24] 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.[14]

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.[34]

7.3.7. Audiometry

All subjects will have audiometry assessment at times specified in the Schedule of Activities. Audiometry assessment taken at Screening or within 8 weeks prior to Day 1 must have results available prior to Day 1. In addition to audiogram, information including auditory medical history and additional examinations (ie, otoscopic exam) will be collected. For subjects that terminate early from the study, efforts must be made to complete the audiometry testing and obtain the results.

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

At subsequent visits, audiograms will be performed; based upon results, additional audiometry assessments may be required and performed by qualified medical personnel based on local guideline or equivalent.

If there is a clinically-meaningful, treatment-related decline in hearing from baseline, the subject will be followed up off treatment with appropriate testing at regular intervals, until hearing returns to baseline or is determined to be clinically stable. Treatment-relatedness (or causality) will be assessed by the investigator as described in Section 8.1.5.

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) will be requested to be forwarded to Pfizer (and/or designee) at any time during the study.

7.3.8. Clinical Laboratory Tests

7.3.8.1. Blood Volume

Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.

7.3.8.2. 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-investigational product s) for an 8-hour overnight fast prior to fasting lipid profile panel collection according to Schedule of Activities. All other labs [redacted] do not require fasting.

Laboratory Tests

Hematology	Blood Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine	pH	HIV[a]
Hematocrit	Cystatin C[h]	Glucose (qual)	HBsAg[a]
RBC count	Creatine Phosphokinase	Protein (qual)	HBcAb[a]
Reticulocyte count	Glucose	Blood (qual)	HepB reflex (HBsAb[b]), if applicable
Platelet count	Na+, K+, Cl- ,Ca++	Ketones	HBV DNA[m]
WBC count with differential	Total CO2 (Bicarbonate)	Nitrites	HCVAb[a]
Total neutrophils (%, Abs)	AST, ALT	Leukocyte esterase	Serum pregnancy test[a,c]
Eosinophils (%, Abs)	Total Indirect & Direct Bilirubin	Microscopy and/or culture[d]	Urine pregnancy test[c]
Monocytes (%, Abs)	Alkaline phosphatase		FSH[a,g]
Basophils (%, Abs)	Uric acid		QFT-G or other IGRA, or PPD[a,e]
Lymphocytes (%, Abs)[l]	Albumin		EBV, CMV, HSV1, HSV2, VZV
	Total protein		HbA1c[a]
	Fasting lipid Profile Panel:[f]		CCI [redacted]
	Total cholesterol		Urine Myoglobin[k]
	LDL		CCI [redacted]
	HDL		Skin swab for herpetiform rash[i]
	Triglycerides		Skin swab for potential drug-related rash[j]
			CCI [redacted]
			ESR[n]

[a] At Screening only.

[b] HepB reflex testing only if HBsAg negative but HBcAb positive at Screening.

[c] Pregnancy tests (serum/urine) for females of childbearing potential. Serum pregnancy test must be performed at Screening.

[d] Only if urine analysis is positive for blood, protein, nitrites, or leukocyte esterase.

[e] PPD results should be read within 48 to 72 hours.

[f] Fasting lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed as specified in SOA, and will include total cholesterol, LDL, HDL, and triglycerides.

[g] Females of non-child bearing potential.

[h] Cystatin C will be measured and cystatin C based eGFR will be calculated for subjects who receive PF-06700841.

[i] In case of a herpetiform rash (eg, suspected herpes zoster and herpes simplex) as specified in Section 7.3.6.1.1.

j In case of a potential drug-related rash as specified in Section 7.3.6.1.2.

k At Screening and in case of CK >3 x ULN.

[redacted]

m Japan, Korea and Taiwan only as specified in Appendix 10.

n For Germany only: ESR will be performed at local laboratory.

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 5 for laboratory discontinuation criteria.

7.4. Clinical Efficacy Assessments

7.4.1. Facial Vitiligo Area Scoring Index (Facial-VASI)—Central Read

The central read facial-VASI will be assessed based on the facial photographs taken at the site that are detailed in Section 7.7 by the central reader(s).[50]

The central read facial-VASI is calculated using a formula that includes contribution of affected facial surface areas showing all six (6) different depigmentation rates (0.1, 0.25, 0.5, 0.75, 0.9 and 1) with a modified method described by Hamzavi et al:[9]

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

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

Affected Facial Surface Area X 4 = % Affected Total Body Surface Area.

Face is defined as the area from the hairline on top of the forehead to the jawline at the bottom of the cheeks. Facial-VASI (central read) will range from 0.000 to 4.000 by defining the affected Facial Surface Area (expressed as the value between 0.0 to 1.0) being 4% of total Body Surface Area.

For example: 25% affected Facial Surface Area (0.25) represents 1% total body surface area (0.25 X 4). 15% affected Facial Surface Area (0.15) represents 0.6% total body surface area (0.15 X 4).

The extent of depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented exceeded the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeded the depigmented area; and at 10%, only specks of depigmentation are present.

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

Details of the central read process, including the information flow will be described in a separate charter/exploratory analysis plan.

