Protocol Title: A PHASE 3 OPEN-LABEL, MULTI-CENTER, LONG-TERM STUDY INVESTIGATING THE SAFETY AND EFFICACY OF PF-06651600 IN ADULT AND ADOLESCENT PARTICIPANTS WITH ALOPECIA AREATA

Protocol Number: B7981032

Amendment Number: 6

Compound Number: PF-06651600

Study Phase: Phase 3

Short Title: Study Evaluating PF-06651600 in Adults and Adolescents with Alopecia Areata

Sponsor Name: Pfizer, Inc

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	ID
IND	131503
EudraCT	2019-001084-71

Approval Date: 28 March 2022

For Japan only: Upon approval of ritlecitinib for alopecia areata in Japan the terms “clinical study/clinical trial” and “study intervention” in the protocol and related documents may also be interpreted as “post-marketing clinical study” and “post-marketing study drug,” respectively.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	03 April 2019
Amendment 1	15 October 2019
Amendment 2	05 February 2020
Amendment 3	28 April 2020
Amendment 4	31 August 2020
Amendment 5	23 April 2021
Amendment 6	28 March 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

Amendment 6 (28 March 2022)

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Objectives, Estimands and Endpoints; Section 1.1 Intervention and Duration; Section 1.2 Schema; Section 1.3.2.1 Treatment period 1: Week 2 through Month 24; Section 1.3.2.2 Treatment Period 1: Month 28 to Month 36; Section 1.3.2.3 Treatment Period 2: Month 40 to Month 60; Section 4.1 Overall Design; Section 4.2 Scientific Rationale for Study Design; Section 4.3 Justification for Dose; Section 4.4 End of Study Definition; Section 8.1.2.1.1 Androgenetic Alopecia SALT Score; Section 8.2.11 Pregnancy Testing; Section 9.4.2 Efficacy Analysis; Section 10.8.2 Discontinuation Section 10.13.3.1 Laboratory Testing; Section 10.14 Appendix 14: Management of Participants with a Positive Tuberculosis Test Result on Day 1 or Annual Tuberculosis Testing	Study extension for all participants (de novo or originating from Study B7981015 or B7931005) to continue to receive open-label 50 mg PF-06651600 QD. Study updated to have 2 treatment periods in addition to follow-up. Treatment up to 36 months is TP1. TP2 will be of variable length for individual participants; assuming a participant does not require discontinuation per protocol, a participant may continue to receive study intervention in TP2 for a maximum of 24 months or until availability of commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first. Clarifications added throughout document regarding the extension of the study and its impact on endpoint collection, analysis, and reporting.	In order to allow study participants continued access to study intervention with collection of additional long-term safety and efficacy data, study duration is extended up to 60 months (or until availability of commercial product in the country or until the sponsor terminates the study in that country).

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 3 Objectives, Estimands and Endpoints	Added secondary safety and tolerability objectives.	Added objectives and endpoints as a result of the study extension.
Section 3 Objectives, Estimands and Endpoints	Added tertiary/exploratory efficacy endpoints, patient-centered outcomes and biomarkers.	Added endpoints as a result of the study extension.
Section 1.1 Synopsis; Section 3 Objectives, Estimands and Endpoints	Update language of Alopecia Areata Patient Priority Outcomes (AAPPO) endpoint. Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) scales through Month 36.	This update was made to correct the text for accuracy.
Section 2.2.2 Non-clinical and Phase 1 Efficacy and Safety Data; Section 6.1 Study Intervention Administered; Section 6.2 Preparation/Handling/ Storage/Accountability; Section 6.4 Study Intervention Compliance; Section 10.13.4 Appendix 13: Study Intervention	PF-06651600 bioequivalence between tablets and capsules was established in completed Phase 1 Study B7981029. Dosage form, packaging, and labeling updated to allow tablet or capsule.	The study extension of up to 24 months of treatment beyond Month 36 may result in a transition of PF-06651600 dosage form from tablet to capsule and from blister to bottles.
Section 1.3.3 Early Termination and Follow-up; Section 10.8.2 Discontinuation	12- lead ECG is not to be collected during ET visit for participants who have completed the Month 36 visit.	These changes were made for consistency with Section 1.3.2 in which 12-lead ECG is not collected after Month 36. The sponsor has performed an analysis of applicable nonclinical and clinical data that indicate that the risk for PF-06651600 to cause clinically meaningful QT prolongation in humans is low.
Section 1.3.2.3 Treatment Period 2: Month 40 to Month 60; Section 1.3.3 Early Termination and Follow-up; Section 10.2. Appendix 2: Clinical Laboratory Tests; Section 10.13.3.1 Laboratory Testing	Fasting Lipid Panel is not to be collected for participants who have completed the Month 36 visit. For participants who have completed the Month 36 visit, urinalysis will be performed	These changes were made for consistency with Section 1.3.2 in which fasting lipid panel, creatine kinase, urine samples, urinalysis, urine myoglobin, assessment

Section # and Name	Description of Change	Brief Rationale
	only if considered clinically indicated by the investigator. Clinical Assessments (Assessment of Fingernails Affected by AA and CGI-AA) and PROs (AAPPO and HADS) will not be collected for participants who have completed the Month 36 visit. For participants who have completed the Month 36 visit, creatine kinase and urine myoglobin will not be tested. Urine culture will be performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.	of Fingernails Affected by AA, CGI-AA, AAPPO and HADS are not collected after Month 36. Based on recent safety data analyses, it has been considered that measurements of fasting lipid panel, creatine kinase, urine myoglobin (reactive) and urinalysis are no longer warranted after Month 36. Note that urinalysis can still be performed if considered clinically indicated by the investigator. Assessment of Fingernails Affected by AA and CGI-AA are exploratory endpoints in TP1 and AAPPO is a secondary endpoint in TP1. The collection of these measurements is not needed beyond Month 36. Note that the other efficacy endpoints will continue to be collected in TP2.
Section 4.4.1 Extended Study Duration	Section deleted.	This Section was no longer needed based on the up to 24 months extension of treatment added.
Section 5.3.1 Contraception	Added additional clarifications on the contraception check. If in the event the participant discontinues contraception method, the Investigator will "document the requirement to use an alternate protocol-specified method, including if the participant will	This update was made to provide additional clarification on the requirements and timing for contraception check.

Section # and Name	Description of Change	Brief Rationale
	no longer use abstinence as the selected contraception method" and "The contraception check for WOCBP will be performed during each study visit and monthly between study visits at time of the phone contact to check the at-home pregnancy test results."	
Section 1.1 Synopsis; Section 1.2 Schema; Section 1.3.3 Early Termination and Follow-up; Section 4.1 Overall Design; Section 7.1.1 Permanent Discontinuation; Section 7.1.1.1 Observation Period; Section 9.4 Statistical Analyses; Section 9.4.2 Efficacy Analyses	Added detail on permanent discontinuation and defined the Observation Period. Added two subsections under Section 7.1 (Section 7.1.1 and Section 7.1.1.1). If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever occurs first.	Added in order to collect data in participants who have discontinued study intervention.
Section 8 Study Assessments and Procedures	Updated the amount of blood to be collected from each participant in Study B7981032.	This change was made to align with the extended Intervention Period for up to 24 additional months.
Section 9.4.1 Timing of Analyses; Section 9.4.2 Efficacy Analyses; Section 9.4.3 Safety Analyses	Added information on analyses to be provided in the supplemental CSR.	This information was added as a result of the study extension.
Section 10.14 Appendix 14: Management of Participants with a Positive Tuberculosis Test Result on Day 1 or Annual Tuberculosis Testing	Updated the annual visit in which study intervention is permitted to be re-started "If study intervention is permitted to be re-started, at the next annual visit (ie, Month 12, 24, 36, 48 or 60), a chest radiograph is required to be performed (a QFT G, T-SPOT, or PPD test need not be obtained)." "If study intervention is permitted to be re-started,	This update was made for consistency with the study extension.

Section # and Name	Description of Change	Brief Rationale
	QFT-G testing (or T-SPOT or PPD, if applicable) will be required at the next visit per the protocol Schedule of Activities (ie, Month 12, 24, 36, 48 or 60); in this case the recent test has been effectively deemed a 'false positive' by the specialist and the participant is considered to be WITHOUT a true positive QFT-G (or T-Spot or PPD, if applicable) test result at this visit."	
Section 10.10 Appendix 10	Updated timing for which participants from the main B7981032 study can participate in the vaccine sub-study	This change was made to align with the extended Intervention Period for up to 24 additional months.
Section 8.1.3.1. Alopecia Areata Patient Priority Outcomes (AAPPO)	Updated language to amend wording for response categories for items from 1 to 11.	This update was made to correct the text of original protocol.
Section 8.2.9.1 Columbia Suicide Severity Rating Scale (C-SSRS); Section 10.8.2 Discontinuation	Added details on participants with suicidal ideation.	This update was made to provide details on participants with suicidal ideation and discontinuation criteria.
Section 9.4 Statistical Analyses	Clarified that data analysis from participants who discontinued treatment but remained on study will be described in the statistical analysis plan.	This update was made for consistency with Section 7.1.
Section 10.1.5.2. Adjudication/Review Committee Submission	Updated language regarding events requiring submission to an adjudication/review committee.	This update was made to provide clarification on events requiring submission to an adjudication/review committee.
Section 10.4.3 Women of Childbearing Potential	Updated text regarding confirmation of post-menopausal status during the study.	This update was made to provide additional clarification on the procedure for confirming postmenopausal status.
Section 10.8.1 Monitoring	Updated hemoglobin values requiring re-testing.	Based on a recent review of clinical safety data for PF-06651600 and a review of cases meeting the >2 g/dL

Section # and Name	Description of Change	Brief Rationale
		change from baseline threshold in this study, it has been considered that this criterion is no longer warranted, and that a participant's safety is adequately monitored based on re-testing required for hemoglobin values <10.0 g/dL.
Section 4.3 Justification for Dose Table 1	Mean Clinical AUC and Calculated Safety Margin updated.	This update was made in alignment with Investigator Brochure version 8.0 December 2021.
Section 10.11 Appendix 11: Discontinuation Criteria for Worsening of Alopecia Areata for VHP Countries in the EU; Section 10.12 Appendix 12: Study Intervention Continuation Criteria for Adolescents	Clarified the discontinuation requirements.	This update was made for consistency with Section 7.1 in Amendment 5.
Section 2.2.3 Clinical Experience; Section 2.2.3.2 Phase 2b/3 Study in Alopecia Areata; Section 2.3 Benefit/Risk Assessment	Provided updated numbers of participants in Phase 2 and Phase 3 clinical studies. Added information on Phase 2b/3 Study B7981015 in Alopecia Areata.	This update was made in alignment with Investigator Brochure version 8.0 December 2021.
Title Page and Section 10.1.1. Regulatory and Ethical Considerations	Language added for compliance with Japan regulatory requirements.	This information was added for consistency with GCP for J-NDA. Clinical Trials of "unapproved drug" should be conducted under GCP for J-NDA (Article 2, 14, 14(3) etc). After regulatory approval, clinical trials of "approved drug" should be conducted under GCP and GPSP for Re-Examination (Article 14-4(1), 14-4(4) etc).
Section 10.16 Appendix 16: Protocol Amendment History	Moved table for Amendment 5 descriptions of changes and brief rationales to this appendix.	Following Pfizer's standard procedure for the common protocol template.

Section # and Name	Description of Change	Brief Rationale
Throughout document	Other relatively minor administrative/typo/abbreviation /formatting updates.	Updated for grammatical correctness, clarity, consistency with Pfizer Global Style Guide and protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A PHASE 3 OPEN-LABEL, MULTI-CENTER, LONG-TERM STUDY INVESTIGATING THE SAFETY AND EFFICACY OF PF-06651600 IN ADULT AND ADOLESCENT PARTICIPANTS WITH ALOPECIA AREATA
Short Title: Study Evaluating PF-06651600 in Adults and Adolescents with Alopecia Areata

Rationale:
PF-06651600 inhibits JAK3 and members of the tyrosine kinase family expressed in hepatocellular carcinoma (TEC) and is being developed as an oral treatment for patients with alopecia areata (AA). Since CD8+ T cells, NK cells and mast cells have all been implicated in the pathophysiology of AA, inhibition of TEC kinases has the potential to contribute to efficacy in this disease by modulating the functional activity of pathogenic effector cells.

Objectives, Estimands and Endpoints

Primary Objectives	Primary Endpoints
• To evaluate the long-term safety and tolerability of PF-06651600 in adult and adolescent participants with AA.	Through the time the last participant completes the Follow-up visit or 28 days after the Month 36 visit: • Incidence of treatment-emergent adverse events (TEAEs); • Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation; • Incidence of clinically significant abnormalities in vital signs; • Incidence of clinically significant abnormalities in clinical laboratory values.
Secondary Objectives	Secondary Endpoints
• To evaluate the long-term safety and tolerability of PF-06651600 in adult and adolescent participants with AA.	Through the time of the last participant visit: • Incidence of TEAEs; • Incidence of SAEs and AEs leading to discontinuation;

	• Incidence of clinically significant abnormalities in vital signs; • Incidence of clinically significant abnormalities in clinical laboratory values.
• To evaluate the long-term efficacy of PF-06651600 in adult and adolescent participants with AA.	• Response based on achieving absolute Severity of Alopecia Tool (SALT) score ≤10 through Month 36, for overall and AA SALT score; • Response based on achieving absolute SALT score ≤20 through Month 36, for overall and AA SALT score; • Change from baseline in SALT score through Month 36, for overall and AA SALT score; • Response based on achieving at least 75% improvement in SALT (SALT75) from baseline through Month 36, for overall and AA SALT score; • Response based on achieving at least a 2-grade improvement from baseline or a score of 3 in Eyebrow Assessment (EBA) score through Month 36; • Response based on achieving at a least 2-grade improvement from baseline or a score of 3 in Eyelash Assessment (ELA) score through Month 36.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit	• PGI-C response defined as PGI-C score of "moderately improved or greatly improved" through Month 36;

from the patient perspective and to demonstrate value.	• Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) scales through Month 36; • Change from baseline in the depression subscale score of the Hospital Anxiety and Depression Scale (HADS) through Month 36; • Change from baseline in the anxiety subscale score of the HADS through Month 36; • Improvement on HADS among participants with a baseline subscale score indicative of depression who achieved a "normal" subscale score indicative of an absence of depression through Month 36[79,90]; • Improvement on HADS among participants with a baseline subscale score indicative of anxiety who achieved a "normal" subscale score indicative of an absence of anxiety through Month 36[79,90].

See Appendix 10 for vaccine sub-study objectives and endpoints.

Overall Design:
Study B7981032 will investigate PF-06651600 in participants with AA. This is a Phase 3, open-label, multi-center, long-term study designed to evaluate the safety and efficacy of PF-06651600 in adults and adolescents ≥12 years of age. Eligible prior participants in the index studies B7931005 and B7981015 will be given the opportunity to enroll, as well as approximately 450 de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015). It is estimated that a total of approximately 960 participants will be enrolled.

Disclosure Statement:

This is a Single Group Treatment study with 1 Arm that has No masking.

Number of Participants:
Eligible prior participants from the index studies B7931005 and B7981015 will be given the opportunity to enroll, as well as approximately 450 de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015), for a total of approximately 960 participants.

Intervention Groups and Duration:
Prior participants from Studies B7931005 and B7981015 as well as de novo participants will be eligible to participate in this study.

Study B7981032 has 2 treatment periods and an observation period.

TP1:

- Participants enrolling from B7931005 and B7981015 who received study intervention in one of these studies will receive open-label 50 mg QD PF-06651600 for 36 months.

- De novo participants (ie, those who have not previously received study intervention in study B7931005 or B7981015) will receive open-label 200 mg PF-06651600 QD for 4 weeks followed by open-label 50 mg QD PF-06651600 for 35 months.

- The total duration of participation TP1 is up to approximately 38 months, including up to 5 weeks for screening (for de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the last dose in Study B7931005 or B7981015 and their first visit in Study B7981032), 36 months study intervention, and a follow-up period of 4 weeks after completion of TP1 (for participants not continuing to TP2) or discontinuation of study intervention (See Schema).

- Participants in countries where PF-06651600 is not commercially available at the time of their Month 36 visit will have the opportunity to enter TP2, as described below. In this case, the Follow-up visit will be completed at the end of their participation in TP2.

TP2:

- TP2 will be of variable length for individual participants; assuming a participant does not require discontinuation per protocol, a participant may continue to receive PF-06651600 in TP2 for a maximum of 24 months or until availability of commercial product in their country, or until the sponsor terminates the study in that country, whichever occurs first.

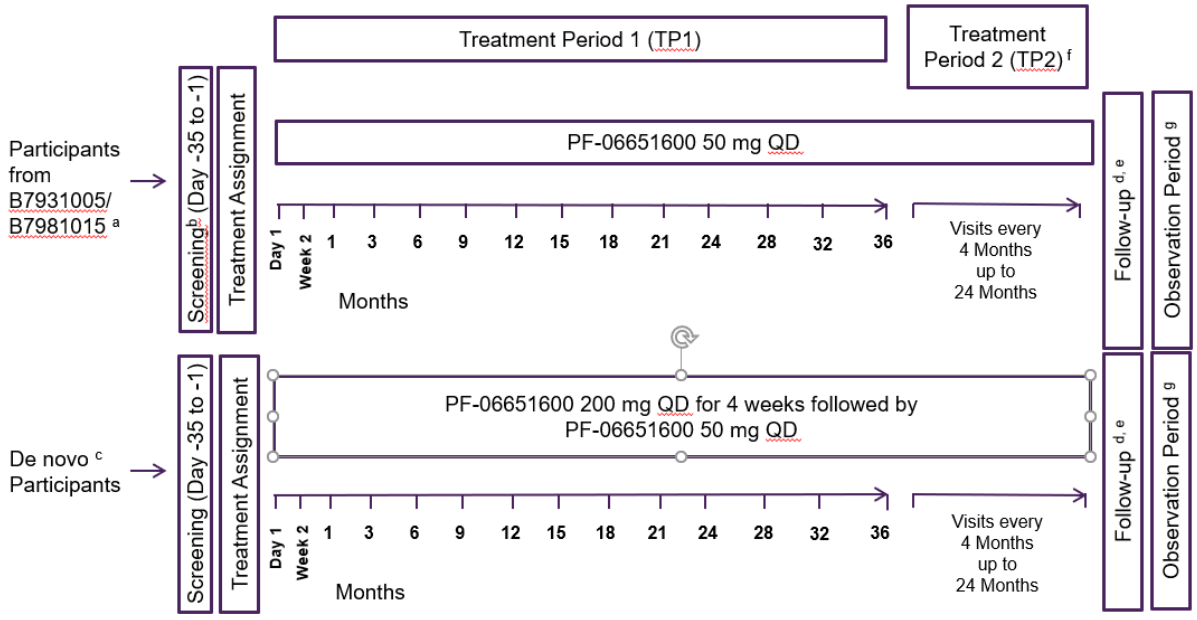
- In TP2, participants will receive 50 mg QD PF-06651600. The total duration of participation in TP2 is approximately 25 months, including up to 24 months of study intervention and a Follow-up period of 4 weeks after completion or discontinuation of study intervention (See Section 1.2 Schema).

Observation Period:

- If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever occurs first; refer to Section 7.1.1.1 for further details.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: QD = once daily

a. Participants originating from Study B7931005 or B7981015 are defined as those who received study intervention in one of these studies.
b. Participants with ≤30 days between the first study visit in B7981032 and the last dose in Study B7981015 will not require a screening period.
c. De novo participants are defined as those who did not previously receive study intervention in Study B7931005 or B7981015; this includes, but is not limited to, those consented and screened for Study B7931005 or B7981015 but who did not receive study intervention in one of these studies.
d. After completion of TP1 (for participants not continuing to TP2) or discontinuation of study intervention, a Follow-up period of 4 weeks will occur. Participants in countries where PF-06651600 is not commercially available at the time their Month 36 visit will have the opportunity to enter TP2.
e. In TP2, after completion or discontinuation of study intervention, a Follow-up period of 4 weeks will occur.
f. TP2 will be of variable length for individual participants for a maximum of 24 months or until availability of commercial product in their country, or until the sponsor terminates the study in that country, whichever occurs first.
g. If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit for the Observation Period without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever occurs first.

1.3. Schedule of Activities (SoA)

De novo participants are defined as those who did not previously receive study intervention in Study B7931005 or B7981015; this includes, but is not limited to, those consented and screened for Study B7931005 or B7981015 but who did not receive study intervention in one of these studies.

Participants originating from Study B7931005 or B7981015 are defined as those who received study intervention in one of these studies.

A = De novo participants;
B = Participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015;
C = Participants originating from Study B7981015 with >14 days to ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015;
D = Participants originating from Study B7981015 with ≤14 days between the first visit of Study B7981032 and the last dose in Study B7981015;
E = All participants originating from Study B7931005;
X = All participants

See Appendix 10 for vaccine sub-study schedule of activities.

If participant visits or procedures are affected by a public emergency, including the coronavirus disease 2019 (COVID-19) pandemic, please refer to Appendix 13.

1.3.1. Screening and Day 1

Screening is only applicable for de novo participants (Group A) and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the dose in Study B7931005 or B7981015 (Group B). The screening visit date is defined as the date that informed consent/assent is obtained for Study B7981032.

Procedures conducted as part of the participant's routine clinical management (eg, chest x-ray or other appropriate diagnostic imaging such as computed tomography or magnetic resonance imaging [MRI]) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA. This includes procedure(s) which were completed for participants consented and screened for study B7981015 but who did not receive study intervention in study B7981015. Separate informed consent/assent for Study B7981032 must be obtained prior to use of data in Study B7981032 per Section 10.1.3.

Procedure	Screening	Day 1	Notes
Visit Window (±Days)	None	None	
Visit Identifier	1	2	
Day	-35 to -1	1	
Enrollment procedures			
Informed consent/assent	A, B	C, D	Must be obtained before the participant is enrolled in the study per Section 10.1.3
Inclusion and exclusion criteria	A, B	X	
Demography	A, B	C, D	
Medical history	A, B	C, D	Refer to the CRF completion guidelines for specific information regarding medical history information to be collected for each group of participants. Section 8.2.1

Procedure	Screening	Day 1	Notes
AA disease history, smoking and alcohol history	A, B		Section 8.2.1
Medical procedures			
Full physical examination, including dermatological full body examination	A, B	A, B	Section 8.2.1
Targeted physical examination		C	Section 8.2.1
Vital signs	A, B	A, B, C	Section 8.2.3
12-lead ECG	A, B	A, B	Section 8.2.5
Height and weight	A, B	A, B	Height will not be collected at the Day 1 visit in participants who are ≥18 years of age at this visit (ie, height will only be collected at screening in these participants). Section 8.2.1
Tanner Stages of Development		X	For participants who are <18 years of age at the Day 1 visit in Study B7981032. Section 8.2.2
Chest radiograph	A, B		Chest radiograph (ie, chest x-ray or other appropriate diagnostic imaging such as CT or MRI) must be taken at screening if not performed within 3 months prior to the screening visit. Exclusion Criterion 19 in Section 5.2.2, Section 8.2.4
Audiological Evaluation	A, B		De novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 must have a full audiological assessment completed at screening or within 8 weeks prior to Day 1. Section 8.2.6

Procedure	Screening	Day 1	Notes
Laboratory			
Hematology and Serum Chemistry	A, B	A, B, C	Section 8.2.8, Appendix 2
Fasting Lipid Panel		A, B	Section 8.2.8, Appendix 2
Urinalysis	A, B	A, B, C	Appendix 2
Serum FSH	A, B		To confirm postmenopausal status in females under 60 years old who are not using hormonal contraception or hormonal replacement therapy. This test is not to be performed for WOCBP. Appendix 2, Section 10.4.3
Pregnancy test (WOCBP only)	A, B	X	Day 1 test does not need to be performed for participants with testing in Study B7931005 or B7981015 on the same day as the Study B7981032 Day 1 visit. Section 8.2.11, Appendix 2, Appendix 4
HIV testing	A, B		Appendix 2
Hepatitis B and Hepatitis C Screening	A, B		Appendix 2
HBVDNA (applicable countries)	A, B		For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on the screening results from Study B7981032. See Appendix 7 for Japan specific requirements. Section 8.2.8.5, Appendix 6
Varicella Zoster Virus immunoglobulin G antibody (VZV IgG Ab) (adolescents only, if applicable)	A, B		VZV IgG Ab is only required in adolescent participants 12 to <18 years of age without documented evidence of having received varicella vaccination (2 doses). Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses) per Exclusion #16. Section 8.2.8.3, Appendix 2

Procedure	Screening	Day 1	Notes
Collection of sample for potential viral screen		A, E	For participants from Study B7981015 a sample will be collected for Study B7981032 if it was tested in Study B7981015. Section 8.2.8.4, Appendix 2
Screening tuberculosis test	A, B		Exclusion Criterion 19 in Section 5.2.2, Section 8.2.8.1, Section 8.2.8.1.2, Appendix 2
Day 1 tuberculosis testing/chest radiograph		C, D	Section 8.2.8.1, Section 8.2.8.1.2, Appendix 2
Pharmacodynamics markers			
FACS-TBNK		A, B	Section 8.6
Immunoglobulins (IgA, IgG, IgM)		A, B	Section 8.6
Trial treatment			
IRT registration	A, B	C, D	
IRT study intervention assignment		X	
Study intervention dispensing		X	Section 6.2
Study intervention administration		X	Section 6.1
Clinical assessments			
SALT	A, B	A, B	Section 8.1.2.1.

Procedure	Screening	Day 1	Notes
AA eligibility assessment	A, B	A, B	Scalp hair loss due to AA to be assessed to verify eligibility for de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose of study intervention in Study B7931005 or B7981015. Section 8.1.2.1.2.
EBA and ELA	A, B	A, B	Section 8.1.2.2, Section 8.1.2.3
Photography	A, B	A, B	Section 8.1.4
Assessment of Fingernails Affected by AA		A, B, E	Collected at Day 1 in all de novo participants, all participants originating from B7931005, and participants originating from Study B7981015 with >30 days between the first visit of B7981032 and the last dose in Study B7981015. Section 8.1.2.4
CGI-AA	A, B	A, B	Section 8.1.2.5
C-SSRS	A, B	A, B, C	For de novo participants and participants originating from B7931005 or B7981015 with >30 days between the last dose in the prior study and the first visit in Study B7981032 the C-SSRS for screening and Day 1 visits will be used at screening and Day 1. For participants originating from B7981015 with >14 days to ≤30 days between the last dose in the prior study and the first visit in Study B7981032, the C-SSRS for visits after Day 1 will be used and the results must be evaluated against the protocol discontinuation criteria in Section 10.8.2 before the participant is assigned to study intervention. Section 8.2.9
Patient reported outcomes			
AAPPO		A, B, E	Section 8.1.3.1
PHQ-8	A, B		Section 8.2.10

Procedure	Screening	Day 1	Notes
HADS		A, B, E	Section 8.1.3.4
SF36v2 Acute		A, B, E	Section 8.1.3.6
EQ-5D-5L (adults) or EQ-5D-Y (adolescents)		A, B, E	Participants who are <18 years at the time of the Day 1 visit of B7981015 or B7981032 will use the EQ-5D-Y (age for participants from B7931005 will be based on their age on Day 1 of B7981032). Section 8.1.3.5
AARU		A, B, E	For participants originating from Study B7981015 with <3 months between the Day 1 visit of Study B7981032 and the last visit at which the AARU was performed in Study B7981015, the AARU will not be collected until the Month 3 visit (ie, the AARU will not be collected at the Day 1 visit for this group). For de novo participants, all participants originating from B7931005, and participants originating from Study B7981015 with ≥3 months between the Day 1 visit of Study B7981032 and the last visit at which the AARU was performed in Study B7981015, the AARU will be collected at Day 1. Section 8.1.3.7
WPAI: AA		A, B, E	Adolescents aged 12 to <18 years at the time of the Day 1 visit of B7981015 or B7981032 will not complete this assessment. Section 8.1.3.8
Observer Reported Outcomes			
BRIEF®2		X	Only in countries where the BRIEF®2 questionnaire is available and only for participants who are <18 years of age at the time of the Study B7981032 Day 1 visit. The parent/caregiver will complete the questionnaire. Section 8.1.3.9

Procedure	Screening	Day 1	Notes
Other			
Prior and current concomitant medications and treatment(s) monitoring	A, B	X	
Adverse event monitoring	A, B	X	On Day 1, for participants originating from Study B7931005 or B7981015, AEs (for the time in between studies and at Day 1 of Study B7981032) must be compared against B7981032 discontinuation criteria. Participants with AEs meeting the B7981032 protocol discontinuation criteria cannot be enrolled in the B7981032 Study
Contraception check for WOCBP	A, B	X	
Check for initiation of menarche	A, B	X	For premenarchal females only. Section 8.2.12

1.3.2. Intervention Period

1.3.2.1. Treatment Period 1: Week 2 to Month 24

For procedures to be performed in TP1 from Month 28 to Month 36, refer to Section 1.3.2.2.
For procedures to be performed in TP2 from Month 40 to Month 60, refer to Section 1.3.2.3.

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Visit Window (±Days)	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	
Visit Identifier	3	4	5	6	7	8	9	10	11	12	
Day	15	31	91	181	271	361	451	541	631	721	
Medical procedures											
Full physical examination, including dermatological full body examination				X		X		X		X	Section 8.2.1
Targeted physical examination		X	X		X		X		X		Section 8.2.1
Vital signs		X	X	X	X	X	X	X	X	X	Section 8.2.3
12-lead ECG		X		X		X				X	Section 8.2.5
Height and weight				X		X		X		X	Height will not be collected from participants who are ≥18 years of age at the time of the visit. Section 8.2.1

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Tanner Stages of Development						X				X	For participants who were <18 years of age at the Day 1 visit in Study B7981032. Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on all applicable domains. For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males). Section 8.2.2.
Audiological Evaluation				X		X		X		X	Section 8.2.6
Laboratory											
Hematology and Serum Chemistry	X	X	X	X	X	X	X	X	X	X	Section 8.2.8, Appendix 2
Fasting Lipid Panel		X	X	X		X		X		X	Section 8.2.8, Appendix 2
Urinalysis		X	X	X		X		X		X	Appendix 2
Pregnancy test	X	X	X	X	X	X	X	X	X	X	For WOCBP only. Monthly urine pregnancy tests will be performed by the participant between scheduled study visits starting after the Month 1 visit through the Month 24 visit. The pregnancy testing between visits may occur outside of the study site. Site personnel will contact participants (or their legally authorized representative, if appropriate) via telephone between study visits to obtain monthly pregnancy test result and ensure this contact and the result of the pregnancy test are recorded in participant source documentation and CRF. Section 8.2.11, Appendix 2, Appendix 4

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
HBVDNA (applicable countries)			X	X	X	X	X	X	X	X	For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on the screening results from Study B7981032. For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on screenings result from the index study. See Appendix 7 for Japan specific requirements. Section 8.2.8.5, Appendix 6
Annual tuberculosis testing/chest radiograph						X				X	Section 8.2.8.1, Section 8.2.8.1.2, Appendix 2
FACS-TBNK samples collected for possible reflex testing	X	X	X	X	X		X	X	X		Appendix 2
Pharmacodynamics markers											
FACS-TBNK						X				X	Section 8.6
Immunoglobulins (IgA, IgG, IgM)						X				X	Section 8.6

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Trial treatment											
Study intervention dispensing	X	X	X	X	X	X	X	X	X	X	At the Week 2 visit, the participant will return the package containing the study intervention which was dispensed at the Day 1 visit for accountability. The Day 1 package will then be returned to the participant for administration and dispensing at the Week 2 visit. Section 6.2
Study intervention administration	X	X	X	X	X	X	X	X	X	X	Section 6.1
Study intervention accountability and compliance	X	X	X	X	X	X	X	X	X	X	Section 6.2, Section 6.4
Clinical assessments											
SALT		X	X	X	X	X	X	X	X	X	For participants with known androgenetic alopecia, this includes a separate assessment of scalp hair loss due to androgenetic alopecia at the final on-therapy visit for each treatment period (ie, at Month 36 or Early Termination in TP1, and at Month 60, the last on-therapy visit, or Early Termination in TP2). Section 8.1.2.1
EBA and ELA		X	X	X		X		X		X	Section 8.1.2.2, Section 8.1.2.3
Photography			X	X		X		X		X	Section 8.1.4
Assessment of Fingernails Affected by AA		X	X	X		X		X		X	Section 8.1.2.4
CGI-AA		X	X	X	X	X		X		X	Section 8.1.2.5

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
C-SSRS		X	X	X	X	X	X	X	X	X	Section 8.2.9
Patient reported outcomes											
AAPPO		X	X	X	X	X		X		X	Section 8.1.3.1
PGI-C and P-Sat		X	X	X	X	X		X		X	Section 8.1.3.2, Section 8.1.3.3
HADS		X	X	X	X	X		X		X	Section 8.1.3.4
SF36v2 Acute		X	X	X		X		X		X	Section 8.1.3.6
EQ-5D-5L (adults) or EQ-5D-Y (adolescents)		X	X	X		X				X	Participants who are <18 years at the time of the Day 1 visit of B7981015 or B7981032 will use the EQ-5D-Y (age for participants from B7931005 will be based on their age on Day 1 of B7981032). Participants who reach the age of 18 years during Study B7981032 will continue to use the EQ-5D-Y for the remainder of the study. Section 8.1.3.5
AARU			X	X	X	X	X	X	X	X	Section 8.1.3.7
WPAI: AA		X	X	X		X				X	Adolescents aged 12 to <18 years at the time of the Day 1 visit of B7981015 or B7981032 will not complete this assessment. Section 8.1.3.8

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Observer Reported Outcomes											
BRIEF®2				X		X		X		X	Only in countries where the BRIEF®2 questionnaire is available and only for participants who are <18 years of age at the time of the Study B7981032 Day 1 visit. The parent/caregiver will complete the questionnaire. For participants who have already started the study when the BRIEF®2 questionnaire is approved and available for use at the participant's site, the BRIEF®2 questionnaire will be administered at the next scheduled study visit and then at the remaining visits per the Schedule of Activities for the BRIEF®2. The BRIEF®2 questionnaire will not be collected for participants who are ≥18 years of age at the time of the visit. Section 8.1.3.9
Pharmacokinetic											
PK sampling		X	X								Month 1: Predose, 1 hour post dose (±15 min). Month 3: Predose, 0.5 (±10 min) and 3 hours (±30 min) post dose. Section 8.5 If samples are not collected at the Month 3 visit, then they should be collected at the next study visit.

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Other											
Study intervention continuation criteria for adolescents			X	X							Refer to Appendix 12 for full study intervention criteria to be assessed in participants aged ≥12 to <18 years at the time of the Day 1 visit of B7981015 (for the participants originating from B7981015) or the Day 1 visit of B7981032 (for de novo participants). For those participants who have completed the B7981032 Month 3 visit but not the Month 6 visit at the time of Protocol Amendment 4 approval for a site, only the Month 6 criteria will be checked at the scheduled Month 6 visit. For participants who have already completed the B7981032 Month 6 visit at the time of Protocol Amendment 4 approval for a site, the Month 6 criteria must be checked at the next scheduled visit.
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	
Contraception check for WOCBP	X	X	X	X	X	X	X	X	X	X	The contraception check will also be performed monthly between study visits at the time of the phone contact to check the at-home pregnancy test results (see Section 8.2.11 for information on pregnancy testing). Section 5.3.1

Procedure	Intervention Period (Months)										Notes
Visit	Week 2	1	3	6	9	12	15	18	21	24	
Check for initiation of menarche	X	X	X	X	X	X	X	X	X	X	For premenarchal females only. Section 8.2.12

1.3.2.2. Treatment Period 1: Month 28 to Month 36

For procedures to be performed in TP1 from Week 2 to Month 24, refer to Section 1.3.2.1.

For procedures to be performed in TP2 from Month 40 to Month 60, refer to Section 1.3.2.3.

Procedure	Intervention Period (Months)			Notes
Visit	28	32	36	
Visit Window (±Days)	±7	±7	±7	
Visit Identifier	14	15	16	
Day	841	961	1081	
Medical procedures				
Full physical examination, including dermatological full body examination			X	Section 8.2.1
Targeted physical examination	X	X		Section 8.2.1
Vital signs	X	X	X	Section 8.2.3
12-lead ECG			X	Section 8.2.5
Height and weight			X	Height will not be collected from participants who are ≥18 years of age at the time of the visit. Section 8.2.1
Tanner Stages of Development			X	For participants who were <18 years of age at the Day 1 visit in Study B7981032, Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on all applicable domains. For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males). Section 8.2.2.

Procedure	Intervention Period (Months)			Notes
Visit	28	32	36	
Audiological Evaluation			X	Section 8.2.6
Laboratory				
Hematology and Serum Chemistry	X	X	X	Section 8.2.8, Appendix 2
Fasting Lipid Panel			X	Section 8.2.8, Appendix 2
Urinalysis			X	Appendix 2
Pregnancy test	X	X	X	For WOCBP only. Monthly urine pregnancy tests will be performed by the participant between scheduled study visits starting after the Month 1 visit through the Month 36 visit. The pregnancy testing between visits may occur outside of the study site. Site personnel will contact participants (or their legally authorized representative, if appropriate) via telephone between study visits to obtain monthly pregnancy test result and ensure this contact and the result of the pregnancy test are recorded in participant source documentation and CRF. Section 8.2.11, Appendix 2, Appendix 4
HBVDNA (applicable countries)	X	X	X	For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on the screening results from Study B7981032. For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on screenings result from the index study. See Appendix 7 for Japan specific requirements. Section 8.2.8.5, Appendix 6
Annual tuberculosis testing/chest radiograph			X	Section 8.2.8.1, Section 8.2.8.1.2, Appendix 2

Procedure	Intervention Period (Months)			Notes
Visit	28	32	36	
FACS-TBNK samples collected for possible reflex testing	X	X		Appendix 2
Pharmacodynamics markers				
FACS-TBNK			X	Section 8.6
Immunoglobulins (IgA, IgG, IgM)			X	Section 8.6
Trial treatment				
Study intervention dispensing	X	X	X	Study intervention will only be dispensed and administered at the Month 36 visit for participants continuing to TP2.
Study intervention administration	X	X	X	Study intervention will only be dispensed and administered at the Month 36 visit for participants continuing to TP2. Section 6.1
Study intervention accountability and compliance	X	X	X	Section 6.2, Section 6.4
Clinical assessments				
SALT	X	X	X	For participants with known androgenetic alopecia, this includes a separate assessment of scalp hair loss due to androgenetic alopecia at the final on-therapy visit for each treatment period (ie, at Month 36 or Early Termination in TP1, and at Month 60, the last on-therapy visit, or Early Termination in TP2). Section 8.1.2.1

Procedure	Intervention Period (Months)			Notes
Visit	28	32	36	
EBA and ELA			X	Section 8.1.2.2, Section 8.1.2.3
Photography			X	Section 8.1.4
Assessment of Fingernails Affected by AA			X	Section 8.1.2.4
CGI-AA			X	Section 8.1.2.5
C-SSRS	X	X	X	Section 8.2.9
Patient reported outcomes				
AAPPO			X	Section 8.1.3.1
PGI-C and P-Sat			X	Section 8.1.3.2, Section 8.1.3.3
HADS			X	Section 8.1.3.4

Procedure	Intervention Period (Months)			Notes
Visit	28	32	36	
Observer Reported Outcomes				
BRIEF®2	X	X	X	Only in countries where the BRIEF®2 questionnaire is available and only for participants who are <18 years of age at the time of the Study B7981032 Day 1 visit. The parent/caregiver will complete the questionnaire. For participants who have already started the study when the BRIEF®2 questionnaire is approved and available for use at the participant's site, the BRIEF®2 questionnaire will be administered at the next scheduled study visit and then at the remaining visits per the Schedule of Activities for the BRIEF®2. The BRIEF®2 questionnaire will not be collected for participants who are ≥18 years of age at the time of the visit. Section 8.1.3.9
Other				
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	
Adverse event monitoring	X	X	X	
Contraception check for WOCBP	X	X	X	The contraception check will also be performed monthly between study visits at the time of the phone contact to check the at-home pregnancy test results (see Section 8.2.11 for information on pregnancy testing). Section 5.3.1
Check for initiation of menarche	X	X	X	For premenarchal females only. Section 8.2.12

1.3.2.3. Treatment Period 2: Month 40 to Month 60

For procedures to be performed in TP1 from Week 2 to Month 24, refer to Section 1.3.2.1.

For procedures to be performed in TP1 from Month 28 to Month 36, refer to Section 1.3.2.2.