7.4.2. Vitiligo Area Scoring Index (VASI)

The total body VASI will be assessed by the Investigator. The total body VASI will be calculated using a formula that includes contribution from all body regions (possible range, 0-100) with a modified method described by Hamzavi et al:[9]

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

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

The body will be divided into 6 separate and mutually exclusive regions: face/neck, hands, upper extremities (excluding hands), trunk, lower extremities (excluding the feet), and feet. The axillary regions are included with the upper extremities, while the buttocks and inguinal regions are included with the lower extremities. Genital area is included in trunk. Face and neck lesions will be measured in this study.

The extent of depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented exceeded the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeded the depigmented area; and at 10%, only specks of depigmentation are present.

7.4.3. Facial Vitiligo Area Scoring Index (Facial-VASI)-Site Assessment

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

$$\text{Facial VASI} = [\text{Digit Units}] \times [\text{Depigmentation}] \times 0.1$$

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

The extent of depigmentation is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented exceeded the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeded the depigmented area; and at 10%, only specks of depigmentation are present.

7.4.4. Static Investigator Global Assessment (sIGA)

Static Investigator Global Assessment (sIGA) Score

Score	*Short descriptor*	*Detailed descriptor*
0	Clear	• No signs of loss of pigmentation with natural light or with Woods lamp examination.
1	Almost clear	• Faint, barely detectable loss of pigmentation mainly located on dorsal hands, feet, bony prominences, and/or limited areas. • Approximately 90% pigmentation within lesions. • No or rare signs of Koebner phenomenon, confetti-like or trichrome lesions may be present.
2	Mild vitiligo	• Mild loss of pigmentation mainly located on dorsal hands, feet, bony prominences, and/or limited areas. • Approximately 75% pigmentation within lesions. • Few signs of Koebner phenomenon, confetti-like or trichrome lesions may be present.
3	Moderate vitiligo	• Moderate loss of pigmentation affecting several areas of the body with large patches. • Approximately 50% pigmentation within lesions. • Moderate number of signs of Koebner phenomenon, confetti-like or trichrome lesions may be present.
4	Severe vitiligo	• Extensive loss of pigmentation affecting most areas of the body. • Approximately 25% or less pigmentation within lesions. • Many signs of Koebner phenomenon, confetti-like or trichrome lesions affecting several areas of the body may be present.

7.4.5. Body Surface Area (BSA)

The number of hand units of skin afflicted with vitiligo in a body region can be used to determine the extent (%) to which a body region is involved with vitiligo. When measuring, the hand unit refers to the size of each individual subject's palm plus the volar surface of all the digits in a closed position. Rule of 9 is used to estimate BSA (Head/neck 9%; Upper extremities excluding hands 14%; Hands 4%; trunk including genital area 33%; Lower extremities excluding feet 36%; Feet 4%).

7.4.6. Vitiligo Extent Score (VES)

Vitiligo Extent Score is a measure to express the overall vitiligo involvement of the body (extent).[31] Clinical illustrations for 19 separate body areas that reflect different degrees of involvement (1, 5, 10, 25, 50, and 75% depigmentation) are chosen to represent the subject's skin lesions to get the total extent of the disease (Appendix 6). VES is a sum of all surface measurement that is similar to VASI.

7.4.7. Dermoscopy

Dermoscopy will be performed per SOA. At least 2 different anatomical regions based on VES will be selected on Screening. At least two fields (possibly peripheral and central) from the largest lesion in the selected anatomical region will be examined to determine if white hair is present in less than 30% of hair in the depigmented lesion. Number of fields with less than 30% of white hair will be recorded. The same chosen lesions will be assessed per SOA. The same dermoscopy should be used throughout the study.

7.4.8. Target Lesion(s) Assessment

One isolated and completed stable lesion (if applicable) will be identified as the stable target lesion on Day 1. Photographs of the lesion will be obtained (according to the separately provided Photography Instructions) at various time points as per SOA (Section 7.7). The extent of depigmentation of the target lesion is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeded the depigmented area; and at 10%, only specks of depigmentation are present. The same target lesion will be assessed per SOA. Note: No depigmentation (0) may be achieved during the study but should not be observed on Day 1.

In case of mixed Vitiligo, one isolated segmental vitiligo lesion (if applicable) will be identified as the segmental target lesion on Day 1. Photographs of the lesion will be obtained (according to the separately provided Photography Instructions) at various time points as per Schedule of Activities (Section 7.7). The extent of depigmentation of the target lesion is expressed by the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented exceeds the pigmented area; at 50%, the depigmented and pigmented areas are equal; at 25%, the pigmented area exceeded the depigmented area; and at 10%, only specks of depigmentation are present. The same target lesion will be assessed per SOA. Note: No depigmentation (0) may be achieved during the study but should not be observed on Day 1.

Target lesion assessment for active vitiligo lesion is not required. Photographs of active lesion, stable lesion, and segmental vitiligo lesion (if applicable) will be obtained according to SOA (Section 7.7).

7.5. Columbia Suicide Severity Rating Scale (C-SSRS)

Columbia Suicide Severity Rating Scale (C-SSRS) is a validated tool to evaluate suicidal ideation and behavior (Appendix 6).

At Screening Visit and Baseline Visit, if there are "yes" answers on items 4, 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the subject will not be included in the study.