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
Visit Window (±Days)	±7	±7	±7	±7	±7	±7	
Visit Identifier	17	18	19	20	21	22	
Day	1201	1321	1441	1561	1681	1801	
Medical procedures							
Full physical examination, including dermatological full body examination			X			X	Section 8.2.1
Targeted physical examination	X	X		X	X		Section 8.2.1
Vital signs	X	X	X	X	X	X	Section 8.2.3
Height and weight			X			X	Height will not be collected from participants who are ≥18 years of age at the time of the visit. Section 8.2.1

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
Tanner Stages of Development			X			X	For participants who were <18 years of age at the Day 1 visit in Study B7981032, Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on all applicable domains. For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males). Section 8.2.2
Audiological Evaluation			X			X	Section 8.2.6
Laboratory							
Hematology and Serum Chemistry	X	X	X	X	X	X	For participants who have completed the Month 36 visit, creatine kinase will not be tested. Section 8.2.8, Appendix 2
Urinalysis	X	X	X	X	X	X	For participants who have completed the Month 36 visit, urinalysis will be performed only if considered clinically indicated by the investigator. Appendix 2

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
Pregnancy test	X	X	X	X	X	X	For WOCBP only. Monthly urine pregnancy tests will be performed by the participant between scheduled study visits starting after the Month 1 visit through the Month 60 visit. The pregnancy testing between visits may occur outside of the study site. Site personnel will contact participants (or their legally authorized representative, if appropriate) via telephone between study visits to obtain monthly pregnancy test result and ensure this contact and the result of the pregnancy test are recorded in participant source documentation and CRF. Section 8.2.11, Appendix 2, Appendix 4
HBVDNA (applicable countries)	X	X	X	X	X	X	For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on the screening results from Study B7981032. For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on screenings result from the index study. See Appendix 7 for Japan specific requirements. Section 8.2.8.5, Appendix 6
Annual tuberculosis testing/chest radiograph			X			X	Section 8.2.8.1, Section 8.2.8.1.2, Appendix 2
FACS-TBNK samples collected for possible reflex testing	X	X		X	X		Appendix 2
Pharmacodynamics markers							
FACS-TBNK			X			X	Section 8.6

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
Immunoglobulins (IgA, IgG, IgM)			X			X	Section 8.6
Trial treatment							
Study intervention dispensing	X	X	X	X	X		
Study intervention administration	X	X	X	X	X		Section 6.1
Study intervention accountability and compliance	X	X	X	X	X	X	Section 6.2, Section 6.4
Clinical assessments							
SALT	X	X	X	X	X	X	For participants with known androgenetic alopecia, this includes a separate assessment of scalp hair loss due to androgenetic alopecia at the final on-therapy visit for each treatment period (ie, at Month 36 or Early Termination in TP1, and at Month 60, the last on-therapy visit, or Early Termination in TP2). Section 8.1.2.1
EBA and ELA			X			X	Section 8.1.2.2, Section 8.1.2.3
Photography			X			X	Section 8.1.4
C-SSRS	X	X	X	X	X	X	Section 8.2.9
Patient reported outcomes							

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
PGI-C and P-Sat			X			X	Section 8.1.3.2, Section 8.1.3.3
Observer Reported Outcomes							
BRIEF®2	X	X	X	X	X	X	Only in countries where the BRIEF®2 questionnaire is available and only for participants who are <18 years of age at the time of the Study B7981032 Day 1 visit. The parent/caregiver will complete the questionnaire. For participants who have already started the study when the BRIEF®2 questionnaire is approved and available for use at the participant's site, the BRIEF®2 questionnaire will be administered at the next scheduled study visit and then at the remaining visits per the Schedule of Activities for the BRIEF®2. The BRIEF®2 questionnaire will not be collected for participants who are ≥18 years of age at the time of the visit. Section 8.1.3.9
Other							
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	X	X	X	
Adverse event monitoring	X	X	X	X	X	X	

Procedure	Intervention Period (Months)						Notes
Visit	40	44	48	52	56	60	
Contraception check for WOCBP	X	X	X	X	X	X	The contraception check will also be performed monthly between study visits at the time of the phone contact to check the at-home pregnancy test results (see Section 8.2.11 for information on pregnancy testing). Section 5.3.1
Check for initiation of menarche	X	X	X	X	X	X	For premenarchal females only. Section 8.2.12

1.3.3. Early Termination and Follow-up

If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever occurs first. Refer to Section 7.1.1.1 for further details.

Procedure	ET	Follow-up	Notes
			ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
Visit Window (±Days)	±7	+7	
Visit Identifier		13	
Day		EOS	
Medical procedures			

Procedure	ET	Follow-up	Notes
			ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
Full physical examination, including dermatological full body examination	X		Section 8.2.1
Targeted physical examination		X	Section 8.2.1
Vital signs	X	X	Section 8.2.3
12-lead ECG	X		Section 8.2.5 12-lead ECG is not to be collected during ET visit for participants who have completed the Month 36 visit.
Height and weight	X		Section 8.2.1
Tanner Stages of Development	X		For participants who were <18 years of age at the Day 1 visit in Study B7981032, Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on all applicable domains. For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males). Does not need to be collected if performed within 2 months of the ET visit. Section 8.2.2.
Audiological Evaluation	X		Section 8.2.6
Laboratory			

Procedure	ET	Follow-up	Notes ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
Hematology and Serum Chemistry	X	X	For participants who have completed the Month 36 visit, creatine kinase will not be tested. Section 8.2.8, Appendix 2
Fasting Lipid Panel	X		Fasting Lipid Panel is not to be collected during ET visit for participants who have completed the Month 36 visit. Section 8.2.8, Appendix 2
Urinalysis	X	X	For participants who have completed the Month 36 visit, urinalysis will be performed only if considered clinically indicated by the investigator during ET and Follow-up visits. Appendix 2
Pregnancy test (WOCBP only)	X	X	Section 8.2.11, Appendix 2, Appendix 4
HBVDNA (applicable countries)	X		For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on the screening results from Study B7981032. For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in the index study, testing will be dependent on screening result from the index study. See Appendix 7 for Japan specific requirements. Section 8.2.8.5, Appendix 6
FACS-TBNK samples collected for possible reflex testing		X	Appendix 2
Pharmacodynamics markers			

Procedure	ET	Follow-up	Notes ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
FACS-TBNK	X		Section 8.6
Immunoglobulins (IgA, IgG, IgM)	X		Section 8.6
Trial treatment			
Study intervention accountability and compliance	X		Section 6.2, Section 6.4
Clinical assessments			
SALT	X		For participants with known androgenetic alopecia, this includes a separate assessment of scalp hair loss due to androgenetic alopecia. Section 8.1.2.1
EBA and ELA	X		Section 8.1.2.2, Section 8.1.2.3
Photography	X		Section 8.1.4
Assessment of Fingernails Affected by AA	X		Section 8.1.2.4 Assessment of Fingernails affected by AA is not to be collected during ET visit for participants who have completed the Month 36 visit.
CGI-AA	X		Section 8.1.2.5 CGI-AA is not to be collected during ET visit for participants who have completed the Month 36 visit.

Procedure	ET	Follow-up	Notes ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
C-SSRS	X		Section 8.2.9
Patient reported outcomes			
AAPPO	X		Section 8.1.3.1 AAPPO is not to be collected during ET visit for participants who have completed the Month 36 visit.
PGI-C and P-Sat	X		Section 8.1.3.2, Section 8.1.3.3
HADS	X		Section 8.1.3.4 HADS is not to be collected during ET visit for participants who have completed the Month 36 visit.
SF36v2 Acute	X		Section 8.1.3.6 The SF36v2 Acute is not to be collected at the ET visit for participants who have completed the Month 24 visit.
EQ-5D-5L (adults) or EQ-5D-Y (adolescents)	X		Participants who are <18 years at the time of the Day 1 visit of B7981015 or B7981032 will use the EQ-5D-Y (age for participants from B7931005 will be based on their age on Day 1 of B7981032). Participants who reach the age of 18 years during Study B7981032 will continue to use the EQ-5D-Y for the remainder of the study. Section 8.1.3.5 The EQ-5D-5L and EQ-5D-Y are not to be collected at the ET visit for participants who have completed the Month 24 visit.

Procedure	ET	Follow-up	Notes ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
AARU	X		Section 8.1.3.7 The AARU is not to be collected at the ET visit for participants who have completed the Month 24 visit.
WPAI: AA	X		Adolescents aged 12 to <18 years at the time of the Day 1 visit of B7981015 or B7981032 will not complete this assessment. Section 8.1.3.8 The WPAI:AA is not to be collected at the ET visit for participants who have completed the Month 24 visit.
Observer Reported Outcomes			
BRIEF®2	X		Only in countries where the BRIEF®2 questionnaire is available and only for participants who are <18 years of age at the time of the Study B7981032 Day 1 visit. The parent/caregiver will complete the questionnaire. The BRIEF®2 questionnaire will not be collected for participants who are ≥18 years of age at the time of the visit. Does not need to be collected if already performed within 2 months of the ET visit. Section 8.1.3.9
Other			
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	

Procedure	ET	Follow-up	Notes ET visit will be performed on the last day the participant takes the study intervention or as soon as possible thereafter. Follow-up visit is 28 days after last dose
Adverse event monitoring	X	X	
Contraception check for WOCBP	X	X	
Check for initiation of menarche	X	X	For premenarchal females only. Section 8.2.12

Abbreviations: AA = alopecia areata; AAPPO = Alopecia Areata Patient Priority Outcomes; AARU = Alopecia Areata Resource Utilization; BRIEF®2 = Behavior Rating Inventory of Executive Function®, Second Edition; CGI-AA = Clinician Global Impression - Alopecia Areata; C-SSRS = Columbia Suicide Severity Rating Scale; EBA = Eyebrow Assessment; ECG = electrocardiogram; ELA = Eyelash Assessment; EQ-5D-5L = EuroQoL 5 Dimensions; EQ-5D-Y = EuroQoL 5 Dimensions-Youth; EOT = End of Treatment; ET = Early Termination; FACS-TBNK = fluorescence-activated cell sorting for T-cells, B-cells, and natural killer (NK) cells; FSH = follicle stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HBVDNA = hepatitis B viral DNA; Hep B = hepatitis B; Hep C = hepatitis C; HEENT = head, eyes, ears, nose and throat; HIV = human immunodeficiency virus; Ig = Immunoglobulin; IRT = Interactive Response Technology; PGI-C = Patient's Global Impression of Change; PHQ-8 = Patient Health Questionnaire – 8 items; PK = Pharmacokinetic; P-Sat = Patient's Satisfaction with Hair Growth; SALT = Severity of Alopecia Tool; SF36v2 = 36-Item Short Form Health Survey version 2; TP1 = Treatment Period 1; TP2 = Treatment Period 2; VZV IgG Ab = varicella zoster virus immunoglobulin G antibody; WOCBP = women of childbearing potential; WPAI:AA = Work Productivity and Activity Impairment: Alopecia Areata.

2. INTRODUCTION

PF-06651600 is an orally bioavailable, small molecule that is currently being investigated in patients with alopecia areata (AA). PF-06651600 inhibits Janus kinase 3 (JAK3) and the tyrosine kinase family members expressed in hepatocellular carcinoma (TEC) (BTK, BMX, ITK, TEC, TXK), by irreversibly blocking the adenosine triphosphate (ATP) binding site with high selectivity over the other three JAK isoforms (JAK1, JAK2, and tyrosine kinase 2 [TYK2]) as well as over the broader kinome. PF-06651600 potently inhibits signaling of the common gamma (γ)-chain receptors for interleukin (IL)-15 and IL-21, which have been implicated in the pathogenic pathways of AA.[1] Additionally, PF-06651600 inhibits the cytotoxic function of cluster of differentiation (CD)8^+ T cells and natural killer (NK) cells which have also been implicated in the pathogenic process of AA.[2,3] This inhibition may be mediated through mechanisms dependent on JAK3 and TEC kinase family members.[4-6]

See Appendix 10 for vaccine sub-study introduction.

2.1. Study Rationale

PF-06651600 is being developed as an oral treatment for patients with AA based on its mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies as outlined below. This study is specifically designed to evaluate the long-term safety, tolerability and efficacy of PF-06651600 in adults and adolescents with AA.

See Appendix 10 for vaccine sub-study rationale.

2.2. Background

AA is a chronic relapsing T-cell mediated autoimmune disorder characterized by non-scarring hair loss affecting children and adults across all ages, races, and sexes.[7,8] AA is associated with other immune diseases including asthma, allergic rhinitis, atopic dermatitis, and autoimmune diseases such as thyroiditis and vitiligo.[8]

$CD8^+$ T cells, NK cells, and mast cells are involved in the pathogenesis of AA. The possible inflammatory pathways in AA include cytokines from the type 1 helper T cell (TH1) axis, including interferon (IFN) alpha (α), IFN gamma (γ), and IFNγ-induced protein 10 (IP-10).[9,10] Mouse models have shown that IL-2 and IL-15 play a role in the initiation of auto-reactive $CD8^+$ cells that attack hair follicles.[1] IL-12 and IL-23 may also play a role in the pathogenesis of AA.[11]

Clinical presentation of AA can be limited to small, circular patches of scalp hair loss (patchy hair loss, alopecia focalis), involve complete loss of hair on the scalp (alopecia totalis [AT]), or total loss of hair on the scalp, face, and body (alopecia universalis [AU]).[12] Patchy alopecia is the most common form of AA which may develop into the more extensive and often treatment-resistant forms of AA, especially with earlier age of onset.[13] It is estimated that AA affects as many as 6 to 7 million individuals in the US[8] and 147 million worldwide.[14]

Further, there is evidence that AA can become refractory to JAK inhibition if it has been present for a substantial period of time. Specifically, a recent case series demonstrated that

AA patients whose current episode of AT or AU had lasted more than 10 years were highly non-responsive to off-label tofacitinib treatment in comparison with patients with shorter duration.[15]

Depression, anxiety, and panic disorders are often observed in patients with AA and the coping mechanisms of AA patients mirror those of grief and bereavement.[16,17] A substantial body of evidence demonstrates a widespread impact of AA on the psychological health of both adult and pediatric patients with AA, including impairment in self-esteem, increased incidence of anxiety and depressive disorders and other psychological conditions,[18-22] problems with social relations,[23] decreased health-related quality of life (HRQoL) and general quality of life (QoL), as well as the QoL of their families.[24-32]

AA is a disease with significant pediatric prevalence, in addition to the burden of disease seen in adults, and ample evidence is available on the impact of AA on the mental health of adolescent patients. In a United States (US) study, children with AA had more psychological problems than those without AA. Specifically, those with AA exhibited more anxiety, depression, tendencies to withdraw, aggression, and delinquency. In addition, children with AA were more likely to exhibit somatic problems as well as problems in social relations and in attention span. Girls with AA seem to be affected more in dimensions of total problems, anxiety/depression, and internalizing/externalizing syndromes. Children with AA were also less likely to have experienced positive life events in the year prior to exhibiting AA symptoms.[23]

In addition to experiencing a significant mental health burden, children with AA report experiencing other negative impacts to their QoL. Specifically, 75% of children aged 15-19 years reported instances of effects on QoL, 50% reported that the disease limited their participation in activities, 40% reported instances of bullying, and 35% reported that others noticed and commented on their condition. Rates of decrement in QoL, limitations on participation in activities, and bullying were heightened in older children ages 15-19 years compared to younger children.[33]

Given the finding that complete scalp hair loss with duration >10 years in adults is less likely to respond to treatment, it is conceivable that pursuing treatment in younger patients with stable, severe AA may prevent future irreversible hair loss.[15] Additionally, an earlier age of first onset has been reported to correspond to an increased lifetime risk of extensive disease. Differences in treatment responses are not expected for adolescent versus adult AA patients as suggested in 2 reports of tofacitinib (off-label use).[15,34]

No drugs have been approved for the treatment of AA in most countries/regions, including the United States and the European Union (EU). Review of the treatment guidelines and recommendations indicate that a number of off-label therapies are frequently used after assessing factors such as the age of the patient, disease extent, and disease duration. There is neither a cure for AA nor is there a therapy convincingly demonstrated to induce and sustain remission long term.[35-39]

2.2.1. Drug Development Rationale

The JAK family, including JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function.[40,41] 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.[40,41]

JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including IL-2, IL-4, IL-5, IL-6, IL-12, IL-13, IL-15, IL-21, IL-23, IL-31, IFNα, and IFNγ.[41]

The cytokine signaling pathways of IFNγ and IL-15, among others, can be blocked via JAK inhibition, supporting the rationale of a JAK inhibitor in the treatment of AA.[42] Treatment with the JAK inhibitors tofacitinib and ruxolitinib are reported to reverse AA in a mouse model.[2] Clinically, there are case reports and case series reporting that these JAK inhibitors demonstrate efficacy in AA.[2,15,43-49]

The tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family of protein kinases consists of five members (Bruton's tyrosine kinase [BTK], bone marrow tyrosine kinase on chromosome X [BMX], interleukin 2 inducible T cell kinase [ITK], TEC and tyrosine kinase expressed in T cells [TXK]) primarily expressed in hematopoietic cells.[50,51] T cells express three TEC kinases, ITK, TEC and TXK that are activated downstream of the T cell receptor (TCR). BTK plays crucial roles in B cell development and function and is activated downstream of the B cell receptor (BCR). Additionally, TEC kinases have overlapping roles in mediating activation signals in NK cells, mast cells and other hematopoietic cells.[52] Since CD8+ T cells, NK cells and mast cells have all been implicated in the pathophysiology of AA[2,3,10,53] inhibition of TEC kinases has the potential to contribute to efficacy in this disease by modulating the functional activity of pathogenic effector cells.

Based on the mechanism of action of PF-06651600, this candidate is expected to inhibit the signaling of multiple soluble cytokines and signaling pathways contributing to the AA pathogenesis.

2.2.2. Nonclinical and Phase 1 Efficacy and Safety Data

The no observed adverse effect levels (NOAELs) in the 6-month rat and second 9-month dog studies were 200 and 10 mg/kg/day, respectively. In the second 9-month dog toxicity study, the NOAEL of 10 mg/kg/day was based on adverse over-immunosuppression and axonal dystrophy (not axonal degeneration) in the central nervous system and peripheral nervous system at ≥20 mg/kg/day, accompanied by functional auditory deficits (brainstem auditory evoked potentials [BAEP]) at the highest dose of 40 mg/kg/day (a 29-fold exposure multiple relative to the clinical dose of 50 mg). The area under the concentration time curve (AUC)

exposure margins in this second 9-month dog study at the NOAEL at study end were approximately 1.5× and 6.5× relative to the predicted exposures at the 200 mg and 50 mg clinical doses, respectively (refer to Table 1).

The potential for PF-06651600 to be involved in drug-drug interactions (DDI) is being investigated. If results exclude a clinically meaningful DDI (eg, relative to AUC [area under the curve]) between PF-65551600 and a perpetrator or victim drug then that perpetrator or victim drug will no longer be prohibited as a prior or concomitant medication based on DDI; this information will be communicated via an administrative letter. Refer to Exclusion Criterion 25, Section 6.5.2, and Section 10.9.1 for medications prohibited to be used prior to and during the study.

PF-06651600 bioequivalence between tablets and capsules was established in completed Phase 1 Study B7981029.

Data from nonclinical and Phase 1 clinical studies, including pharmacokinetics, bioavailability and food effect, support the planned clinical trials with PF-06651600. For a complete description of these studies please refer to the current version of the Investigator's Brochure (IB).

2.2.3. Clinical Experience

There are complete and ongoing Phase 2 and Phase 3 studies with PF-06651600 in a number of disease indications. 42 participants with rheumatoid arthritis (RA) were exposed to PF-06651600 in the Phase 2a Study B7981006. 150 participants with ulcerative colitis were exposed to PF-06651600 in the Phase 2b Study B7981005. 364 and 238 participants with vitiligo in Phase 2b Study B7981019 were exposed to PF-06651600 in the dose-ranging period and in the extension period, respectively. 48 participants were exposed to PF-06651600 in the Phase 2a AA Study B7931005 in the initial 24-week period, and 715 participants with AA were treated with PF-06651600 in the Phase 2b/3 Study B7981015, with key results presented below. There is an ongoing study in participants with Crohn's disease (Phase 2a Study B7981007).

For description and/or results of these studies, please refer to the current version of the PF-06651600 IB.

2.2.3.1. Phase 2a Study in Alopecia Areata

Study B7931005 was a Phase 2a, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety profile of PF-06651600 and PF-06700841 (a TYK2/JAK1 inhibitor) compared with placebo in adult (18-75 years old) participants with AA with scalp hair loss of ≥50% at baseline. The study consisted of an initial 24-week double-blind treatment period, an up to 12-month extension period, and a 6-month cross-over open label extension period. A total of 142 participants were randomized to study treatment: 47 participants received placebo, 48 participants received PF-06651600, and 47 participants received PF-06700841.