At any post-baseline visits during Dosing Ranging Period or Extension Period, if there are "yes" answers on items 4, 5 or on any question in the suicidal behavior section of the C-SSRS, the subject will be discontinued from the IP 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.

7.6. Patient Report Outcome (PRO) Measures

Every effort should be made to have the subject complete all patient reported outcome (PRO) questionnaires before any other evaluations. All PROs should be completed in the order specified in as following: SA-VES, VitiQoL, DLQI, HADS, PHQ-8, PGIC-V, EQ-5D-5L, HCRU and VNS, at those visits where they are to be administered except for Screening Visit and Baseline Visit. All of the PROs are administered as electronic version on a tablet with the exception of the VNS which will be administered as a paper version.

7.6.1. Self-Assessment Vitiligo Extent Score (SA-VES)

The Self-Assessment Vitiligo Extent Score (SA-VES) is a validated patient report outcome measurement instrument to provide information about disease extent. SA-VES should be completed as per Schedule of Activities.

7.6.2. Vitiligo-Specific Quality of Life (VitiQoL) and Patient Global Impression of Severity of Vitiligo (PGIS-V)

The Vitiligo-Specific Quality of Life Instrument (VitiQoL) is a reliable and validated vitiligo disease-specific HRQoL instrument which measures concepts relevant to vitiligo subjects. The VitiQoL is a 15-item PRO measure which measures concepts of symptoms, daily activities, leisure activities, work, personal relationships and treatment. Responses range from "not at all" (scored 0) to "most of the time" (scored 6) and gives a minimum and maximum score from 0-90, with higher scores representing greater burden. A minimally important difference has not yet been established for the questionnaire. The VitiQoL should be completed as per Schedule of Activities.

The Patient Global Impression of Severity of Vitiligo (PGIS-V) is 1-item within the VitiQoL questionnaire which asks the subject to determine how severe they feel their skin condition is at that point in time on a 7-point Likert response from "no skin involvement" to "most severe case".

7.6.3. Dermatology Life Quality Index (DLQI)

The DLQI is a general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimal clinically important difference for the DLQI has been estimated as a 2 to 5 point change from baseline. The DLQI should be completed as per Schedule of Activities.

7.6.4. Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item PRO measure used to detect states of anxiety and depression over the past week. Items are rated on a 4-point severity scale. The HADS produces two scales, one for anxiety (HADS–A) and one for depression (HADS–D), differentiating the two states. Scores of greater than or equal to 11 on either scale indicate a definitive case. The HADS should be completed as per Schedule of Activities.

7.6.5. Patient Health Questionnaire – 8 items (PHQ-8)

Patient Health Questionnaire – 8 items is a patient-reported outcomes questionnaire which consists of 8 items to screen for the subject depression level.

The PHQ-8 should be completed at the Screening Visit. At Screening Visit, if PHQ-8 total score ≥15, the subject will not be included in the study.

7.6.6. Patient Global Impression of Change- Vitiligo (PGIC-V)

The PGIC-V is a 1-item questionnaire is designed to assess a subject's impression of disease improvement relative to before the intervention on a 7 point Likert scale ranging from "Very much improved" to "Very much worse" with "no change" in the middle. The PGIC-V should be completed as per Schedule of Activities.

7.6.7. EQ-5D-5L

The EQ-5D-5L and VAS is a validated, standardized, generic instrument that is the most widely used preference-based health-related quality of life questionnaire in cost-effectiveness and health technologies assessment (HTA).[5,11,15,32] The measure is a well-established instrument used to measure health states and utilities in various diseases areas. The measure contains five items that cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as well as a VAS to assess overall health status. The EQ-5D-5L should be completed as per Schedule of Activities.

7.6.8. Healthcare Resource Utilization (HCRU)

In order to get an assessment of the subject's Healthcare Resource Utilization (HCRU), subjects will be asked about the number of visits and use of the healthcare system outside of that provided within the clinical trial. Questions will be asked to gauge any hospitalizations, surgical procedures, or medical visits stratified by those which are vitiligo related or not. The HCRU questionnaire will also measure certain concepts related to sexual function

(eg, libido) which have been incorporated from the vitiligo impact patient scale questionnaire. The HCRU should be completed as per Schedule of Activities.

7.6.9. Vitiligo Noticeability Scale (VNS)

The Vitiligo Noticeability Scale is a 1-item patient completed scale that assesses noticeability of vitiligo patches "now" compared with before treatment - as a way of evaluating treatment effect from the patient perspective (Batchelor, 2016).[49] The scale includes 5 point Likert options ranging from 1= more noticeable to 5= no longer noticeable. Participants will complete this scale onsite and will be required to review their Day 1 facial images (before treatment) and look at their face in the mirror the day of which the scale is completed (per SOA) to complete their response on this scale. Facial images from Day 1 will be available to the site for patient review.

7.7. Photography

Photographs of face will be taken at the site Screening Visit and Baseline Visit to verify eligibility (BSA ≥0.25% involvement on the face).

Photographs of facial and non-facial treatment-eligible vitiligo lesions will be obtained (according to the separately provided Photography Instructions) at various time points as per Schedule of Activities. For non-facial vitiligo lesions, two lesions will be selected. One lesion will be active lesion and the other will be stable lesion (stable target lesion). In case of mixed Vitiligo, one isolated segmental vitiligo lesion (segmental target lesion, if applicable) will be selected. Areas photographed should be recorded in study documents so that the same body region(s) will be photographed during the study. Additional photographs may also be taken at the investigator's discretion.

Photographic services will 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 will be reviewed by independent blinded consultant(s)/reader(s) to confirm the eligibility and evaluate the facial-VASI. This score will be used for the primary analysis.

Additional reader(s) may evaluate the photographs for at least 10% of the subjects to assess inter/intra rater variability for facial-VASI. Details of the inter/intra rater variability will be described in a separate exploratory analysis plan.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

7.10. Viral Surveillance

Blood sample for the analysis of CMV, EBV, HSV-1, HSV-2 and VZV will be collected according to the times outlined in the Schedule of Activities. Additional sample collection instructions will be provided in the lab manual.

Note: Due to long turnaround time, the retrospective nature of these labs might make their reporting time quite delayed.

In addition to time points specified, a blood sample for viral surveillance sample may also be taken at the time of an adverse event, as clinically appropriate.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

7.12. Rater Qualifications

Clinical evaluations of vitiligo 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 vitiligo clinical trials may be permitted to perform the clinical evaluations of vitiligo 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.

7.13. Sun Exposure Check

The sun exposure information will be captured daily via electronic-diary (E-diary) as per Schedule of Activities. Compliance of E-diary will be monitored. Delegated site staff will review compliance with subjects at each visit and counsel as appropriate. If a subject has repeated non-compliance, the subject should be re-trained. If a subject is unable to complete the E-diary due to documented technical disability or other limitation, the subject will be permitted to enter or remain in the study. No deviations will be recorded in regards to E-diary compliance.

7.14. Fitzpatrick Skin Type Assessment

The skin type assessment will be done at the Screening visit using the Fitzpatrick Skin Phototype assessment (Appendix 9). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

7.15. Requests for Results of Tests and Procedures Not Part of the Study (if applicable)

If during the event adjudication (Section 9.9), the specific documents are needed to support event adjudication by the Adjudication/Review Committees, additional tests or procedures that are not part of the study but that could be related to the study may be requested. Copies of the reports of these tests may be requested.

Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

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), **except occupational exposure**	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. Adverse Reactions and Serious Adverse Reactions

An adverse reaction (AR) is any untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered. This implies a reasonable possibility of a causal relationship between the event and the IMP.

A serious adverse reaction (SAR) is an adverse reaction which meets the criterion of 'seriousness' as described in Section 8.2.3.

Suspected unexpected serious adverse reactions (SUSARs) are serious adverse reactions (SARs) that are unexpected per the reference safety information (RSI) in the respective IBs for PF-06651600 and PF-06700841.

8.2.5. 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.

8.4.1.1. 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 (× 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 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × 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 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × 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 × ULN; or >8 × 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 × ULN or if the value reaches >3 × 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.

8.4.2. 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).

All subjects who are assigned to receive PF-06700841 in the Extension Period will have serum creatinine based and serum cystatin-C based eGFR calculated at EXD1 Visit 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) {Levey, 2009 #25} and serum cystatin C (2012 CKD-EPI eGFR)[14] will be determined at times specified in the Schedule of Activities. If an individual subject who is assigned to receive PF-06700841 in the Extension Period demonstrates a **CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥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 ±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 ≥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 assigned to receive PF-06700841 in the Extension Period.

8.4.3. 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.

8.4.3.1. 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 multiple concomitant medications including an herbal supplement which carried a pregnancy warning.

8.4.3.2. 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.

8.4.3.3. 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.

8.4.4. Medication Errors

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

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

8.4.4.1. 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 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.

Data may be cleaned, a snapshot of the database may be created, and efficacy and safety data from the 24-week Dose Ranging Period may be summarized in an interim CSR and/or top line report and published once the last subject last visit occurs for the 24-week Dose Ranging Period. The interim study report may be shared with the PI when it is available.

9.1. Sample Size Determination

The sample size rationale is based on the primary efficacy endpoint percent change from baseline in central read facial-VASI score at Week 24. The null hypothesis to be tested is that the difference between PF-06651600 and placebo is less than or equal to 0 in percent change from baseline in central read facial-VASI score vs the alternative hypothesis that the difference between PF-06651600 and placebo is greater than 0%.

There will be a total of 5 pairwise comparisons reported: PF-06651600 200 mg >50 mg vs placebo, PF-06651600 100 mg >50 mg vs placebo, PF-06651600 50 mg vs. placebo, PF-06651600 30 mg vs placebo, and PF-06651600 10 mg vs placebo. However the sample size calculation will account for the multiplicity adjustment to ensure a strong control of the type-1 error for comparisons of PF-06651600 200 mg >50 mg vs. placebo, PF-06651600 100 mg >50 mg vs. placebo, and PF-06651600 50 mg vs. placebo. The PF-06651600 30 mg and PF-06651600 10 mg dose groups are included for the characterization of the dose response curve.

CCI

CCI [redacted]

9.2. Efficacy Analysis

All subjects who receive at least one dose of randomized investigational product and have a baseline measurement will be included in the efficacy data analyses. Alpha adjustments for primary will be described in the SAP.