During the initial 24-week treatment period, participants randomized to PF-06651600 were treated with 200 mg QD during a 4-week induction phase followed by dosing with 50 mg QD in a maintenance phase. The primary efficacy endpoint in the study was change from baseline in Severity of Alopecia Tool (SALT) score at Week 24. Analysis of the initial 24-week treatment period provided data on both efficacy and safety, and indicated clinical improvement with PF-06651600. PF-06651600 met the primary endpoint of change from baseline (CFB) in SALT score. The Mixed Model for Repeated Measures (MMRM) estimates for PF-06651600 compared to placebo at Week 24 for SALT mean CFB (95% CI) were 33.6 [95% CI= (21.4, 45.7); Hochberg p (1-sided) <0.0001]. PF-06651600 differentiated from placebo (statistically significant), as early as Week 6. The placebo response was almost negligible. PF-06651600 also differentiated from placebo on the proportion of responders in absolute SALT score ≤10, eyelash assessment (ELA) and eyebrow assessment (EBA).

During the initial 24-week treatment period of Study B7931005, there were no deaths and no participant in the PF-06651600 treatment group experienced a serious adverse event (SAE). The proportion of participants who experienced treatment-emergent adverse events (TEAEs) in the placebo treatment group (74.5%) was comparable with the PF-06651600 treatment group (62.5%). The TEAEs reported in more than 5% of participants with AA receiving PF-06651600 were headache, infections of upper respiratory tract, acne, diarrhea, nausea, and skin infections. The majority of events were mild. No serious infections, malignancies, cases of herpes zoster, or cases of herpes simplex were reported in the PF-06651600 group.

Hematological changes were observed in both active groups during the induction and maintenance periods, but were not associated with clinically relevant TEAEs. During the induction period, when participants received PF-06651600 200 mg QD for 4 weeks, decreases in mean platelet and lymphocyte counts (-18% and -24% mean CFB, respectively) were observed in the PF-06651600 group. During the maintenance period, when participants received 50 mg QD for 20 weeks, there was improvement in the platelet and lymphocyte counts in the PF-06651600 group (-10% and -9% mean CFB, respectively, at Week 24). Neutrophil counts were increased at Week 4 (12% CFB) and Week 24 (10% CFB) in the PF-06651600 treatment group. Two participants in the PF-06651600 group discontinued due to TEAEs (blood creatine phosphokinase increase and angioedema).

The final study results, including the results of the two extension periods, are described in the current version of the PF-06651600 IB.

2.2.3.2. Phase 2b/3 Study in Alopecia Areata

B7981015 was a Phase 2b/3, randomized, double blind, placebo controlled, dose ranging study to investigate PF-06651600 in both adolescent (≥12 to <18 years old) and adult (≥18 years old) participants with ≥50% scalp hair loss due to AA. The study had a maximum duration of approximately 57 weeks. This included an up to 5-week Screening period, a 48-week treatment period, and a 4-week follow up period. The treatment period was comprised of a placebo-controlled period that included a 4-week loading phase and a 20-week maintenance phase, followed by a 24-week extension phase.

Eligible participants were randomized to blinded PF-06651600 and matching placebo in a 2:2:2:2:1:1:1 (200 mg/50 mg, 200 mg/30 mg, 50 mg, 30 mg, 10 mg, placebo-200 mg/50 mg, and placebo-50 mg, respectively) manner for a total of 7 treatment sequences. All participants began dosing during the loading phase according to their assigned sequence. Following the 4-week loading phase, participants continued dosing according to their assigned sequence in the 20-week maintenance phase. At the end of the maintenance phase, placebo treated participants were advanced in a prespecified, blinded manner to one of 2 active treatment sequences for the remainder of the treatment period (through Week 48).

PF-06651600 200/50 mg, 200/30 mg, 50 mg and 30 mg were significantly superior to placebo at Week 24 on clinician-assessed and patient-reported endpoints related to scalp hair regrowth (including response based on absolute SALT ≤20, response based on absolute SALT ≤10, and PGI-C response). Exposure response modelling based on SALT ≤20 and SALT ≤10 response at Week 24 showed a positive relationship between dose and response. PF-06651600 200/50 mg, 200/30 mg, 50 mg and 30 mg were also nominally superior to placebo at Week 24 in producing improvement in eyebrows and eyelashes. Continued improvement in efficacy endpoints was seen between Week 24 and Week 48.

The proportion of participants who experienced all-causality TEAEs was similar across treatment groups up to Week 24 (placebo-controlled period) and up to Week 48 (overall). The most frequently reported TEAEs in any group included nasopharyngitis, headache, and upper respiratory tract infection. Up to week 24, the incidence of nasopharyngitis, folliculitis, urticaria, dizziness, upper respiratory tract infection and urinary tract infection was higher in participants treated with PF-06651600 (particularly 200/50 mg and 200/30 mg) than placebo. Most TEAEs were mild to moderate in severity. Fourteen (14) participants experienced 16 SAEs up to Week 48:

- 200/50 mg (4 participants): appendicitis; empyema and sepsis; invasive lobular breast carcinoma, spontaneous abortion.
- 200/30 mg (2 participants): appendicitis; chemical poisoning and suicidal behavior.
- 50 mg (2 participants): breast cancer; pulmonary embolism.
- 30 mg (1 participant): diverticulitis.
- 10 mg (2 participants): suicidal behavior; eczema.
- Placebo-200/50 mg: no SAEs.
- Placebo-50 mg (3 participants): spontaneous abortion; conversion disorder; heavy menstrual bleeding. These treatment-emergent SAEs were all reported during the Placebo-Controlled Period.

Of the 16 SAEs, 12 were considered by the investigator as unrelated to study intervention. The 4 SAEs that were considered related to study intervention in the opinion of the investigator were sepsis and empyema (both in 1 participant); breast cancer; and eczema. There were no deaths in the study.

Treatment with PF-06651600 was associated with changes in hematological parameters, some of which were dose dependent. In the first weeks of the study, there were slight, transient decreases in hemoglobin and small, variable changes in neutrophil and leukocyte

levels. Small, early decreases in platelets were observed with PF-06651600 treatment; these levels remained stable up to Week 48. Dose-dependent early decreases in absolute lymphocyte levels, CD3 (T lymphocytes) and T lymphocyte subsets (CD4 and CD8) were observed. There was a dose-dependent early decrease in CD16/56 (NK cells), particularly in groups who had received a 200 mg loading dose of PF-06651600 for 4 weeks. Overall, there were no clinically meaningful effects of PF-06651600 on ALT, AST, bilirubin, or alkaline phosphatase. The incidence of elevation in hepatic enzymes was low and not dose dependent. Up to Week 48, there were no potential Hy's law cases.

For a complete description and results of this study, please refer to the current version of the PF-06651600 IB.

2.3. Benefit/Risk Assessment

PF-06651600 is an immunomodulator and, as such, can be associated with the potential risk of infection (including serious infection), opportunistic infections, and viral reactivation. The risk of infection is monitored and evaluated in clinical studies of PF-06651600.

In animals, PF-06651600 administration was associated with effects on fetal development including skeletal and visceral organ malformations, and lower fetal body weights. It is not known whether PF-06651600 is secreted into human milk. Because of the investigational nature of PF-06651600, it should not be administered to pregnant women, breastfeeding women, or fertile women of childbearing potential who are unwilling or unable to use contraception as defined in the study protocol. Men in the study are not required to use birth control because PF-06651600 is not likely to transfer to a partner through semen at pharmacologically relevant levels.

In the Phase 2a proof-of-concept Study B7931005 in adult participants with AA, PF-06651600 met its primary endpoint of improvement in SALT score relative to placebo at Week 24. PF-06651600 appeared generally safe and well tolerated. Reductions in platelet counts and lymphocyte counts were observed during treatment with 200 mg QD, but were not considered clinically meaningful and improved after switching to 50 mg QD during the maintenance phase of the study.

These clinical data, including the pivotal Phase 2b/3 B7981015 study described in Section 2.2.3.1, indicate that PF-06651600 at doses up to 200 mg QD for 4 weeks followed by 50 mg QD, has a favorable benefit: risk profile and provides meaningful clinical benefit in a serious disease with no approved treatment options. This study will extend the analysis of benefit: risk for up to 5 years.

The benefit of evaluating PF-06651600 in adolescents was demonstrated in Study B7981015 and is additionally supported by prevalence of AA in adolescents, the significant psychological burden of the disease in this population, and a case series suggesting that extended duration of AA appears to increase likelihood of being refractory to off-label tofacitinib treatment.

See Appendix 10 for vaccine sub-study benefit/risk assessment.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06651600 may be found in the current version of the PF-06651600 IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of PF-06651600 in adult and adolescent participants with AA.	Through the time the last participant completes the Follow-up visit or 28 days after the Month 36 visit: • Incidence of treatment-emergent adverse events (TEAEs); • Incidence of serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation; • Incidence of clinically significant abnormalities in vital signs; • Incidence of clinically significant abnormalities in clinical laboratory values.
Secondary	
To evaluate the long-term safety and tolerability of PF-06651600 in adult and adolescent participants with AA.	Through the time of the last participant visit: • Incidence of TEAEs; • Incidence of SAEs and AEs leading to discontinuation; • Incidence of clinically significant abnormalities in vital signs; • Incidence of clinically significant abnormalities in clinical laboratory values.

Objectives	Endpoints
• To evaluate the long-term efficacy of PF-06651600 in adult and adolescent participants with AA.	• Response based on achieving absolute Severity of Alopecia Tool (SALT) score ≤10 through Month 36, for overall and AA SALT score; • Response based on achieving absolute SALT score ≤20 through Month 36, for overall and AA SALT score; • Change from baseline in SALT score through Month 36, for overall and AA SALT score; • Response based on achieving at least 75% improvement in SALT (SALT75) from baseline through Month 36, for overall and AA SALT score; • Response based on achieving at least a 2-grade improvement from baseline or a score of 3 in Eyebrow Assessment (EBA) score through Month 36; • Response based on achieving at least a 2-grade improvement from baseline or a score of 3 in Eyelash Assessment (ELA) score through Month 36.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	• PGI-C response defined as PGI-C score of "moderately improved" or "greatly improved" through Month 36; • Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) scales through Month 36; • Change from baseline in the depression subscale score of the Hospital Anxiety and Depression Scale (HADS) through Month 36;

Objectives	Endpoints
	• Change from baseline in the anxiety subscale score of the HADS through Month 36; • Improvement on HADS among participants with a baseline subscale score indicative of depression who achieved a "normal" subscale score indicative of an absence of depression through Month 36[79,90]; • Improvement on HADS among participants with a baseline subscale score indicative of anxiety who achieved a "normal" subscale score indicative of an absence of anxiety through Month 36[79,90].
Tertiary/Exploratory	
• To evaluate the long-term efficacy of PF-06651600 in adult and adolescent participants with AA.	• Response based on achieving at least 50% improvement in SALT (SALT50) from baseline through Month 36, for overall and AA SALT score; • Absolute SALT scores through Month 36, for overall and AA SALT score.
	For all scheduled timepoints after Month 36 through Month 60: • Response based on achieving absolute SALT score ≤10, for overall and AA SALT score; • Response based on achieving absolute SALT score ≤20, for overall and AA SALT score; • Change from baseline in SALT score, for overall and AA SALT score; • Response based on achieving at least a 2-grade improvement from

Objectives	Endpoints
	baseline or a score of 3 in EBA score; • Response based on achieving at least a 2-grade improvement from baseline or a score of 3 in ELA score.
• To evaluate the effect of PF-06651600 on patient-centered outcomes and payer relevant measures to assess treatment benefit from the patient perspective and to demonstrate value.	• Change from baseline in EuroQoL 5 dimensions (EQ-5D-5L) or EuroQoL 5 dimensions-Youth (EQ-5D-Y) through Month 24; • Improvement on PGI-C defined as "slightly improved", "moderately improved", or "greatly improved" through Month 36; • Improvement on Patient's Satisfaction with Hair Growth (P-Sat) items defined as slightly, moderately, or very satisfied through Month 36; • Change from baseline in Alopecia Areata Resource Utilization (AARU)through Month 24; • Change from baseline in Work Productivity and Activity Impairment items: Alopecia Areata (WPAI: AA) through Month 24. • Change from baseline in 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) through Month 24; • Behavior Rating Inventory of Executive Function (BRIEF®2) index scores through Month 36. • PGI-C response defined as PGI-C score of "moderately improved" or "greatly improved" after Month 36 through Month 60; • Improvement on P-Sat items defined as slightly, moderately, or very

Objectives	Endpoints
	satisfied after Month 36 through Month 60; • BRIEF®2 index scores after Month 36 through Month 60.
• To evaluate the long-term efficacy of PF-06651600 in AA nail disease over time.	• Change from baseline in fingernails affected by AA through Month 36.
• To evaluate the long-term effect of PF-06651600 on the clinician global impression of severity of scalp hair loss.	• Change from baseline in the Clinician Global Impression - Alopecia Areata (CGI-AA) through Month 36.
• To evaluate pharmacodynamic and disease-related biomarkers over time.	• Change from baseline in lymphocyte subsets (T-cell, B-cell, and natural killer [NK] cells) through Month 36; • Change from baseline in immunoglobulins (IgA, IgG, IgM) through Month 36. • Change from baseline in lymphocyte subsets (T-cell, B-cell, and NK cells) after Month 36 through Month 60; • Change from baseline in immunoglobulins (IgA, IgG, IgM) after Month 36 through Month 60.
PK Objectives	
• To characterize the pharmacokinetics of PF-06651600.	• Plasma concentrations of PF-06651600 at Month 1 and Month 3.

See Section 9.4.1 and Section 9.4.2 for baseline definition for analyses of efficacy and safety, respectively.
See Appendix 10 for vaccine sub-study objectives and endpoints.

4. STUDY DESIGN

4.1. Overall Design

Study B7981032 will investigate PF-06651600 in participants with AA. This is a Phase 3, open-label, multicenter, long-term study designed to evaluate the safety and efficacy of PF-06651600 in adults and adolescents ≥12 years of age. The maximum duration of

participation of any individual participant will be approximately 62 months. The study consists of two treatment periods, TP1 and TP2.

TP1:

TP1 includes up to a 5-week screening period, a 36-month open-label treatment period, and a 4-week follow-up period after completion of TP1 (for participants not continuing to TP2) or discontinuation of study intervention (see Schema). Eligible participants will be given the opportunity to enroll from the index studies B7931005 and B7981015, as well as de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015).

It is estimated that a total of approximately 960 participants will be enrolled. This will include eligible prior participants from the index studies B7931005 and B7981015, as well as approximately 450 de novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015).

To be eligible to enroll in this study, participants enrolling from Study B7931005 or B7981015 must not have had any events meeting the B7981032 discontinuation criteria or discontinued for safety-related events. In addition, participants enrolling from Study B7931005 must have taken their last dose of PF-06700841 (a TYK2/JAK1 inhibitor) in Study B7931005 >12 weeks prior to the B7981032 Day 1 visit. There is no necessary washout period for participants who took PF-06651600 in Study B7931005 or B7981015. Participants enrolling from B7981015 must have completed ≥34 weeks of study intervention. De novo participants ≥12 to <18 years of age must have a clinical diagnosis of AA with no other etiology of hair loss other than androgenetic alopecia with ≥50% terminal hair loss of the scalp due to AA at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy. De novo participants ≥18 years of age and participants originating from Study B7931005 or B7981015 with >30 days between the last dose in Study B7931005 or B7981015 and their first visit in Study B7981032 must have a clinical diagnosis of AA with no other etiology of hair loss other than androgenetic alopecia with ≥25% terminal hair loss of the scalp due to AA at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy. The full list of eligibility criteria for the study is included in Section 5.

Screening will occur within 35 days prior to the first dose of study intervention to confirm that selection criteria for the study are met for de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the last dose in Study B7931005 or B7981015 and their first visit in Study B7981032.

Participants enrolling from B7931005 and B7981015 will receive open-label 50 mg PF-06651600 QD for 36 months and de novo participants will receive open-label 200 mg PF-06651600 QD for 4 weeks followed by open-label 50 mg PF-06651600 QD for 35 months.

Following the last dose of study intervention, both discontinued and completed participants not continuing to TP2 will enter into a 4-week follow-up period for safety monitoring. Participants in countries where PF-06651600 is not commercially available at the time of their Month 36 visit will have the opportunity to enter TP2, as described below. In this case, the Follow-up visit will be completed at the end of their participation in TP2.

TP2:

TP2 will be of variable length for individual participants; assuming a participant does not require discontinuation per protocol, a participant may continue to receive PF-06651600 in TP2 for a maximum of 24 months or until availability of commercial product in their country, or until the sponsor terminates the study in that country, whichever occurs first.

In TP2, participants will receive 50 mg QD PF-06651600. The total duration of participation in TP2 is approximately 25 months, including up to 24 months of study intervention, and a Follow-up period of 4 weeks after completion or discontinuation of study intervention (See Section 1.2 Schema).

Observation Period:

If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever occurs first; refer to Section 7.1.1.1 for further details.

Vaccine Sub-study:

See Appendix 10 for vaccine sub-study design.

4.2. Scientific Rationale for Study Design

This study is being conducted to evaluate the long-term safety and efficacy of PF-06651600 dosed 50 mg QD over a 60-month maximum treatment duration. Because in the proof-of-concept Study B7931005 participants naïve to prior PF-06651600 treatment received the initial 200 mg QD loading dose for 4 weeks, followed by the 50 mg QD dose, this regimen will be provided to de novo participants in this study.

In addition to safety, another objective of this study is to evaluate long-term efficacy in this population. To evaluate efficacy, response will be assessed based on SALT, an instrument that is widely used to assess severity of AA by visual determination of the amount of terminal hair loss and summing across four views of the scalp (left side, right side, back and top; range 0-100%).[54,55] This tool has been well accepted and used in multiple AA clinical trials (NCT02691117; NCT01950780; NCT01797432; in addition to Study B7981015, NCT03732807) as a reliable and reproducible measure of AA severity.[15,43,47,56]

Inclusion of patients with ≥25% terminal scalp hair loss due to AA in this study, which the investigator has additionally determined to be appropriate for systemic therapy, is considered

to be justified. While there is not a generally accepted definition of mild, moderate, and severe AA, interviews of dermatologists and patients with an AA history of ≥50% scalp hair loss indicated that scalp hair loss >20% represents moderate to very severe hair loss.[57]

The total sample size for the study is estimated to be approximately 960 participants.

4.3. Justification for Dose

This study will evaluate PF-06651600 administered at a loading dose of 200 mg QD for 4 weeks followed by a maintenance dose of 50 mg QD for a maximum of 59 months for de novo participants and at a dose of 50 mg QD for a maximum of 60 months for participants enrolling from studies B7931005 and B7981015. The rationale for the selection of the doses and regimens is based on:

- Efficacy and safety results for the initial 24 weeks of PF-06651600 treatment from Study B7931005 in participants with AA.
- Dose/Exposure response relationships observed for PF-06651600 relevant biomarkers.
- Safety results for PF-06651600 from Study B7981006 in participants with RA.
- Exposure margins of proposed clinical doses relative to nonclinical no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) exposures (Table 1).

An analysis of the initial 24 weeks (primary objective) of the ongoing Phase 2a Study B7931005 was performed at Week 24. In that study, PF-06651600 was evaluated at 200 mg QD for 4 weeks followed by 50 mg QD for 20 weeks compared to placebo. Both safety and efficacy data from the analysis suggest that this dosing regimen of PF-06651600 is appropriate for further investigation.

The need for a loading-dose regimen for de novo participants is based on the hypothesis that maximal inhibition of the relevant immunomodulatory pathways at the beginning of treatment can more rapidly initiate clinical response, which can be sustained by the subsequent lower maintenance dose. The 200 mg dose chosen as the loading dose is expected to produce a >70% IL-15 and IL-21 in vitro signaling inhibition, with ~40% reduction in IP-10 levels from baseline. The 200 mg dose has demonstrated acceptable safety over 4 weeks in B7931005 in AA participants and 8 weeks in B7981006 in moderate to severe RA participants.

The maintenance dose of 50 mg for de novo participants and participants continuing from studies B7931005 and B7981015 is expected to produce ~30-40% IL-15 and IL-21 based on in vitro signaling inhibition, with ~18% reduction in IP-10 in vivo levels from baseline. The 50 mg maintenance dose demonstrated acceptable safety over a 20-week period in Study B7931005 in AA participants.

Exposure margins of the proposed clinical doses relative to the nonclinical no observed adverse effect level (NOAEL) exposures are summarized in Table 1.

Table 1. PF-06651600 Exposure Margins and No Observed Adverse Effects Level

	Dose/Route	Mean AUC in Dogs (unbound, ng•hr/ml)	Mean Clinical AUC (unbound, ng•hr/ml)	Calculated Safety Margin
Safety Exposure Margins for Human 200 mg QD Dose in AA patients				
Dog 2-month toxicology (Study 1)	NOAEL: 45 mg/kg oral	44100	5310	8.3
Dog 9-month toxicology (Study 2)	NOAEL: 10 mg/kg oral	7940	5310	1.5
Safety Exposure Margins for 50 mg QD Dose in AA patients				
Dog 2-month toxicology	NOAEL: 45 mg/kg oral	44100	1070	41
Dog 9-month toxicology (Study 2)	NOAEL: 10 mg/kg oral	7940	1070	7.4

Abbreviations: AUC = area under the concentration-time curve; NOAEL = no observed adverse effect level; QD = once daily.

4.4. End of Study Definition

A participant is considered to have completed the study:

- If participant has completed all phases of TP1, including follow-up visit and does not continue to TP2 due to local commercial availability of PF-06651600 for AA; OR
- If participant has completed all phases of TP2, including Follow-up visit; OR
- If participant discontinued from the study during TP2 due to local commercial availability of PF-06651600 for AA.

The primary completion date (PCD) is defined as the date when the last participant completes the Follow-up visit or 28 days after the Month 36 visit. The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

While B7981015 is enrolling, participants who are eligible for B7981015 may not be enrolled directly into Study B7981032 (for sites enrolling participants into both Study B7981015 and Study B7981032).

De novo participants are eligible to be included in the study only if all of the inclusion and exclusion criteria listed below apply (unless specified otherwise).

The inclusion and exclusion criteria listed below for all participants originating from Study B7931005 or B7981015 need to be applied, unless specified otherwise.

For participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose of the index Study, adverse events, laboratory results, medical conditions and prior and current treatments occurring during those studies and at any time between those studies and Study B7981032 must also be checked against all of the Study B7981032 entry criteria listed below.

For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose of the index study, adverse events, laboratory results, medical conditions and prior and current treatments during those studies and at any time between those studies and Study B7981032 must also be checked against the Study B7981032 safety discontinuation criteria (see Appendix 8, Section 10.8.2). Participants meeting the B7981032 protocol safety discontinuation criteria must not be enrolled in Study B7981032.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

NOTE: There are certain eligibility requirements specific to participants within Voluntary Harmonisation Procedure (VHP) countries in the EU. The VHP countries participating in this study are: Czech Republic, Germany, Hungary, Poland, and Spain.

See Appendix 10 for vaccine sub-study inclusion/exclusion criteria.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following applicable criteria apply:

5.1.1. Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032

The following inclusion criteria must be met for de novo participants and those originating from B7931005 and B7981015 with >30 days from the first study visit of Study B7981032 and the last dose in the index study.

Type of Participant and Disease Characteristics

1. Participants must meet the following AA criteria:

    - Have a clinical diagnosis of AA with no other etiology of hair loss (including, but not limited to traction and scarring alopecia, telogen effluvium). Androgenetic alopecia coexistent with AA is allowed provided that the following criteria are met;

    - For de novo participants ≥12 to <18 years of age at the time of signing of the informed consent/assent: ≥50% terminal scalp hair loss due to AA (including AT and AU), as measured by SALT, at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy;

- For de novo participants ≥18 years of age at the time of signing of the informed consent/assent and participants originating from B7931005 or B7981015 with >30 days between the index study and Study B7981032: ≥25% terminal scalp hair loss due to AA (including AT and AU), as measured by SALT, at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy;

- Hair loss must be carefully reviewed to verify the required percentage of terminal scalp hair loss is due to AA (ie, SALT [AA] score is ≥25% or ≥50%, as applicable).

    - If, in cases of concomitant AA and androgenetic alopecia, it cannot be verified that the participant has the required SALT (AA) score, then the participant must be excluded from the study.

- No evidence of terminal scalp hair regrowth in areas affected by AA within 6 months of both the screening and Day 1 visits (for de novo participants only);

- Current episode of terminal scalp hair loss due to AA ≤10 years (for de novo participants only).

    - When determining the duration of "current episode of terminal scalp hair loss", the initiation of the current episode should be the last time when the patient had substantial scalp hair (regardless of whether that hair growth occurred spontaneously or was the result of interventional treatment).

5.1.2. Inclusion Criteria for All Participants Originating from B7931005 or B7981015

The following inclusion criteria must be met for all participants originating from B7931005 and B7981015.

Prior B7931005 or B7981015 Clinical Study Experience

2. Participants enrolling from Study B7931005 must have:

    - Taken the last dose of PF-06700841 (a TYK2/JAK1 inhibitor) in Study B7931005 >12 weeks prior to the Study B7981032 Day 1 visit.

3. Participants enrolling from Study B7981015 must have:

    - Completed ≥34 weeks of study intervention.

5.1.3. Inclusion Criteria for All Participants

The following inclusion criteria must be met for all participants.

Age

4. All participants must be ≥12 years of age, at the time they or their parent or guardian signs the informed consent. Participants below the age of 18 years will only be enrolled into this study if permitted by the sponsor, local competent authority, and institutional review board (IRB)/ethics committee (EC). Otherwise, only participants 18 years or older (or age by applicable reviewer) will be enrolled in those countries, regions or sites. Within the VHP countries in the EU, de novo participants must be aged 18 through 74 years at the time of informed consent (see Section 5 for a list of VHP countries participating in this study). Within the UK, participants must be 18 years of age or older.

Sex

5. Male or Female

For all participants contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

No contraceptive measures required.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP), see Appendix 4 (Section 10.4.3)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 (Section 10.4.4) during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test (urine or serum as required by local regulations) at the Day 1 visit before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. All participants must be capable of giving signed informed consent/assent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
7. All participants must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Prior/Concomitant Therapy

8. If receiving permitted concomitant medications for any reason other than AA, participants should 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. Participants must be willing to stay on a stable regimen during the duration of the study (see Section 6.5).
9. All participants must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply.

5.2.1. Exclusion Criteria for Participants Originating from B7981015 with ≤30 Days between Studies

Participants originating from B7981015 with ≤30 days from the first study visit of Study B7981032 and the last dose in the index study are excluded from the study if any of the following criteria apply.

1. During Study B7981015 or in the period between the index study and Study B7981032, presence of safety events meeting discontinuation criteria in Appendix 8, Section 10.8.2 (eg, serious infections, laboratory results, ECG results).
2. Discontinuation from Study B7981015 for safety-related events. Participants discontinued from Study B7981015 due to issues other than safety-related events must be discussed with the sponsor prior to enrollment in Study B7981032.

5.2.2. Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032

De novo participants and those originating from B7931005 and B7981015 with >30 days from the first study visit of Study B7981032 and the last dose in the index study are excluded from the study if any of the following criteria apply.

Medical Conditions

3. Other scalp disease that may impact AA assessment (eg, scalp psoriasis, dermatitis, etc).
4. Active systemic diseases that may cause hair loss (eg, lupus erythematosus, thyroiditis, systemic sclerosis, lichen planus, etc).
5. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria:

   a. 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 8.2.9).

   b. For participants who had previous history of suicidal behaviors in the past >1 year to <5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS or any lifetime history of serious or recurrent suicidal behavior, a risk assessment must be performed, and documented, by a qualified mental health professional to assess whether it is safe for the participant to participate in the trial.

   c. The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.

   d. Clinically significant depression as indicated by a Patient Health Questionnaire-8 Items (PHQ-8) total score ≥15 (Section 8.2.10).

   NOTE: For any participant who has significant depression or any suicidal behavior, the participant will not be assigned to study intervention and should be referred for appropriate evaluation and treatment.

6. Have hearing loss with progression over the previous 5 years, or 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 acute, fluctuating or progressive.

   - Participants originating from Study B7931005 or B7981015 with occurrences of any of the above either during the index study or between the end of the index study and Study B7981032 can only be enrolled in Study B7981032 with prior approval of the sponsor.

7. 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 (particularly thyroid disease which can be associated with hair loss), 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 study intervention administration, or interfere with the interpretation of study results; or in the opinion of the investigator or Pfizer (or designee), the participant is inappropriate for entry into this study, or unwilling/unable to comply with study procedures (Section 8) and Lifestyle Considerations (Section 5.3).

8. Any present malignancies or 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.
9. 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.
10. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.
11. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1 (for criteria regarding Tuberculosis [TB] infection, see Exclusion Criterion 19 in Section 5.2.2).
12. Known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.
13. Positive serology for human immunodeficiency virus (HIV) at screening.
14. Significant trauma or major surgery within 1 month of the first dose of study intervention.
15. Considered in imminent need for surgery. Participants with elective surgery scheduled can only be enrolled in Study B7981032 with the approval of the sponsor.
16. Adolescent participants 12 to <18 years of age without one of the following:

- Documented evidence of having received the varicella vaccine (2 doses); or
- Evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (ie, a positive VZV immunoglobulin G antibody [VZV IgG Ab] result) at screening.

  Note: Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses). If serological testing is performed in the presence of documented evidence of having received varicella vaccination (2 doses), participants are eligible to enter the study regardless of the result of serological testing.

  This criterion is not applicable to sites where enrollment of adolescent participants is not permitted (see Inclusion #4).

17. Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or any active infection not meeting other exclusion criteria within 1 week prior to Day 1. NOTE: participants may be rescreened after the infection resolves.
18. Infection with hepatitis B or hepatitis C viruses according to protocol-specific testing algorithm.

    a. For hepatitis B, participants will undergo testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Participants who are HBsAg positive will not be eligible for this study. Participants who are HBsAg negative but HBcAb positive will be reflex tested for hepatitis B surface antibody (HBsAb). Participants who are HBsAg negative but HBcAb positive and HBsAb negative will not be eligible for the study. Additional reflex testing for hepatitis B virus deoxyribonucleic acid testing (HBVDNA) is also required for participants who are HBsAg negative and HBcAb positive in countries in which Hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care. Please refer to Appendix 6 for testing algorithm, reflex testing, and full eligibility criteria. Refer to Appendix 7 for Japan specific requirements.

    b. For hepatitis C, all participants will undergo testing for hepatitis C antibody (HCVAb) during screening. Participants who are HCVAb positive will be reflex-tested for hepatitis C ribonucleic acid (HCV RNA). Participants who are HCVAb and HCV RNA positive are not eligible for the study.

19. Have evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection as evidenced by the following:

    a. A positive QuantiFERON®-TB Gold In-Tube test (QFT-G) or positive or borderline T-SPOT®.*TB* (T-Spot test) performed within the 3 months prior to Day 1 (Visit 2). If the laboratory reports the test as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a purified protein derivative (PPD) test may be substituted for the QFT-G test or T-Spot test only with approval from the Pfizer Medical Monitor on a case-by-case basis.

    b. Chest radiograph (ie, chest x-ray or other appropriate diagnostic imaging such as computed tomography or MRI) with changes suggestive of active TB infection within 3 months prior to Screening. Chest radiograph should be performed according to local standards of care or country-specific guidelines.

    c. History of either untreated or inadequately treated latent or active TB infection.

    If a participant has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active

(acceptable multi-drug regimen) TB infection, neither a QFT-G test, a T-Spot test, nor a PPD test need be obtained. Details of the previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.

A chest radiograph (ie, chest x-ray or other appropriate diagnostic imaging such as computed tomography or MRI) must be obtained at screening if not done within the 3 months prior to screening (see Section 8.2.4). To be considered eligible for the study, the chest radiograph must be negative for active TB infection.

A participant who is currently being treated for active TB infection must be excluded from the study.

A participant who is being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi-drug resistant TB infection, documentation of an adequate treatment regimen, and prior approval of the sponsor.

Diagnostic Assessments

20. Abnormal findings on the screening chest radiographs (eg, chest x-ray) including, but not limited to, presence of active TB, infection, cardiomyopathy, or malignancy. NOTE: Chest radiograph examination may be performed up to 3 months prior to Screening visit. Documentation of the reading by a qualified radiologist or pulmonologist must be available in the source documentation.
21. **ANY** of the following conditions at screening:
    a. Screening 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 QT corrected using Fridericia's correction factor (QT_{cF}) prolongation (>450 milliseconds).

    b. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes (TdP).

22. **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:
    a. Absolute neutrophil count <1.2 x 10^9/L (<1200/mm^3);

b. Hemoglobin <11.0 g/dL or hematocrit <33%;

c. Platelet count <150 × 10^9/L (<150,000/mm^3);

d. Absolute lymphocyte count of <0.8 x 10^9 /L (<800/mm^3);

e. Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 based on the Cockcroft-Gault formula adjusted for the body surface area;

f. Enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 × upper limit of normal (ULN);

g. Total bilirubin >1.5 × ULN; participants with Gilbert's syndrome would be eligible for this study provided the direct bilirubin is ≤ULN;

h. In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that that could affect interpretation of study data or the participant's participation in the study.

Prior/Concurrent Clinical Study Experience

23. Discontinuation from Study B7931005 or B7981015 for safety-related events. Participants discontinued from Study B7931005 or B7981015 due to issues other than safety-related events must be discussed with the sponsor prior to enrollment in Study B7981032.

5.2.3. Exclusion Criteria for All Participants

The following exclusion criteria are applicable to all participants, who are excluded from the study if any of the following criteria apply.

Prior/Concomitant Therapy

24. Anticipated treatment with prohibited concomitant medication(s) (Section 6.5.2 and Appendix 9) during the course of the study.
25. Received any of the following treatment regimens specified in the timeframes outlined below:
    a. **At any time:** previous use of any non-B-cell selective lymphocyte-depleting agent (eg, alefacept, alemtuzumab).
    b. **Within 6 months** of first dose of study intervention or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer: any B-cell-depleting agents including but not limited to rituximab.
    c. **Within 12 weeks** of first dose of study intervention or 5 half-lives (if known), whichever is longer:
        - Any JAK inhibitor for use in any disease indication (other than PF-06651600 received in Study B7931005 or B7981015);
        - Other immunomodulatory biologic agents.

Note: Discontinuation of any JAK inhibitor due to a treatment-related safety event is exclusionary.

d. **Within 8 weeks** of first dose of study intervention or within 5 half-lives (if known), whichever is longer:

- Other systemic treatments that could affect AA including:
  - Immunosuppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib).
  - Intralesional, oral, or injectable steroids.
  - Oral minoxidil.

e. **Within 6 weeks** of first dose of study intervention: vaccination with live or attenuated live vaccine.
f. **Within 4 weeks** of first dose of study intervention: Ultraviolet B (UVB) phototherapy, Psoralen Ultraviolet A (PUVA) therapy, other phototherapy, contact immunotherapy (eg, diphenylcyclopropenone [DPCP], squaric acid dibutylester [SADBE], and 1-chloro-2,4-dinitrobenzene [DNCB]), topical irritants (eg, anthralin), and liquid nitrogen cryotherapy.
g. **Within 4 weeks** of first dose of study intervention or 5 half-lives (if known), whichever is longer: prohibited Cytochrome P450, family 3, subfamily A (CYP3A) inducers as described in Appendix 9.
h. **Within 2 weeks** of first dose of study intervention: topical steroids (eg, steroid cream, steroid ointment) on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails).
i. **Within 1 week** of first dose of study intervention:

- Herbal medications with either unknown properties or pharmaceutical properties that impact AA.
- Prohibited CYP3A substrates as described in Appendix 9 (within 7 days or 5 half-lives, whichever is longer).

26. For participants without concomitant androgenetic alopecia, receipt of any of the following treatment regimens specified in the timeframes outlined below. Participants with known androgenetic alopecia receiving the following treatments for androgenetic alopecia must have been receiving the treatment(s) at a stable dose and regimen for at least 6 months prior to the Day 1 visit of Study B7981032 and plan to take them at a stable dose and regimen throughout Study B7981032; participants with

androgenetic alopecia who wish to withdraw from these permitted treatments prior to the study must meet the washout criteria stated below.

a. **Within 8 weeks** of first dose of study intervention or within 5 half-lives (if known), whichever is longer:

   - 5α-Reductase inhibitors (5-ARIs) (eg, finasteride, dutasteride) unless used for androgenetic alopecia.

   - Spironolactone unless taken for androgenetic alopecia or a medical condition other than AA (eg, hypertension).

b. **Within 2 weeks** of first dose of study intervention: topical treatments not otherwise prohibited (eg, medicated shampoo, minoxidil) on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails) that could affect AA unless used for androgenetic alopecia.

Prior/Concurrent Clinical Study Experience

27. Participation in studies other than B7931005 or B7981015 involving investigational products (eg, drugs or vaccines) within 8 weeks (12 weeks for JAK inhibitors other than PF-06651600 received in Study B7931005 or B7981015) or within 5 half-lives (if known), whichever is longer, prior to study entry and/or during study participation.

Other Exclusions

28. 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 participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.
29. Participants with shaved heads must not enter the study until hair has grown back and is considered stable by the investigator.
30. Have an active history of alcohol or substance abuse within 1 year prior to Day 1.
31. Donation of blood in excess of 500 mL within 8 weeks prior to Day 1.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant (and the parent/legal guardian if required for adolescent participants), will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner(s), if applicable, from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities (Section 1.3), the investigator or designee will inform the participant (and the parent/legal guardian if required for adolescent participants) of the need to use highly effective contraception consistently and correctly from the time of the Screening visit and through 28 days after the last dose of study

intervention. The conversation and the participant's affirmation will be documented in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner. The contraception check for WOCBP will be performed during each study visit and monthly between study visits at the time of the phone contact to check the at-home pregnancy test results (see Section 8.2.11).

5.3.2. Cosmetic Treatments/Applications

Following the Screening visit and through 28 days after the last dose of study intervention, participants must not shave the hair on the scalp, eyebrows, or eyelashes. Participants wishing to keep their hair short are permitted to do so and an appropriate length should be discussed with the investigator to allow for assessment of hair re-growth.

In addition, the following applies to other cosmetic treatments/applications:

1. Hair transplants and tattooing of scalp, eyebrows, and eyelashes, including procedures such as microblading, are not permitted during the course of study but these procedures performed prior to screening may not, in the investigator's opinion, exclude a participant from enrollment.

2. Hair prosthetics (eg, wigs, hair extensions) are permitted but must be removed for clinical assessments of AA at all study visits.

3. Hair dye is permitted to be used during the study but participants should be discouraged from undergoing any hair dying process for 7 days prior to a study visit.

4. Mascara and false eyelashes are permitted but must be removed for clinical assessments of AA at all study visits. The use of false eyelashes with adhesive should be discouraged, where possible, due to the risk of eyelash loss during removal.

5. Nail polish/varnish is permitted but must be removed for assessments of fingernails affected by AA.

6. False fingernails or gel applications to the fingernails should be discouraged, where possible, due to the risk of damage to the participant's natural fingernails, and must be removed for clinical assessments of fingernails at all study visits.

5.3.3. Meals and Dietary Restrictions

On study visit days when lipid panel will be collected (see Schedule of Activities), participants must comply with fasting requirements for at least 8 hours prior to the visit. Water and permitted non-study medications are allowed (Section 8.2.8).

5.3.4. Caffeine, Alcohol, and Tobacco

Participants will abstain from using tobacco products or ingesting caffeine- or xanthine- containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 30 minutes before pulse rate and blood pressure measurements.

5.3.5. Elective Surgery

From the time of the Screening visit through 28 days after the last dose of study intervention, no elective surgery should occur without first consulting with the sponsor. Preferably, elective surgery should occur before the study or be delayed until participation in the study is completed. Participants who require elective surgery should temporarily discontinue study intervention for one week prior to the surgical procedure and remain off study intervention after the surgical procedure until sutures/staples are removed. If absorbing sutures or chemical closure methods are utilized, study intervention can be resumed when the operative site is sufficiently healed and risk of infection is minimal. Per Section 6.4, if the participant interrupts study intervention for >14 consecutive days, this must be discussed with the sponsor for possible withdrawal from the study. Refer to Section 6.5.4 for additional guidance regarding surgeries.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

For de novo participants and participants originating from B7931005 or B7981015 with >30 days prior to enrolling in Study B7981032, screening laboratory tests with abnormal results may be repeated **once** to confirm abnormal results (with the same screening number); the last value will be used to determine eligibility. If results return to normal within the 5-week screening period, the participant may enter the study.