9.2.1. Analysis of the Primary Endpoint

The primary efficacy endpoint is percent change from baseline in the central read facial-VASI score. The primary time point is Week 24. 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 central read facial-VASI and investigator site, and a random effect for subject, will be used to analyze the percent change from baseline in the central read facial-VASI score (this will be denoted as the primary analysis). This model may also include effects for treatment by time interaction and baseline value of central read facial-VASI by treatment interaction and skin type (Fitzpatrick scale). If data permits, sun exposure data may be included as a covariate in the analysis model. 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 percent change from baseline in central read facial-VASI estimates at Week 24 for PF-06651600 vs. placebo will be computed. If there are extreme outliers using percent change from baseline data, a non-parametric analysis may be conducted to compare active and placebo at Week 24 and other intermediate time points. Alpha adjustments for the pairwise comparisons for the primary endpoint and details about the analyses will be described in the SAP. The SAP will also describe how data from visits affected by COVID-19 will be treated in the analysis.

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 percent change from baseline values by treatment group and visit.

The overall Type 1 error rate is controlled at 0.05 (one-sided). Multiple comparisons will be conducted applying a Hochberg[37] procedure using observed p-values.

Three pairwise comparisons will be adjusted for multiplicity for the primary endpoint in this hierarchy: PF-06651600 200 mg ->50 mg vs placebo, PF-06651600 100 mg ->50 mg vs placebo and then PF-06651600 50 mg vs. placebo.

A secondary objective for the primary endpoint is to characterize the dose response for the percent change from baseline in central read facial-VASI. To achieve this objective, a Bayesian 4 parameter e_{max} model may be used to characterize the dose response relationship. Details of the dose response model and assessment of the loading dose will be described in the SAP.

9.2.2. Analysis of Secondary Endpoints

No multiplicity adjustments will be done for the key secondary and secondary endpoints.

9.2.2.1. Analysis of the Key Secondary Endpoint

The key secondary efficacy endpoint is the proportion of subjects achieving central read facial-VASI 75 at Week 24.

The central read facial-VASI 75 response rate will be analyzed by first treating the missing data (non-COVID19 related) as non-responders and then applying Chan and Zhang[38] exact confidence interval (CI) method at Week 24 (and other intermediate time points). Missing data impacted due to COVID-19 for central read facial-VASI75 will be removed from analysis.

9.2.2.2. Analysis of Other Secondary Endpoints

The secondary efficacy endpoints are the proportions of subjects achieving VASI50/75/90/100, central read and site assessment of the facial-VASI50/75/90/100 at all intermediate timepoints (except Week 24 for central read facial-VASI75).

The secondary endpoints will be analyzed by first treating the missing data as non-responders and then applying Chan and Zhang[38] exact confidence interval (CI) method at Week 24 (and other intermediate time points). Missing data due to COVID-19 for these binary endpoints will be removed from analysis.

Percent change from baseline in VASI at Week 24 and change from baseline in VASI at Week 24 will be analyzed using the same statistical model as the primary endpoint.

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

CCI [redacted]

9.5. Safety Analysis during the Dose Ranging 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) 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 [redacted] There will be no adjustment for multiple comparisons or stratification factor in the analyses unless specified.

Data relevant to the assessment of suicidality will be mapped to the Columbia-Classification Algorithm of Suicide Assessment (C-CASA) codes. Baseline and post-baseline C-SSRS data (mapped to C-CASA scores) will be summarized descriptively by treatment group at baseline and each post-baseline visit.

9.6. Analysis during the Extension Period

CCI [redacted]

CCI [redacted]

9.6.3. Safety Analysis

A set of safety summary tables will be produced to evaluate potential risks associated with the safety and tolerability of administering the investigational product. 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) will be summarized using n, mean, median, standard deviation etc.

Change from baseline on selected safety endpoints may be additionally summarized. Subject listings may also be produced for these safety endpoints. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. Detailed methodologies of these analyses will be described in the SAP.

9.7. Interim Analysis during the Dose Ranging Period

The statistical analysis plan and the interim analysis plan for this protocol may include an interim analysis using percent change from baseline in VASI score for all 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 24 visit. 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 will be based on a total of approximately 165 subjects who complete or had the chance to complete Week 24.

9.8. 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 9.6. 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.

9.9. Safety Adjudication Committees

The identification of events requiring submission to an adjudication/review committee may be made by the study site and communicated to Pfizer or designee. Events requiring review, including opportunistic infections, cardiovascular, and malignancy events may also be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject's study records. The Pfizer Study Team or designee will notify the study site of any events should they identify.

The Pfizer Study Team or designee will provide a listing of specific documents needed to support event adjudication by the Adjudication/Review Committees. Obtaining and submitting the documentation will be the responsibility of the study site. Event documentation will vary with the event requiring adjudication and may include (but not be limited to): hospital discharge summaries, operative reports, clinic notes, diagnostic tests, pathology reports, autopsy reports and death certificate information, as applicable.

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. 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, unless a waiver of informed consent has been granted by an IRB/EC. 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 All Participating Countries

End of trial in all 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 (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or 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

Pfizer posts clinical trial US Basic Results on 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 European Union (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

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 for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to 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.