De novo participants and participants originating from B7931005 or B7981015 with >30 days prior to enrolling in Study B7981032 who do not meet the criteria for participation in this study (screen failure) may be rescreened (with a new screening number) following an agreement with the sponsor.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

See Appendix 10 for vaccine sub-study information.

6.1. Study Intervention(s) Administered

Participants enrolling from B7931005 and B7981015 who received study intervention in one of these studies will receive open-label PF-06651600 50 mg QD.

De novo participants (ie, those who have not previously received study intervention in Study B7931005 or B7981015) will receive open-label PF-06651600 200 mg QD for 4 weeks followed by open-label 50 mg PF-06651600 QD.

ARM Name	PF-06651600 200 mg QD (4 week loading dose for de novo participants only)	PF-06651600 50 mg QD
Intervention Name	PF-06651600	PF-06651600
Type	Small molecule	Small molecule
Dosage Form	Tablet	tablet or capsule
Dose Strength	50 mg	50 mg
Dosage	50 mg – 4 tablets	50 mg – 1 tablet or 1 capsule
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and Labeling	Study Intervention will be provided in blister cards. Each blister card will be labeled as required per country requirement.	Study intervention will be provided in blister cards (for tablets) or bottles (for capsules). Each blister card and each bottle will be labeled as required per country requirement.

Abbreviations: QD = once daily

Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

6.2. Preparation/Handling/Storage/Accountability

1. The study intervention will be dispensed using an Interactive Response Technology (IRT) management system at each visit as specified in the Schedule of Activities. At the Week 2 visit, the participant will return the package containing the study intervention which was dispensed at the Day 1 visit for accountability. The Day 1 package will then be returned to the participant for administration and dispensing at the Week 2 visit.

2. A qualified staff member will dispense the study intervention in blister cards or bottles via unique container numbers. The participant/caregiver should be instructed to maintain the product in the blister cards or bottles provided throughout the course of dosing and return the blister cards or bottles to the site at the next study visit. Site staff will instruct participants on the proper storage requirements for study intervention that is taken home.
3. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
4. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
5. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
6. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label using central study intervention assignment via (IVRS/IWRS)	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an Interactive Voice Response System /Interactive Web Response Systems (IVRS/IWRS). The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance with the dosing of study intervention will be monitored and verified by delegated site personnel through a combination of counting returned tablets or capsules, and discussion with the participant, which will be documented in the source documents. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic Case Report Form (eCRF). When study intervention is administered at the clinic, it will be administered by the appropriately designated staff at the investigator site.

Participants should take the tablets or capsules, orally according to the dosing instructions provided with the study intervention. Participants will be encouraged to take the study intervention in the morning whenever possible. Participants should take the study intervention at approximately the same time every day. However, for study visit days,

participants are to be instructed to refrain from dosing at home, and are to take the dose in the clinic.

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

The study intervention may be temporarily withheld for a maximum of 14 consecutive days at the discretion of the investigator. Participants interrupting study intervention for >14 consecutive days for any reason must be discussed with the sponsor for possible withdrawal from the study. For participants who are considering elective surgery refer to Section 5.3.5 regarding information on temporary withholding of study intervention for elective surgery.

If compliance is <80%, the investigator or designee is to counsel the participant and ensure steps are taken to improve compliance. If the participant is over-compliant (>120%) with study intervention (intentional or accidental), the investigator or designee is to counsel the participant and ensure correct understanding of the study intervention dosing regimen. The investigator should contact the Pfizer Study Clinician promptly with any over-compliance that may potentially impact the safe use of study intervention or that may result in a SAE.

6.5. Concomitant Therapy

Medications/treatments that are taken in the screening period (after informed consent is obtained and before the first dose of study intervention) as well as any medications/treatments taken for the treatment of AA at any time prior to the screening visit will be documented as prior medications/treatments. Medications/treatments taken after the first dose of study intervention has been administered will be documented as concomitant medications/treatments.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Concomitant Medications

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 participant 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 on the case report form (CRF).

With the exception of those medications prohibited for use in Section 6.5.2, CYP3A inhibitors are permitted to be used during the study. Sensitive and moderate sensitive CYP3A substrates permitted to be used during the study are listed in Section 10.9.2.

Acetaminophen may be used intermittently (not to exceed 3.0 g/day).

Participants are not allowed any other investigational drugs or treatments during the study.

Participants with known androgenetic alopecia may receive the following treatments provided that the dose and regimen are held stable for at least 6 months prior to the Day 1 visit of Study B7981032 and throughout Study B7981032. Participants who wish to withdraw from these treatments prior to the study must meet the washout criteria in Section 5.2.3.

- Systemic treatments: 5-ARIs (eg, finasteride, dutasteride), spironolactone.
- Topical treatments: medicated shampoo, minoxidil.

In cases other than those described above for androgenetic alopecia, participants should **refrain from starting new or changing doses** of permitted prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and prior to study visits throughout the study, unless otherwise noted below.

Participants 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 participant's record and CRF.

Unless a prohibited medication or treatment, participants 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.

6.5.2. Prohibited Concomitant Medications

Participants will abstain from all prohibited medications as described in Section 5.2 and Appendix 9 from the time period described in Section 5.2 and through 28 days after the last dose of study intervention. Medically necessary medications should not be discontinued without prior evaluation of acceptable alternatives, including consultation with prescribing health professional.

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

All medications and treatments that could affect AA must be discontinued from the time period described in Section 5.2 and through 28 days after the last dose of study intervention (with the exception of those listed in Section 6.5.1 for participants with androgenetic alopecia). During this time period, if it is discovered that a participant has been taking a medication or treatment that could affect AA, the investigator should contact the sponsor for each case to determine whether the participant should be discontinued.

Participants must also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources from the time of the Screening visit and through 28 days after the last dose of study intervention.

Prohibited Concomitant Medications/Treatments:

The following medications and treatments are prohibited for use from the time period described in Section 5.2 and through 28 days after the last dose of study intervention. Participants with androgenetic alopecia are not allowed to start or change the dose or regimen of treatments permitted for androgenetic alopecia during the study. Participants who are treated with any prohibited medication or treatment during the course of the study may be discontinued after discussion with the sponsor. NOTE: Examples provided do not represent an all-inclusive list of medications and treatments. If there is a question about whether a particular medication is prohibited, the medication should be discussed with the sponsor.

- Medications and treatments that could affect AA:
  - JAK inhibitors for use in any disease indication.
  - Immunosuppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib).
  - Intralesional, oral or injectable steroids.
  - Oral minoxidil.
  - 5-ARIs (eg, finasteride, dutasteride) unless used for androgenetic alopecia.
  - Spironolactone unless taken for androgenetic alopecia or a medical condition other than AA (eg, hypertension).
  - Other systemic treatments that could affect AA.
  - Topical steroids (eg, steroid cream, steroid ointment) on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails).
  - Topical treatments (eg, medicated shampoo, minoxidil) that could affect AA on areas under assessment (ie, scalp, eyebrows, eyelashes, and fingernails) unless used for androgenetic alopecia.

- Phototherapy (eg, Ultraviolet B [UVB] phototherapy, Psoralen Ultraviolet A [PUVA]).
- Topical irritants (eg, anthralin), and liquid nitrogen cryotherapy.
- Contact immunotherapy (eg, diphenylcyclopropenone [DPCP], squaric acid dibutylester [SADBE], and 1-chloro-2,4-dinitrobenzene [DNCB]).
- Cosmetic treatments/applications as described in Section 5.3.2.

- Medications with potential drug-drug interactions or potential safety concerns:
  - Lymphocyte-depleting agents/therapies, including both non-B-cell selective and B-cell-depleting agents (eg, alefacept, alemtuzumab, rituximab).
  - Other biologics with immunomodulatory properties.
  - Live attenuated vaccines: restrictions on vaccinations are described in more detail in Section 6.5.3.
  - Moderate to potent CYP3A inducers (See Section 10.9.1).
  - Specific sensitive to moderate sensitive CYP3A substrates as listed in Section 10.9.1.
  - Herbal medications with either unknown properties or pharmaceutical properties that impact AA.
  - Investigational products (eg, drugs or vaccines).

6.5.3. Vaccinations

Vaccination with live attenuated virus is prohibited within the 6 weeks prior to the first dose of study intervention, while receiving study intervention, and for 6 weeks after the last dose of study intervention. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided while receiving study intervention and for 6 weeks after the last dose of study intervention. 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.

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, measles, mumps, rubella (MMR) vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live).

Vaccines (including COVID-19 vaccines) that are not live attenuated are permitted.

6.5.4. Surgery

From the time of the Screening visit through 28 days after the last dose of study intervention, no elective surgery should occur without first consulting with the Pfizer Medical Monitor or designee. Preferably, elective surgery should occur before the study or be delayed until participation in the study is completed. Refer to Section 5.3.5 for guidelines regarding temporary withholding of study intervention prior to and after elective surgery.

The Pfizer Medical Monitor or designee should be notified if a participant requires surgery (including dental surgery) during the study to determine whether the participant should discontinue from the study and/or discontinue study intervention prior to the surgical procedure. The Pfizer Medical Monitor or designee should be notified as soon as possible if a participant undergoes a surgical procedure without first informing the study staff.

6.6. Dose Modification

Dose modification of the study intervention is not permitted in this study. For information on temporary withholding of study intervention (see Section 6.4).

6.7. Intervention after the End of the Study

There is no intervention required by the protocol following the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention are included in Appendix 8, Section 10.8.2, Appendix 11, and Appendix 12.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the assessments at the Early Termination and Follow-up visits. See the Schedule of Activities for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, post-treatment study follow-up, and/or future collection of additional information.

7.1.1.1. Observation Period

Participants will be asked to remain in the study after the Follow-up visit without study intervention. The Period during which participants are in the study after having permanently discontinued study intervention is referred to as the Observation Period. During this period

participants will continue to comply with study visit schedules for approximately 2 years or until study end, whichever occurs first. At visits during the Observation Period, only the SALT, ELA, EBA, PGI-C, and concomitant medications/treatments will be collected at the visits specified in the applicable SoAs in Section 1.3.2; AE and SAE reporting will follow the guidelines in Section 8.3.

Participants will complete the final visit in the Observation Period approximately 2 years after the last dose of study intervention or at study end, whichever occurs first, as follows:

- at the protocol-scheduled visit 24 months after the last dose of study intervention, OR
- at the next scheduled visit after the 24-month time point (if no scheduled visit falls at the 24-month time point), OR
- at study end

For example, if the last dose of study intervention occurs around the time of Month 21 then the final visit in the Observation Period would be conducted at Month 48 (ie, the next scheduled visit occurring 24 months after Month 21).

7.1.2. Temporary Discontinuation

See Section 5.3.5 and Section 6.4.

7.2. Participant Discontinuation/Withdrawal from the Study

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the Schedule of Activities for assessments to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant 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.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed. Visit windows are based on Day 1 visit.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

- Participants will have up to 35 days of a screening period prior to the first dose of study intervention to confirm that they meet the participant selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each participant (or parent(s)/legal guardian and assent from the participant, as appropriate) in accordance with the procedures described in Section 10.1.3.

- For de novo participants and participants originating from B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015, all screening and Day 1 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria prior to randomizing the participant in Impala. For participants who previously participated in Study B7931005 or B7981015, adverse events, laboratory results, medical conditions and prior and current treatments occurring during those studies and in any time elapsed between those studies and Study B7981032 must be checked against the Study B7981032 entry criteria.

- Procedures conducted as part of the participant's routine clinical management (eg, chest x-ray or other appropriate diagnostic imaging such as computed tomography or MRI) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA. This includes procedure(s) which were completed for participants consented and screened for Study B7981015 but who did not receive study intervention in Study B7981015. Separate informed consent/assent for Study B7981032 must be obtained prior to use of data in Study B7981032 per Section 10.1.3.

- The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Due to audiological evaluation and possible need for tuberculin testing and chest radiograph, screening procedures may be performed over more than 1 visit within the 35 days prior to the Day 1 visit for de novo participants and participants with >30 days between the first in Study B7981032 and the last dose in Study B7931005 or B7981015.

- To assure consistency and reduce variability, visits should occur at approximately the same time of day throughout the study. Participants should be encouraged to attend visits in the morning and prior to the participant's dosing of study intervention as participants will receive their dose at the clinic during their study visit.

- Urine pregnancy test must be performed at each visit (and must be negative) prior to dosing with the study intervention for female participants of childbearing potential through follow-up (see Appendix 4 and Section 8.2.11).

- The patient-reported and observer reported outcome assessments should be completed before the other evaluations or treatments at the clinical visits whenever it is possible. The clinician global impression-alopecia areata (CGI-AA) should be completed after other clinical assessments of alopecia areata (ie, SALT, EBA, ELA, and assessment of fingernails affected by AA) whenever it is possible. Vital signs and electrocardiograms (ECGs) should be performed before any laboratory blood collection. All other evaluations (unless noted otherwise) do not need to be performed in any specific order.

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

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

- The maximum amount of blood collected from each participant over the duration of TP1, including all assessments at the screening and follow-up visits, will be approximately 280 mL. The maximum amount of blood collected from each participant over the duration of TP2, including all assessments at the follow-up visit, will be approximately 140 mL. The maximum amount of blood collected from each participant over the duration of the 5-year study, including all assessments at the screening and follow-up visits, will be approximately 400 mL. Participants not requiring laboratory testing at the screening and/or Day 1 visits per the Schedule of Activities will not require the full amount of blood to be collected. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- There may be instances when copies of medical records are requested by Pfizer (eg, for safety monitoring, follow-up of adverse events or laboratory abnormalities, review of local laboratory results, event adjudication). In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of medical records before submission to Pfizer or a third party such as an adjudication committee.

- Refer to Appendix 8 for guidelines on participant safety monitoring and discontinuation.

- Refer to Appendix 11 for information on discontinuation criteria for worsening AA in VHP countries in the EU.

- Refer to Appendix 12 for information on study intervention continuation criteria for adolescents.

- Refer to Appendix 13 for guidelines on alternative measures during public emergencies, including the COVID-19 pandemic.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Diagnosis of AA must be performed by a qualified dermatologist (board certified or equivalent) who has experience with AA. The assessment of fingernails affected by AA must be performed by a qualified dermatologist (board certified or equivalent). An experienced and qualified physician or healthcare professional may be permitted to perform the other clinical evaluations of alopecia (ie, SALT, ELA, EBA, and CGI-AA). The C-SSRS may be performed by site staff. For all assessments, the rater must be formally delegated to perform this assessment by the PI and receive training (with proper documentation) on the protocol and applicable assessment scales prior to performing these evaluations.

To assure consistency and reduce variability, the same rater should assess dermatological clinical evaluations for a given procedure and for an individual participant throughout the study (eg, one rater performs all SALT evaluations throughout the study). The same rater must assess the SALT and CGI-AA for an individual participant. A back-up experienced and qualified, protocol-trained rater will only be allowed in special situations when the designated rater is unable to perform the evaluation. Use of the back-up rater will be documented.

8.1.2. Clinical Assessments

Refer to Section 5.3.2 for information regarding cosmetic treatments and applications which must be adhered to during the study.

8.1.2.1. Severity of Alopecia Tool (SALT)

Severity of Alopecia Tool (SALT) is a quantitative assessment of alopecia severity based on scalp terminal hair loss[59]. The overall SALT score, which does not distinguish the reason for hair loss, will be collected at visits shown in the Schedule of Activities.

Score parameters utilize a visual aid showing the division of the scalp hair into four quadrants (back, top of scalp, and both sides), with each of the four quadrants given an accurate determination of the % of scalp surface area covered, representing 24%, 40%, 18%, and 18% of the total scalp surface area, respectively.

For information on photography required for this protocol, see Section 8.1.4.

Hair prosthetics (eg wigs, hair extensions) must be removed for clinical assessments of AA at all study visits.

8.1.2.1.1. Androgenetic Alopecia SALT Score

In addition to the overall amount of scalp terminal hair loss, scalp hair loss due to androgenetic alopecia will be assessed using the SALT tool. This will only be collected for participants with known androgenetic alopecia. The androgenetic alopecia SALT score (SALT AGA) is only required to be assessed at the final on-therapy visit for each treatment period (ie, in TP1 at Month 36 or Early Termination, and in TP2 at Month 60, the last on-therapy visit, or Early Termination) per the Schedule of Activities.

8.1.2.1.2. Alopecia Areata Eligibility Assessment

In addition to the overall amount of scalp terminal hair loss, scalp hair loss due to alopecia areata will be assessed at the screening and Day 1 visits to verify eligibility of de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose of study intervention in Study B7931005 or B7981015.

8.1.2.2. Eyelash Assessment (ELA)

The eyelash assessment (ELA) is a numeric rating scale (NRS) developed to characterize eyelash hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal) as described below.

Score	Description
0	None Eyelash • No eyelashes of both right and left upper and lower eyelashes.
1	Minimal Eyelash • Modestly or severely decreased density of and/or large gap(s) in one or both upper eyelashes.
2	Moderate Eyelash • Normal density of both upper eyelashes without gap(s), and decreased density or gap(s) is present in one or both lower eyelashes, OR • Normal density of both upper eyelashes with short gap(s), OR • Mildly decreased density of one or both upper eyelashes with or without short gap(s).

Score	Description
3	Normal Eyelash • Normal density of both right and left upper and lower eyelashes from near medial canthus to near lateral canthus without any gap(s).

NOTE:
- Density of lower eyelashes is usually less than upper eyelashes.
- A short gap does not significantly distort the appearance of the eyelash (es).
- Moderate Eyelash score does not require presence of lower eyelashes.

8.1.2.3. Eyebrow Assessment (EBA)

The eyebrow assessment (EBA) is an NRS developed to characterize eyebrow hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal).

Score	Description
0	None Eyebrow • No eyebrow hair.
1	Minimal Eyebrow • Normal or decreased density of one or both eyebrows with large gap(s). • Severely decreased density of one or both eyebrows with or without gap(s).
2	Moderate Eyebrow • Normal density of both eyebrows with short gap(s) that does not significantly distort the appearance of the eyebrows, OR • Mildly decreased density of eyebrows with or without short gap(s), OR • Moderately decreased density of eyebrows without short gap(s). There is visual definition of eyebrows at a distance of 3 feet.
3	Normal Eyebrow • Normal density of both right and left eyebrows spanning usual length (ie, from glabella to near temple) and width. There are no gap(s).

NOTE:
- Density of lateral aspect of eyebrows may be mildly less than medial eyebrows.
- A short gap does not significantly distort the appearance of the eyebrow(s).

8.1.2.4. Assessment of Fingernails Affected by Alopecia Areata

The number of fingernails affected by AA will be counted at Day 1 in all de novo participants, all participants originating from B7931005, and participants originating from Study B7981015 with >30 days between the first visit of B7981032 and the last dose in Study B7981015. The number of affected fingernails will be counted at subsequent visits for all participants (Schedule of Activities). Fingernails may have any of the following changes to be considered "affected": nail pitting; trachyonychia (roughening of nail surface); onychorrhexis (brittle nails); koilonychia (transverse and longitudinal concavity of nail, ie, "spoon shaped"); onychomadesis (separation of nail plate from nail bed); longitudinal ridging or striations; leuconychia (white lines or spots in nail plate); red spotting of the lunulae.[61-78]

Photographs may be taken of affected nails at the Day 1 visit and during study treatment at investigator's discretion.

Nail polish/varnish, false fingernails, and gel applications must be removed for assessments of fingernails affected by AA.

8.1.2.5. Clinician Global Impression - Alopecia Areata (CGI-AA)

The Clinician Global Impression - Alopecia Areata (CGI-AA) is a single clinician-reported item developed to assess clinical impression of severity of scalp hair loss. The rater is asked to rate the participant's current hair loss on a scale ranging from "None (no hair loss)" to "Very severe or complete hair loss" with higher scores indicating more severe hair loss. The CGI-AA should be completed after other clinical assessments of alopecia areata (ie, SALT, EBA, ELA, and assessment of fingernails affected by AA), whenever it is possible.

8.1.3. Patient Reported Outcome (PRO) / Observer Reported Outcome (ObsRO)

Participant completed questionnaires in this study include the AAPPO, PGI-C, P-Sat, HADS, EQ-5D-5L, EQ-5D-Y, SF36v2 Acute, AARU, and WPAI: AA. The BRIEF®2 is a parent/caregiver completed questionnaire. Every effort should be made to have the participant complete all patient reported outcome (PRO) questionnaires and the participant's parent/caregiver complete the observer reported outcome (ObsRO) questionnaire before any other evaluations. All PROs/ObsROs should be completed as shown in the Schedule of Activities.

8.1.3.1. Alopecia Areata Patient Priority Outcomes (AAPPO)

The Alopecia Areata Patient Priority Outcomes (AAPPO) scale is an 11-item self-administered questionnaire that measures hair loss, emotional symptoms, and activity limitations over the past week. This measure was developed based on qualitative patient input as well as review of other data sources (eg, literature, expert input, other existing measures, etc.). The first 4 items of the tool, which cover hair loss from the scalp, eyebrows, eyelashes, and body, ask the patient to describe the current amount of hair loss using a 5-point response scale that ranges from "no hair loss" to "complete (do not have any [insert body location/type of hair])." Items 5-8 are an assessment of emotional symptoms. Response choices on these items are scored from "0=never" to "4=always."-Items 9-11 are an

assessment of activity limitations, with response choices scored from 0="not at all" to 4="completely (did not do any [insert activity] because of hair loss)".

8.1.3.2. Patient's Global Impression of Change (PGI-C)

The Patient's Global Impression of Change (PGI-C) asks the participant to evaluate the improvement or worsening of their AA as compared to the start of the study using a single-item, "Since the start of the study, my alopecia areata has: …". The participants will select one of seven responses ranging from "greatly improved" to "greatly worsened." De novo participants should refer to the start of Study B7981032 and participants originating from Study B7931005 or B7981015 should refer to the start of the index study.

8.1.3.3. Patient's Satisfaction with Hair Growth (P-Sat)

The Patient's Satisfaction with Hair Growth (P-Sat) asks the participant to evaluate his/her satisfaction with the hair that has regrown since the start of the study. This measure is comprised of three items asking about satisfaction with the "amount" and "quality" of hair as well as "overall" satisfaction with the hair. The participants will select one of seven responses ranging from "very satisfied" to "very dissatisfied." De novo participants should refer to the start of Study B7981032 and participants originating from Study B7931005 or B7981015 should refer to the start of the index study.

8.1.3.4. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week. Items are rated on a 4-point severity scale. The HADS produces 2 scales, one for anxiety (HADS-A) and one for depression (HADS-D), differentiating the two states with established normal score cut-offs[90]. The instrument has been validated for use by adolescents aged 12 and older.[79]

8.1.3.5. EuroQoL 5 Dimensions (EQ-5D-5L) and EuroQoL 5 Dimensions-Youth (EQ-5D-Y)

The EuroQoL 5 Dimensions (EQ-5D-5L) is a validated, standardized, generic instrument that is the most widely used preference-based HRQoL questionnaire in cost-effectiveness and health technologies assessment (HTA).[80-82] The measure is a well-established instrument used to measure health states and utilities in various disease areas. The measure contains 5 items that cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale. A version of the instrument specifically developed and validated for use by youths aged 12 to <18 years is called the EuroQoL 5 Dimensions-Youth (EQ-5D-Y) will be used for adolescent participants. Participants who are <18 years at the time of the Day 1 visit of B7981015 or B7981032 will use the EQ-5D-Y (age for participants from B7931005 will be based on their age on Day 1 of B7981032) per the Schedule of Activities. Participants who reach the age of 18 years during Study B7981032 will continue to use the EQ-5D-Y for the remainder of the visits at which the EQ-5D-Y is collected per the Schedule of Activities.

8.1.3.6. 36 -Item Short Form Health Survey Version 2 Acute (SF36v2 Acute)

The 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) is a validated generic health status measure which measures concepts of HRQoL over the past week. It is 36 items and measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains can also be summarized as physical and mental component summary scores.

8.1.3.7. Alopecia Areata Resource Utilization (AARU)

The Alopecia Areata Resource Utilization (AARU) is a PRO that measures the resource utilization associated with AA. The AARU is a 3-item questionnaire which asks participants about medical or nonmedical practitioner visits, cosmetic covering of hair loss, and career impact they may have had over the past 3 months.

8.1.3.8. Work Productivity and Activity Impairment: Alopecia Areata (WPAI: AA)

The Work Productivity and Activity Impairment: Alopecia Areata (WPAI: AA) is a validated scale that was developed to measure the effect on work productivity and regular activities during the past 7 days, which has been modified specifically for participants with AA. The WPAI: AA will be completed by adult participants aged ≥18 years only. Adolescents aged 12 to <18 years at the time of the Day 1 visit of B7981015 or B7981032 will not complete this assessment (age for participants from B7931005 will be based on their age on Day 1 of B7981032).

8.1.3.9. Behavior Rating Inventory of Executive Function®, Second Edition (BRIEF®2)

Only in countries where the questionnaire is available.

The Behavior Rating Inventory of Executive Function®, Second Edition (BRIEF®2), that will be used in this study is an ObsRO parent/caregiver completed scale designed to assess executive behaviors in children and adolescents. The BRIEF®2 will be used in this study to monitor neuropsychological development and executive functions in adolescents. The BRIEF®2 scales assess how well the child is demonstrating behavioral or emotional control, initiating activity, engaging in planful and well-organized problem solving, and monitoring one's own social success and problem-solving outcomes. The BRIEF®2 consists of 63 items and yields scores on nine scales, with the Inhibit and Self-Monitor scales comprising the Behavior Regulation Index (BRI), the Shift and Emotional Control scales comprising the Emotional Regulation Index (ERI), and the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials scales comprising the Cognitive Regulation Index (CRI).[91,92]

For participants who are <18 years of age at the time of the Study B7981032 Day 1 visit, the parent/caregiver will complete the BRIEF®2 questionnaire. The same parent/caregiver should complete the questionnaire at each visit throughout the study whenever possible.

For participants who have already started the study when the BRIEF®2 questionnaire is approved and available for use at the participant's site, the BRIEF®2 questionnaire will be

administered at the next scheduled study visit and then at the remaining visits per the Schedule of Activities for the BRIEF®2. For example, if the BRIEF®2 was approved for use at a site between an adolescent participant's Month 12 and Month 15 visit, the BRIEF®2 would be completed at the Month 15 visit and then at the Month 18 and subsequent visits per the Schedule of Activities.

Once a participant reaches ≥18 years of age, this assessment will no longer be required. At the Early Termination visit, if the BRIEF®2 was administered within 2 months of the Early Termination visit, it does not need to be collected.

BRIEF®2 should be administered as shown in the Schedule of Activities.

8.1.4. Photography

Photographs of study participants will be obtained (according to the separately provided Photography Instructions) at various time points as shown in the Schedule of Activities. Photographic services will be provided through a central photography lab selected by the sponsor. Detailed procedures to assure photographic quality and consistency will be provided separately in a central photography laboratory instruction manual.

Scalp areas photographed should be recorded in study documents so that the same scalp region(s) will be photographed at all time points as applicable. Photographs of eyelashes and eyebrows will also be taken. Photographs of affected fingernails may be taken at the investigator's discretion.

The photographs taken of any participant may be reviewed by an independent consultant(s) to confirm SALT scores.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Safety monitoring and discontinuation criteria are provided in Appendix 8.
For the purposes of safety monitoring and discontinuation, baseline values will be defined as follows:

- For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015:
    - Baseline values will be defined as the values from Day 1 of Study B7981032 (or from screening of Study B7981032 for evaluations not performed at Day 1).

- For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015:
    - Baseline values will be defined as the values from Day 1 of B7981015 (or from screening of Study B7981015 for evaluations not performed at Day 1).

8.2.1. Medical History, Physical Examinations, Height, and Weight

- Complete AA disease history includes collection of details of AA at screening for de novo participants and participants originating from B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015: AA history, AA diagnosis, pattern of scalp hair loss, body hair loss, nail involvement, the use of topical treatments, systemic treatments and other treatments for AA.
- Medical history, including, but not limited to, comorbid conditions, history of drug, alcohol, tobacco use, dermatologic history, and infection will be collected at screening or Day 1 (as applicable per the Schedule of Activities). Refer to the CRF completion guidelines for specific information regarding medical history information to be collected for each group of participants.
- Smoking status and alcohol consumption will also be collected for de novo participants and participants originating from B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015.
- Height and weight will be measured without the participant wearing shoes or outerwear. Height (inches or centimeters) and weight (lbs or kgs) will be measured and recorded in the source document at various time points according to Schedule of Activities. After the screening visit, height will not be collected from participants who are ≥18 years of age at the time of the 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; abdomen; extremities; neurologic function, back, and lymph nodes. In addition, dermatological full body exam must be performed by the investigator, sub investigator or a qualified health professional per local guidelines. Dermatological examinations should also include visual inspection of the breasts and external genitalia.
- Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and should include skin, heart, lung, and abdomen, neurologic function, and examination of body systems where there are symptom complaints by the participant.

- When dermatologic adverse events are identified on physical exam, additional procedures may be required. Please refer to Section 8.2.7.2 for additional details.
- Participants with clinically meaningful changes from baseline in neurologic signs or symptoms should be referred to a neurologist to undergo a formal neurologic evaluation.

8.2.2. Tanner Stages of Development

Determination of physical and sexual maturation will be performed using the Tanner stages of development [84] for participants who are <18 years of age at the Day 1 visit in Study B7981032. For these participants, Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on all applicable domains. For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males). The assessment will be performed by an investigator, sub investigator or a qualified health professional per local guidelines in the presence of a parent/legal guardian or clinic staff member other than the person performing the exam.

The Tanner stages will be assigned by the qualified site staff based on the exam. At the end of the exam, the qualified site staff will assign the best estimate Tanner stage for each domain. In the case of differential maturation within a domain, the higher Tanner stage should be assigned.

8.2.3. Vital Signs

- Oral, tympanic, axillary, or temporal artery temperature, pulse rate, and blood pressure will be assessed. It is preferred that body temperature be collected using the tympanic or oral methods; however, the axillary and temporal artery methods are also permitted. The same method should be used consistently throughout the study. Vital signs should be performed before laboratory blood collection and ECG.
- Blood pressure and pulse measurements will be assessed 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) with a completely automated device. Manual techniques will be used only if an automated device is not available. 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 participant 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.

- Pulse rate should be measured at approximately the same time as BP for a minimum of 30 seconds.
- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements.

8.2.4. 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 or magnetic resonance imaging [MRI]) must be taken at screening or within 3 months prior to screening visit for de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015. The chest radiograph must be read by a qualified radiologist or pulmonologist prior to the Day 1 visit for confirmation of eligibility per Section 5.2.2. Documentation of the reading by the qualified radiologist or pulmonologist must be available in the source documentation.

8.2.5. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT_{cF} intervals (or using an ECG machine which does not automatically calculate QT_{cF} intervals, with the site's qualified medical personnel performing the calculation with the QT_{cF} calculator provided by the sponsor). Refer to Appendix 8 for QT_{cF} withdrawal criteria and any additional QT_{cF} readings that may be necessary.
- ECG should be performed before laboratory blood collection.
- All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and prior to any blood collection.
- A paper or digital copy of the ECG should be filed in the participant's chart and must be available to the sponsor upon request
- To ensure safety of the participants, qualified medical personnel will review all ECGs and make comparisons to the baseline measurements as defined in Section 8.2. 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.

8.2.6. Audiological Evaluation

All participants will have an audiological evaluation at times specified in the Schedule of Activities. When possible, the participant should have the evaluation performed at the same evaluation center during the study.

A full audiological evaluation must be completed at screening or within 8 weeks prior to Day 1 for de novo participants and those with >30 days between Study B7981032 and the last dose in Study B7931005 or B7981015. This evaluation includes: audiological history, otoscopic examination, pure tone audiometry, air and bone conduction, speech audiometry, and immittance audiometry. All screening audiological evaluation results must be available prior to Day 1 to assess eligibility for de novo participants and those with >30 days between Study B7981032 and the last dose in Study B7931005 or B7981015.

At subsequent visits, updated audiological history, otoscopic examination, and pure tone audiometry will be performed for all participants; based upon results, additional audiological assessments may be required.

For participants who terminate early from the study, efforts must be made to complete the audiological evaluation.

If there is a clinically meaningful, treatment-emergent decline in hearing from the baseline measurements (as defined in Section 8.2), the participant must be promptly evaluated by a medically qualified specialist to assess for possible causes. Evaluation results should then be discussed with the sponsor to determine if the participant should be discontinued from the study. Discontinued participants must be followed up off-treatment with appropriate testing at regular intervals, until hearing recovers or is determined to be clinically stable.

Refer to the most current version of the Audiological Evaluation Study Guide for details on audiological evaluation. All procedures must be performed according to the Audiological Evaluation Study Guide.

8.2.7. Special Safety Assessment

8.2.7.1. Suspected Opportunistic Infections

In the event of a suspected opportunistic infection, every effort should be made to identify the pathogen utilizing laboratory or other methods appropriate to the clinical situation.

8.2.7.2. Dermatological Events

All participants will have a dermatological full body exam at Screening Visit and as noted in the Schedule of Activities.

8.2.7.2.1. Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex) or eczema herpeticum specimens for viral deoxyribonucleic acid (DNA) analysis will be

obtained: a swab of the affected area will be collected for confirmation. Details for this collection will be provided in the laboratory manual.

8.2.7.2.2. Potential Drug-Related Rash and Unexplained 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 participants reporting an unexplained skin rash should undergo a formal comprehensive dermatologic evaluation. In addition, the participant will be asked to rate the severity of pruritus within the last 24 hours on a scale from 0 (No itching) to 10 (Worst possible itching). A 4 mm punch biopsy will be taken unless there is a clear, non-drug related etiology (eg, infection, including herpes virus, 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 participant refuses 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.

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.

Photographs of the rash will be taken.

All de-identified biopsy results, culture results, photographs, and any additional relevant test results should be forwarded to the sponsor for review. This should occur within 30 days of receipt of results by the principal investigator (PI).

8.2.8. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

- Participants must abstain from all food and drink (except water and non-study medications) for a minimum of 8-hours prior to fasting lipid profile panel collection according to Schedule of Activities. All other labs (including pharmacokinetic [PK] sample collections) do not require fasting.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes from baseline (as defined in Section 8.2) occurring during the study in the adverse events (AE) section of the CRF. The

laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

    - See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.8.1. Tuberculosis Testing

QuantiFERON®-TB Gold In-Tube (QFT-G) test is the preferred testing method; however, the T-SPOT®.*TB* (T-Spot) test is also permitted.

The QFT-G test is an in vitro diagnostic test using a peptide cocktail simulating early secreted antigenic target of 6 kiloDalton (ESAT-6), culture filtrate protein 10 kiloDalton (CFP-10), and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-gamma by Enzyme-Linked Immunosorbent Assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *M. tuberculosis* infection. The T-Spot test is also an in vitro diagnostic test; however, it differs in that it uses a peptide cocktail simulating ESAT-6 and CFP-10 proteins to stimulate peripheral blood mononuclear cells. Both the QFT-G test and the T-Spot test are indirect tests for *M. tuberculosis* infection (including disease) and are intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

A blood sample will be collected for either the QFT-G or the T-Spot testing. The site must determine which test will be performed as sample collection and processing guidelines differ. QFT-G testing will be performed at the central laboratory and T-Spot testing will be performed at the site's local laboratory. Following QFT-G sample processing, the sample will be shipped to the central laboratory for testing. The procedure for processing and

preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

In addition to TB testing as specified in this clinical protocol, a chest X-ray will be performed as described in Section 8.2.4.

8.2.8.1.1. Screening Tuberculosis Testing

During the screening period, it must be determined and documented that de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 do not have evidence of untreated or inadequately treated active or latent infection with *Mycobacterium tuberculosis* (TB) per Exclusion criteria 19 in Section 5.2.2. The results of TB screening conducted in the within 3 months prior to Day 1 visit or during the screening period must be documented in study records prior to Day 1 (Visit 2).

8.2.8.1.2. Day 1 and Annual Tuberculosis Testing

TB testing will be conducted at Day 1 for participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015, and annually after Day 1 in all participants as described below.

For participants WITHOUT either a positive QFT-G (or T-Spot or PPD) result during prior testing (including screening visits in Study B7931005, B7981015 or B7981032, as applicable) or a history of previous treatment for active or latent TB, the following testing will be conducted:

- QFT-G test or T-Spot test per Section 8.2.8.1. If the laboratory reports the test as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a purified protein derivative (PPD) test may be substituted for the QFT-G test or T-Spot test only with approval from the Pfizer Medical Monitor on a case-by-case basis.

- Participants with a positive result must have a chest radiograph or other appropriate diagnostic image (ie, computed tomography or MRI) performed. The chest radiograph must be read by a qualified radiologist or pulmonologist.

- Participants with a positive result must have study intervention temporarily withheld until it is confirmed by a specialist (eg, pulmonologist or infectious disease specialist) if the participant has latent or active TB and, if applicable, the treatment plan has been approved by the Pfizer Medical Monitor as described below. The actual decision to restart treatment, if applicable, must be approved by Pfizer. For additional details regarding the process to be followed for participants with a positive TB test result, refer to Appendix 14.

- Participants with a negative laboratory result do not require a chest radiograph.

For participants WITH either a positive QFT-G (or T-Spot or PPD) result during prior testing (including screening visits in Study B7931005, B7981015 or B7981032, as applicable) or a history of previous treatment for active or latent TB, the following testing will be conducted:

- Neither a QFT-G test, T-Spot test, nor a PPD test need be obtained.
- A chest radiograph or other appropriate diagnostic image (ie, computed tomography or MRI) must be performed. The chest radiograph must be read by a qualified radiologist or pulmonologist.

Participants with a chest radiograph indicative of active TB must have study intervention withheld until it is confirmed by a specialist (eg, pulmonologist or infectious disease specialist) whether the participant has active TB as described below.

Participants identified as potentially having latent TB (positive QFT-G, T-Spot, or PPD test result and negative chest radiograph for active TB) or active TB must be referred to a specialist (eg, pulmonologist or infectious disease specialist) for evaluation (see Appendix 14 for additional details). If active TB is diagnosed by the specialist, the participant must be permanently withdrawn from study intervention. If latent TB is diagnosed by the specialist, the participant may re-start the study intervention while receiving treatment for latent TB only with approval from the Pfizer Medical Monitor. For participants taking the study intervention during their treatment for latent TB, the only acceptable treatment is isoniazid (INH).

8.2.8.2. Purified Protein Derivative (PPD) Test

If the QFT-G test or T-Spot test cannot be performed, or if the results from the reference laboratory are indeterminate, then participants may be screened using the PPD Tuberculin Test (Mantoux method), with the approval of the Pfizer Medical Monitor.

Participants must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 12 weeks. The test should be performed and interpreted as negative according to local standards (eg, induration of <5 mm).

8.2.8.3. Varicella Zoster Virus Immunoglobulin G Antibody (VZV IgG Ab) Testing

VZV Ig Ab testing (as described in the lab manual) is only required in adolescent de novo participants and those originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 who are 12 to <18 years of age without documented evidence of having received the varicella vaccine (2 doses). Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses) per Exclusion #16.

8.2.8.4. Day 1 Viral Screen

A serum sample will be collected at Day 1 and submitted to the central lab for de novo participants, all participants from Study B7931005, and participants whose sample was tested in Study B7981015. The sample will be stored and analyzed at a later date only at the sponsor's request. In certain cases of suspected viral infection (eg, disseminated herpes zoster or varicella), the sponsor may request to analyze the sample to determine if the participant had exposure to that virus. Additional sample collection instructions and details regarding sample destruction will be provided in the lab manual. The retained samples will be destroyed upon participant completion of this study.

8.2.8.5. Hepatitis B DNA (HBVDNA) Testing

For participants in countries in which hepatitis B prevalence has been reported at a rate of >5.0%[85] or if required by local standard of care, HBVDNA testing will be performed as reflex testing for the following (refer to Appendix 7 for Japan specific requirements):

- At screening for de novo participants or participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 who are HbcAb positive at the B7981032 screening.

In addition, for participants in those regions for which hepatitis B prevalence has been reported as a rate of >5.0% or if required by local standard of care, HBVDNA testing will be performed at additional time points as outlined in the Schedule of Activities for participants who were enrolled with a positive HBcAb and a negative HBVDNA at screening of the applicable study:

- B7981032: de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015.

- B7981015: participants with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015.

Testing at additional time points may be performed as per the local standard of care. Refer to Appendix 6 for testing algorithm, reflex testing, and full eligibility criteria for de novo participants and participants with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 and Study B7981032.

8.2.9. Suicidal Ideation and Behavior Risk Monitoring

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

C-SSRS is a validated tool to evaluate suicidal ideation and behavior.

There are 2 versions of the C-SSRS to be utilized in this study - "C-SSRS for screening and Day 1 visits" and "C-SSRS for any visits after Day 1". The version used is dictated by the actual study visit and the patient population (See the Schedule of Activities).