16. REFERENCES

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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
AE	adverse event
AIFA	Italian Medicines Agency
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time zero to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration time curve from time zero extrapolated to the last quantifiable concentration
AUCτ	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
BBS	biospecimen banking system
BCG	bacille calmette guérin
BID	twice a day
BMX	bone marrow-expressed kinase
BTK	bruton's tyrosine kinase
BP	blood pressure
BSA	Body surface area
BUN	blood urea nitrogen
CDS	core data sheet
CI	confidence interval
CK	creatine kinase
CL	clearance
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	Maximum (peak) plasma concentration
CMV	cytomegalovirus
CO	cross-over
COEOT	cross-over end of treatment
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSA	clinical study agreement
CsA	cyclosporine A

Abbreviation	Term
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CT	computed tomography
CTA	clinical trial application
CTCAE	common terminology criteria for adverse events
CYS	cysteine
DAI	dosage and administration instructions
DDI	drug-drug interaction
DLQI	dermatology life quality index
DMARD	Disease-modifying antirheumatic drug
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
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EE	Ethinyl Estradiol
EFD	embryo-fetal development
E_{max}	maximum effect
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
EQ-5D-5L	EuroQol 5 dimension 5 level
ESR	erythrocyte sedimentation rate
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI	[redacted]
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
GLMM	generalized linear mixed model

Abbreviation	Term
GM-CSF	granulocyte-macrophage colony-stimulating factor
GST	glutathione-S-transferase
HADS	hospital anxiety and depression scale
HbA1c	glycosylated hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCRU	healthcare resource utilization
HCVAb	hepatitis C antibody
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
HSV	herpes simplex virus
HSV1	herpes simplex virus type 1
HSV2	herpes simplex virus type 2
IB	investigator's brochure
IC_{50}	the half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	identification
IFNα	interferon alfa
IFNγ	interferon gamma
CCI	[redacted]
IGA	investigator's global assessment
IGRA	Interferon Gamma Release Assay
CCI	[redacted]
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IP	investigational product
CCI	[redacted]
IRB	institutional review board
IRC	internal review committee
ITK	inducible T-cell kinase
IRT	interactive response technology
IUD	intrauterine device
IVRS	interactive voice response system
IWR	interactive web response
JAK	janus kinase
LFT	liver function test

Abbreviation	Term
LLN	lower limit of normal
LLQ	lower limit of quantitation
LN	levonorgestrel
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
MDR1	multidrug resistance 1 gene
mITT	modified intention-to-treat
MMRM	mixed-effect models repeated measures
MRI	magnetic resonance imaging
CCI	[redacted]
MTX	methotrexate
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
nbUVB	narrow band ultraviolet B
NK	natural killer cells
CCI	[redacted]
NRI	non-responder imputation
NRS	numerical rating scale
OAT2	organic anion transporter 2
OBU	oncology business unit
OC	oral contraceptive
OCT2	organic cation transporter 2
PCD	primary completion date
CCI	[redacted]
PI	principal investigator
PFS	pre-filled syringe
PGIC-V	patient global impression of change in vitiligo
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
PsO	psoriasis
PT	prothrombin time
PtGA	patient global assessment
QD	once daily
QFT-G	QuantiFERON®-TB Gold

Abbreviation	Term
QFT-GIT	QuantiFERON®-TB Gold In-Tube
QTcF	the corrected QT interval by Fredericia
R_{ac}	accumulation ratio
RLK/TXK	resting lymphocyte kinase
CCI [redacted]	[redacted]
RRCK	ralph russ canine kidney cells
RSI	reference safety information
s-IGA	static investigator global assessment
SA-VES	self assessment vitiligo extent score
SAD	single ascending dose
SAE	serious adverse event
SALT	severity of alopecia tool
SAP	statistical analysis plan
SAR	serious adverse reaction
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
SPF	sun protection factor
SRSD	single reference safety document
SSC	special safety concern
STATs	signal transducers and activators of transcription
SUSARs	suspected unexpected serious adverse reactions
$t_{½}$	half life
TB	tuberculosis
CCI [redacted]	[redacted]
TDAR	T cell-dependent antibody response
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TEAE	treatment-emergent adverse event
T_H1	type 1 helper T cell
T_H2	type 2 helper T cell
T_{max}	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
USPI	United States package insert
UVA	ultraviolet A light

Abbreviation	Term
UVB	ultraviolet B light
UVR	ultraviolet radiation
VASI	vitiligo area scoring index
VES	vitiligo extent score
VitiQoL	vitiligo specific quality of life
VNS	Vitiligo Noticeability Scale
V_z/F	Apparent volume of distribution during terminal phase after non-intravenous administration
VZV	varicella zoster virus
WOCBP	woman of child bearing potential

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**	**Sensitive substrate to ABCG2=BCRP**
Amprenavir	Avasimibe#	Simvastatin or Simvastatin-containing products	Quinidine###	Digoxin###	Dofetilide###	Rosuvastatin##
Amiodarone	Bosentan					
Aprepitant	Barbiturates					
Atazanavir	Carbamazepine#					
Boceprevir	Efavirenz					
Casopitant	Etravirine					
Cimetidine	Mitotane#					
Ciprofloxacin	Modafinil					
Clarithromycin#	Nafcillin					
Cobicistat#	Phenobarbital#					
Conivaptan#	Phenytoin#					
Darunavir	Rifabutin#					
Diethyldithiocarbamate	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#						

* Applicable to PF-06651600 and PF-06700841: All prohibited drugs that are CYP3A inhibitors or **strong P-gp inhibitors** (PF-06700841 only) 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 IP.

** Applicable to PF-06651600 and PF-06700841: 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 IP.

Noted as potent inhibitors or inducers.

Applicable to PF-06651600: For Germany only

Applicable to PF-06700841 only.

It is recommended that subjects avoid consumption of grapefruit juice exceeding 8 ounces (~240 ml) total in a day while in the study.

In a situation where appropriate medical care of a subject requires the use of a prohibited CYP3A inhibitor or inducer:

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. ***Note: Amiodarone and mitotane are not permitted for any duration due to their long half-lives.*** Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.

CCI [redacted]

[redacted]

CCI [redacted]

CCI

[redacted]

Appendix 4. Management of Dermatological Events

Dermatologic Event (CTCAE v 4.0)	Course of Management
Acne/Acneiform Rash/Maculopapular Rash	
Grade 1/2	1. Investigator's discretion for withdrawing study medication. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3	1. Discontinue study medication. 2. Monitor to resolution (defined as a Return to Baseline status). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Pruritus	
Grade 1 Mild or localized	1. Investigator's discretion for withdrawing study medication. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 2 Intense or widespread	1. Discontinuation of the study medication may not be required unless condition is sustained >4 days or at the investigator's discretion. 2. Execute reasonable monitoring. 3. Consider treatment with topical agents such as clindamycin or corticosteroids.
Grade 3 Intense or widespread and interfering with activities of daily living	1. Permanently discontinue study medication. 2. Monitor to resolution (Return to Baseline). 3. Consider treatment with topical agents such as clindamycin or corticosteroids.

Appendix 5. Guidelines for Subject Safety Monitoring and Discontinuation

These guidelines for subject safety monitoring and discontinuation are to be applied to all subjects in study B7981019. 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 5.1. 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 (upon receving the laboratory results) **until resolution or agreement with Pfizer:**

- Absolute neutrophil count <2000/mm^3 (2.0 x10^9/L);
- Hemoglobin <9.0 g/dL;
- Platelet count below <100,000/mm^3 (100 x10^9/L);
- Lymphocytes <600/mm^3; <0.6x10^9/L;
- CK >3xULN (this also triggers urine myoglobin).

Appendix 5.2. Discontinuation

Treatment will be discontinued for:

Subjects in Group 2 in Extension Period:

- Subjects have <10% improvement in percent change in VASI at Extension Week 12 from baseline at Week 24.

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 (refer to local guideline or equivalent);
- 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 (Section 7.3.6.1.2).

Potential Cases of Decreased eGFR:

If an individual subject who is assigned to receive PF-06700841 in the Extension Period demonstrates a CONCOMITANT serum creatinine-based AND serum Cystatin C-based eGFR decline of ≥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 ±15% or the renal parameters are deemed to be stable by the nephrologist and/or PI (see protocol Section 8.4.2).

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 Dose Ranging Period or Extension Period 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 (≥24 hrs) or symptomatic increase from baseline, in same posture, by >20 mmHg.

ECG:

The following ECG abnormality will **require discontinuation** if it is confirmed by repeat ECG:

QT prolongation defined as a QTc ≥500 msec or an absolute change in QTc ≥60 msec.

Laboratory Abnormalities:

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

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

[b] 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 ET Visit occurring on the last day the subject takes the investigational product or as soon as possible thereafter. Events will be followed up until the event has returned to normal or baseline levels or is deemed clinically stable. The **End of Study Visit will occur 4 weeks after the ET Visit**. 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. 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.

Appendix 6. Vitiligo Extent Score (VES)

www.vitiligo-calculator .com

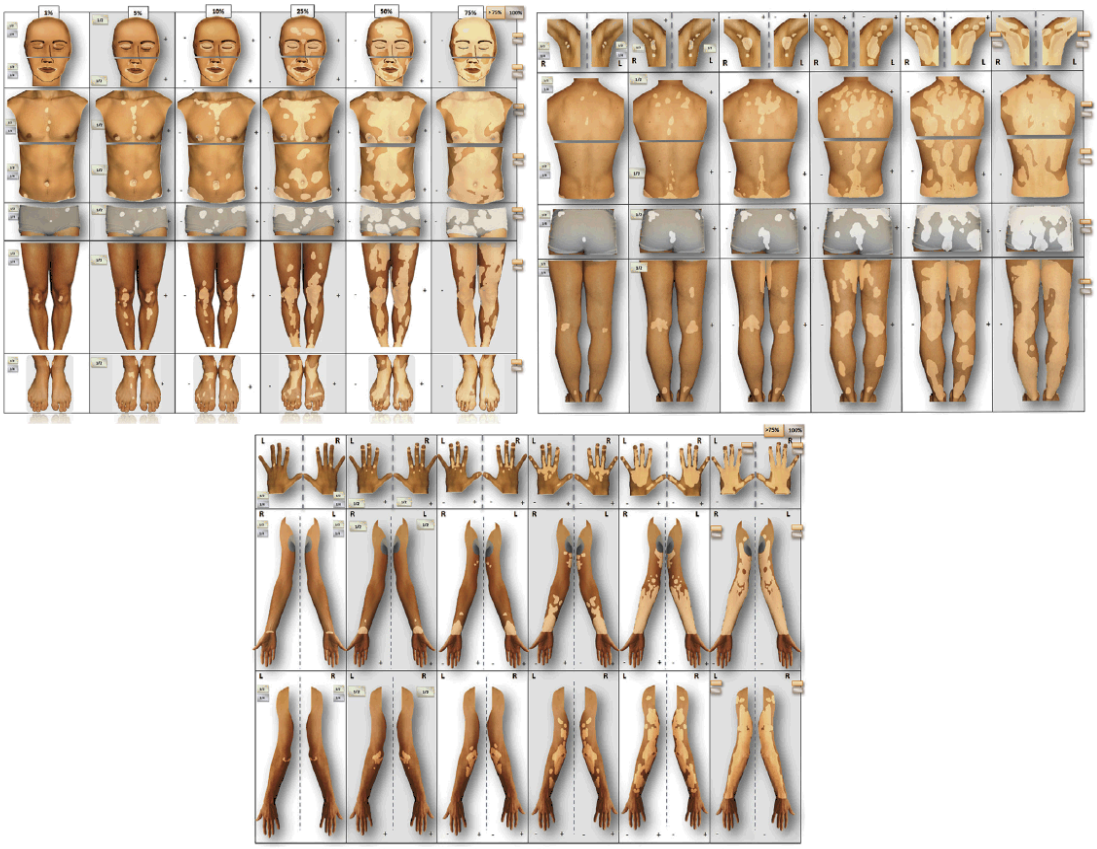

Figure 1. Scoring sheet Vitiligo Extent Score (VES). Example of the new scoring system. The 19 different body areas are scored separately depending on the vitiligo extent (online version available soon: www.vitiligo-calculator.com).

Appendix 7. Columbia Suicide Severity Rating Scale (C-SSRS)[27]

C-SSRS for Screening and Baseline Visit

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) ____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) ____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

CSSRS for any post-baseline visits

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe

Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix 8. Pruritus Numeric Rating Scale (NRS) for Potential Drug-related Rash

Select the number that best describes your itching due to potential drug-related rash over the past 24 hours (check one number only).

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching										Worst possible itching

Appendix 9. Fitzpatrick Skin Type

Phototype	Sunburn and tanning history (defines the phototype)
I	Burns easily, never tans
II	Burns easily, tans minimally with difficulty
III	Burns moderately, tans moderately and uniformly
IV	Burns minimally, tans moderately and easily
V	Rarely burns, tans profusely
VI	Never burns, tans profusely

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

Appendix 11. Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Eligibility

Study B7981019 has been fully recruited and the eligibility criteria are not impacted by any public emergencies, including the COVID-19 pandemic.

Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. The participant site visits may be changed to telehealth visits (if permitted by law or local guidance) to reduce risk of potential participant exposure to COVID-19.

Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Section 4.4.1 and Section 7.1 regarding pregnancy tests.
- Evaluate VASI and facial-VASI (site assessment). Refer to Section 7.4.1, 7.4.2, and 7.4.3. A self-captured photos by the subject may aide in assessment of facial-VASI.
- Complete PRO measures in the following order: VitiQoL, PGIC-V, and VNS. Refer to Section 7.6.

Study participants must be reminded to promptly notify site staff about any change in their health status.

Alternative Facilities for Safety Assessments

Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Clinical laboratory tests listed in Section 7.3.8.2, including hematology, blood chemistry, urinalysis and other protocol specified tests.

- Special safety assessment of serum creatinine and cystatin C, for estimation of eGFR.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

Imaging

If the participant is unable to visit the study site for imaging assessment(s), the self captured photo APP (called "Pfizer Vitiligo Study B7981019" powered by Tissue Analytics) used by the subject may aide in assessment of facial-VASI.

Qualified study site personnel must order, receive, and review results.

Electrocardiograms

If the participant is unable to visit the study site for single 12-lead ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

Study Treatments

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study treatment must be considered.

In situations where participants are quarantined or self-isolating, arrangements to send investigational product via courier may be implemented where allowable by law or by local guidance and with the participant's verbal consent.

Investigational product appropriate for the individual participant based on the study period and treatment group, may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the investigational product. Pfizer does not permit the shipment of investigational product by mail. The tracking record of shipments and the chain of custody of investigational product must be kept in the participant's source documents/medical records.

Similar to investigational product dispensed at the clinical site, PF-06651600 tablets and matching placebo for oral administration will be in blisters and PF-06700841 tablets for oral administration will be in bottles. Investigational products should be stored in their original containers and in accordance with the labels.

Participants will take the medication orally once daily. Participants should swallow the tablets whole with 1 cup (240 mL or 2.4 DL) of ambient temperature water, without any manipulation or chewing. **Participants will be encouraged to take the investigational product after breakfast whenever possible** even though it may be taken with or without food.

Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

Efficacy Assessments

The efficacy assessments will be conducted to the best ability with available telehealth modality and calculate VASI and facial-VASI. If possible, obtain photographs of the target lesion with the best possible compliance with the Photography Instructions.