For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015: At the screening or Day 1 visits, the C-SSRS for screening and Day 1 visits will be used and the results must be evaluated against Exclusion Criterion 5.

For participants originating from Study B7981015 with >14 days to ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015: The C-SSRS for visits after Day 1 will be used at the Day 1 visit and the results must be evaluated against the protocol discontinuation criteria in Appendix 8 before the participant is assigned to study intervention. If the answers meet the discontinuation criteria, the participant will not be included in the study.

For all participants who screen failure due to suicidal behavior, the participant should be referred for appropriate evaluation and treatment.

For all participants with suicidal ideation associated with actual intent and a method or plan in the past year: At any visits after Day 1, if there are "yes" answers on items 4, 5, or on any question in the suicidal behavior section of the C-SSRS, the participant will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment or immediately referred to the Emergency Room at the investigator's judgement.

8.2.10. Patient Health Questionnaire - 8 Items (PHQ-8)

The Patient Health Questionnaire – 8 items (PHQ-8) is a patient reported questionnaire that consists of 8 items to assess participant depression level. De novo participants and participants originating from Study B7931005 or B7981015 with >30 days prior to enrolling in Study B7981032 with clinically significant depression as noted by a PHQ-8 total score ≥15 at screening must not be enrolled in the study.

8.2.11. Pregnancy Testing

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

Pregnancy tests must have a sensitivity of at least 25 mIU/mL. Pregnancy tests should be urine pregnancy tests. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests can be utilized. Pregnancy tests will be performed in WOCBP at the times listed in the Schedule of Activities. Following a negative pregnancy test result at screening, appropriate contraception must be verified and a second negative pregnancy test result will be required at the Day 1 visit prior to the participant receiving the study intervention.

In addition to pregnancy tests performed at the site, site personnel will instruct applicable participants to complete monthly urine pregnancy tests between study visits starting after the Month 1 visit through the Month 60 visit. The pregnancy testing between visits may occur outside of the study site. Urine pregnancy kits will be provided to participants (or their legally authorized representative, if appropriate) at each study visit (starting at Month 1) and site personnel will instruct participants (or their legally authorized representative, if

appropriate) on when and how to administer the pregnancy test and how to interpret the result. The participants (or their legally authorized representative, if appropriate) will be given enough kits to cover the monthly testing between visits (for example, at least 2 kits should be given at the Month 3 visit). Site personnel will be required to document the discussion, including confirmation of participant's willingness to perform the required urine pregnancy tests and understanding of how to perform the test as well as how to interpret the test result. In addition, site personnel will contact participants (or their legally authorized representative, if appropriate) via telephone between study visits to obtain monthly pregnancy test result and ensure that this contact and the result of the pregnancy test are recorded in participant's source documentation and the CRF.

Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study for follow-up.

8.2.12. Check for Initiation of Menarche (for Premenarchal Females Only)

In female participants who are premenarchal at the start of the study, the investigator must confirm with the participant at every visit whether menarche has started since the last visit. If menarche has started, the participant must now be considered of childbearing potential; therefore, from that point forward and starting with the current visit, the participant will be required to establish willingness and ability to comply with contraception requirements (Appendix 4) and to undergo contraception checks and pregnancy testing according to the Schedule of Activities. In addition, the investigator or designee will instruct the participant to contact the site immediately if the participant begins menarche between study visits.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention/study (Section 7 and Appendix 8).

Each participant (or/parent/legal guardian/legally authorized representative) will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention, except as indicated below.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form. Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT (Clinical Trials) SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported (by the participant) AEs and SAEs.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Ethics Committees (EC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant 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.

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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so 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.

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 administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person has unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are provided in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant 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.

8.3.6. Cardiovascular and Death Events (Not Applicable)

8.3.7. Disease-Related Events and/or Disease-Related Outcomes not Qualifying as AEs or SAEs (Not Applicable)

8.3.8. Adverse Events of Special Interest

Refer to Section 8.2.7 for definitions of adverse events of special interest (AESIs).

All AESIs must be reported as an AE or SAE following the procedures described in Section 8.3.1 through Section 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy (Not Applicable)

This section is not applicable as the study intervention administered is not approved for use.

8.3.9. Medical Device Deficiencies (Not Applicable)

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention 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

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

For further clarification, a medication error is:

- Any preventable event causing or leading to inappropriate medication use or patient harm;
- When patient misunderstood, could not read, was not aware of, or not given dosing instructions.

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 within 24 hours.

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.**

8.4. Treatment of Overdose

For this study, any dose of PF-06651600 greater than 800 mg within a 24-hour time period will be considered an overdose.

There is no specific antidote or specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-06651600 (whichever is longer).

3. Obtain a plasma sample for PK analysis within 4 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with a SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

During all study periods, blood samples (~2 mL) to provide plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) anticoagulant at times specified in the Schedule of Activities section of the protocol.

Blood will be collected at the time points identified in the Schedule of Activities section of the protocol. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. For each blood sample collection, the allowable windows are as follows for time post dose: 0.5 hr (±10 min), 1 hr (±15 min) and 3 hr (±30 min). The date and exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF), as well as the date and time of the previous dose. Samples obtained outside the windows specified in the Schedule of Activities will be considered a protocol deviation.

- The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C or colder within 1 hour of collection.

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

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

- As part of understanding the pharmacokinetics of the study intervention, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. These additional exploratory analyses will not be performed on samples collected from participants at sites in China; refer to Section 10.7.2.

8.5.1. Shipment of Pharmacokinetic Samples

The shipment address and assay lab contact information will be provided to the Investigator site prior to initiation of the study. The central laboratory will provide collection materials and directions for packaging and shipment of samples and will forward samples to the contract analytical laboratory.

8.6. Pharmacodynamics

Blood samples (~2.5 mL) will be collected for measurements of immunoglobulin (Ig) (IgA, IgG, IgM) at the time points listed in the Schedule of Activities.

Blood samples (~5.0 mL) will be collected by fluorescence activated cell sorting (FACS) analysis to identify T cell, B cell, and natural killer (NK) cell (FACS-TBNK) subsets at the time points listed in the Schedule of Activities.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These additional exploratory analyses will not be performed on samples collected from participants at sites in China; refer to Section 10.7.2.

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with applicable Pfizer standard operating procedures. The pharmacodynamic (PD) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics.

Banked biospecimens for genetics are not included in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (RNA) Research Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

Banked biospecimens for biomarkers are not included in this study.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Data collected in the Alopecia Areata Resource Utilization (AARU)
- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures

9. STATISTICAL CONSIDERATIONS

See Appendix 10 for vaccine sub-study statistical considerations.

9.1. Estimands and Statistical Hypotheses

There is no formal statistical hypothesis testing for this study.

9.1.1. Estimands

Not applicable to this study.

9.2. Sample Size Determination

Sample size is not based on any formal hypothesis testing but instead driven by the regulatory requirement for the safety database. Sample size is determined by the number of participants who enroll from the Phase 2a Study (B7931005) and participants who enroll from the Phase 2b/3 Study (B7981015), as well as the number of de novo participants enrolled. It is estimated that a total of approximately 960 participants will be enrolled in Study B7981032, including approximately 450 de novo participants. The number of de novo participants enrolled may be modified based on the actual number of participants who continue from Study B7931005 and Study B7981015 into Study B7981032.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Safety	The Safety Analysis Set (SAS) is defined as all participants who received at least 1 dose of study intervention.
Efficacy	The Full Analysis Set (FAS) is defined as all participants, regardless of whether they received study intervention.
PK	The PK concentration population is defined as all enrolled participants who received at least 1 dose of PF-06651600 and in whom at least 1 concentration value is reported.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Data analysis for participants who permanently discontinued treatment but remained in the study (Section 7.1.1) will be described in the statistical analysis plan. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Timing of the Analyses

The PCD clinical study report (CSR) will include analyses of the following:

- All safety data collected through the PCD (Section 4.4).
- Efficacy data collected for the time points as specified in the applicable SoAs through the Month 36 visit for each participant.

The supplemental CSR will include analyses of the following:

- All safety data collected in the entire study.
- Efficacy data collected for the time points post Month 36 visit, as specified in the applicable SoA of TP2.

9.4.2. Efficacy Analyses

For the purpose of analysis of efficacy measures for the participants originating from the index studies, the baseline values are defined as the Day 1 values from Study B7981015 or B7931005. For assessments which were not collected in the respective index study, the baseline value is defined as the value collected on Day 1 of Study B7981032. For the de novo participants, the baseline values are defined as the values collected on Day 1 of Study B7981032.

PCD CSR	
Endpoint	**Statistical Analysis Methods**
Primary	There are no primary efficacy endpoints.
Secondary	Efficacy analyses are descriptive in nature (such as number and percent, mean, standard deviation) at each visit where measured; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported. Displays by de-novo participants (ie, those who did not receive study intervention in either Study B7931005 or B7981015) and participants originating from Study B7931005 or B7981015 (ie, those who received study intervention in either Study B7931005 or B7981015) will also be included. For participants who permanently discontinue from study intervention but remain in the study, efficacy data collected during the observation period (see Section 7.1.1.1) will be included in efficacy listings, but not in the efficacy summaries. Further details will be specified in the statistical analysis plan.
Exploratory	Will be described in the statistical analysis plan.
Supplemental CSR	
Endpoint	**Statistical Analysis Methods**
Primary	There are no primary efficacy endpoints.
Secondary	There are no secondary efficacy endpoints.
Exploratory	Efficacy analyses are descriptive in nature There will be no formal hypothesis testing. For participants who permanently discontinue from study intervention but remain in the study, efficacy data collected during the observation period (see Section 7.1.1.1) will be included in efficacy listings, but not in the efficacy summaries. Further details will be specified in the statistical analysis plan.

For both the PCD CSR and the supplemental CSR the endpoints for SALT include both the SALT overall and SALT AA scores.

The SALT overall score includes any hair loss regardless of etiology (eg, including scalp hair loss due to both androgenetic alopecia and AA). The SALT AGA score only takes into account scalp hair loss due to androgenetic alopecia. The SALT AA score at each visit will be calculated as follows using the applicable SALT AGA score collected at the last visit of the treatment period (as defined in Section 8.1.2.1.1):

SALT AA Score = SALT overall score – SALT AGA score

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. For the purpose of analysis of safety measures for the participants with ≤30 days between the first visit of Study B7981032 and the last dose of study intervention in the index studies, the baseline values are defined as the Day 1 values from Study B7981015 or B7931005. For the de novo

participants and participants with >30 days between the first visit of Study B7981032 and the last dose of study intervention in the index study, the baseline values are defined as the values collected on Day 1 of Study B7981032.

PCD CSR	
Endpoint	**Statistical Analysis Methods**
Primary	The primary endpoints of incidence of TEAEs, SAEs, and AEs leading to discontinuation, clinically significant abnormalities in vital signs, and clinically significant abnormalities in laboratory values will be summarized using descriptive measures such as numbers and percentages. The safety summaries will be reported for all participants, as well as by de-novo participants (ie, those who did not receive study intervention in either Study B7931005 or B7981015) and participants originating from Study B7931005 or B7981015 (ie, those who received study intervention in either Study B7931005 or B7981015). No formal statistical hypotheses will be tested. Further details will be specified in the Statistical Analysis Plan.
Secondary	There are no secondary safety endpoints.
Exploratory	There are no exploratory safety endpoints.
Supplemental CSR	
Endpoint	**Statistical Analysis Methods**
Primary	There are no primary safety endpoints.
Secondary	The secondary endpoints of incidence of TEAEs, SAEs, and AEs leading to discontinuation, clinically significant abnormalities in vital signs, and clinically significant abnormalities in laboratory values will be summarized using descriptive measures. The safety summaries will be reported for all participants, as well as by de novo participants and participants originating from Study B7931005 or B7981015. No formal statistical hypotheses will be tested. Further details will be specified in the statistical analysis plan.
Exploratory	There are no exploratory safety endpoints.

9.4.4. Other Analyses

The PK concentration population is defined as all enrolled participants who received at least 1 dose of PF-06651600 and in whom at least 1 concentration value is reported.

PK concentrations listings and summary by visit and nominal collection time will be provided. A population PK model will be developed to characterize the PK and estimate PK parameters. The detailed analysis plans will be described in a separate pharmacometric analysis plan.

Analyses of pharmacodynamic and disease-related biomarkers will be described in the statistical analysis plan.

9.5. Interim Analyses

Interim analyses may be performed for study monitoring for internal decision making, due to regulatory requests, or to support regulatory submissions. Interim analyses, if any, will primarily be for safety though some measures of efficacy may be analyzed. As no statistical hypotheses will be tested in this study, there are no issues of protecting the Type I error rate.

9.5.1. Data Monitoring Committee (DMC)

This study will use an external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.
  - For Japan only: After approval (if relevant) in Japan by MHLW, this study will be conducted according to GPSP in addition to GCP.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 study intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant (and his/her legally authorized representative for adolescents) and answer all questions regarding the study. The participant (and his/her legally authorized representative for adolescents) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.
- As appropriate, children may be given the opportunity to meet privately with a member of the site staff to ask confidential questions and to decline assent for confidential reasons, which, at their request, would not be shared with their parent/guardian, unless required by local law.
- Participants (and their legally authorized representative for adolescents) must be informed that their participation is voluntary. Participants (and their legally authorized representative, defined as parent(s)/legal guardian, for adolescents) will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative 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 medical record must include a statement that written informed consent (including the legally authorized representative [parent/guardian] consent and child/adolescent assent [if deemed appropriate by local ethics review] for adolescents) was obtained before the participant was enrolled in the study and the date the written consent was obtained. For adolescents, the medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/guardian). The authorized person obtaining the informed consent must also sign the ICF.
- Participants (and their legally authorized representative for adolescents) must be re-consented (and re-assented, if appropriate) to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating, where required by local regulations.
- A copy of the ICF(s) must be provided to the participant (and the participant's legally authorized representative for adolescents).
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' 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, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the

confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

See Section 9.5.1.

10.1.5.2. Adjudication/Review Committee Submission

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

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, ECGs, diagnostic tests, pathology reports, autopsy reports, imaging reports (eg, MRI) and death certificate information, as applicable. These documents may be reviewed by Pfizer.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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 results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts the clinical trial results on EudraCT for all Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.
- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor 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 participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory

authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to contract research organization (CRO) if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.
- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.
- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.
- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. 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 supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and study intervention identifiers, participant 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 participant'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. For sites other than a Pfizer clinical research unit (CRU), the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing

    1. Refer to Section 5.1 Inclusion Criteria and Section 8.2.11 Pregnancy Testing for screening pregnancy criteria.

    2. For details of timing of recommended pregnancy testing see the Schedule of Activities.

Table 2. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes	White blood cell (WBC) count with Differential: Total neutrophils Lymphocytes[1] Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood urea nitrogen (BUN) Creatinine Glucose Potassium Sodium Calcium Chloride	Total CO_2 or bicarbonate Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT)	Alkaline phosphatase Direct and Indirect bilirubin Total Bilirubin Uric Acid	Total Protein Albumin Creatine Kinase[2] Follow-up testing for potential DILI cases[3]
Routine Urinalysis[4]	• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination[5] and urine culture[6]			

Table 2. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	• FSH[7] • Pregnancy tests[8] • HIV[9] • HBsAg • HBcAb • HBsAb[10] • HBVDNA[11] • HCVAb • HCVRNA[12] • VZV[13] • QFT-G test or T-Spot test[14] • Viral Screen[15] • Skin biopsies/swabs[16] • Fasting Lipid profile[17] The results of each test must be entered into the CRF.

NOTES:
1. After the screening visit, participants with absolute lymphocyte counts <500/mm^3 (0.5 × 10^9/L) will be reflex tested for FACS TBNK until the absolute lymphocyte count resolves or stabilizes at a level acceptable to the investigator and the sponsor.
2. In addition to re-testing creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with a creatine kinase >10 × ULN for visits on or before Month 36. For participants who have completed the Month 36 visit, creatine kinase and urine myoglobin will not be tested.
3. In cases of suspected potential drug-induced-liver-injury (DILI), follow-up testing should be performed according to requirements in Appendix 5.
4. For participants who have completed the Month 36 visit, urine samples and urinalysis will be performed only if considered clinically indicated by the investigator.
5. Only if urinalysis is performed and urine dipstick is positive for blood, nitrites, leukocyte esterase, and/or protein.
6. Urine culture will be performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated.
7. To confirm postmenopausal status in females under 60 years old who are not using hormonal contraception or hormonal replacement therapy (HRT). This test is not to be performed for WOCBP. Refer to Section 10.4.3.
8. Pregnancy tests (urine) for women of childbearing potential. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests can be utilized.
9. HIV testing per local regulations. Participants who are positive for HIV antibodies will be screen failed.
10. HBsAb will be performed as reflex testing for any participant who is HBsAg negative but HBcAb positive (refer to Appendix 6 for information regarding which screening laboratory results should be used to determine whether HBVDNA testing should be performed). For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at screening for participants in Japan who are de novo participants or participants originating from study B7981015 with >30 days between the first visit of study B7981032 and the last dose in study B7981015 rather than as a reflex test. For Japan specific requirements see Appendix 7. For all other countries, please refer to Appendix 6 for testing algorithm, reflex testing, and full eligibility criteria.

Table 2. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
11. HBVDNA testing will be performed at the time points stated in the Schedule of Activities for participants who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which Hep B prevalence has been reported at a rate of >5.0% or if required by local standard of care (refer to Section 8.2.8.5 for information regarding which screening laboratory results should be used to determine whether HBVDNA testing should be performed). Testing at additional time points may be performed as per the local standard of care. For Japan specific requirements see Appendix 7. For all other countries refer to Appendix 6 for testing algorithm, reflex testing, and full eligibility criteria. 12. HCVRNA will be performed as reflex testing for any participant who is HCVAb positive. 13. VZV Ig Ab testing is required to confirm eligibility only in adolescent participants 12 to <18 years of age without documented evidence of having received the varicella vaccine (2 doses). Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses) per Exclusion #16. 14. The QFT-G test is preferred; however, the T-Spot test is also permitted as described in Section 8.2.8.1. A PPD test can be substituted for the QFT-G test or T-Spot test only under specific circumstances described in Exclusion criterion 19 in Section 5.2.2 and Section 8.2.8.1.2. 15. A serum sample will be collected at Day 1 and submitted to the central lab. The sample will be stored and analyzed at a later date only at the sponsor's request. In certain cases of suspected viral infection (eg, disseminated herpes zoster or varicella), the sponsor may request to analyze the sample to determine if the participant had exposure to that virus. 16. When required in cases of skin rash adverse events. See applicable sections for herpetiform rash (Section 8.2.7.2.1) and potential drug related rash (Section 8.2.7.2.2). 17. Lipid profile panel will include total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides. A minimum of 8-hour fasting is required for lipid profile evaluation. Lipid profile panel will not be tested after the Month 36 visit.	

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • 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.
• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, 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.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse 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 study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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.

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 study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (And EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor" and "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.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

There are no contraceptive methods required for male participants in this study, because PF-06651600 is not likely to transfer to a partner through semen at pharmacologically relevant blood levels.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

- OR

  - Is a WOCBP and using a contraceptive method (see Section 10.4.4) that is highly effective (with a failure rate of <1% per year), as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Women of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception as outlined in Section 10.4.4. If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy

- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormonal replacement therapy (HRT). This test is not to be performed for WOCBP (refer to Schedule of Activities Section 1.3).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- To confirm post-menopausal status, females taking hormonal contraception or HRT must discontinue these for at least 2 weeks prior to performing FSH testing and must remain abstinent during this period until post-menopausal status is confirmed.

10.4.4. Contraception Methods

Contraceptive use by women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Contraceptive 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. Oral, intravaginal, transdermal, or injectable combined (estrogen- and progestogen-containing) hormonal contraception 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).

6. 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.

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.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants 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 participant’s individual baseline values and underlying conditions (See Section 8.2 for the definition of baseline values to be used for the following criteria). Participants 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:

- Participants 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 participants 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 participant

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 for suspected cases of Hy's Law, additional 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, and alkaline phosphatase. 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) and collection of serum sample for acetaminophen drug and/or protein adduct levels 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 liver function test (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.

10.6. Appendix 6: Hepatitis B Testing Algorithm and Full Eligibility Criteria

All de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 will undergo the following screening for hepatitis B for eligibility. **See Appendix 7 for Japan specific requirements.**

For participants in countries in which hepatitis B prevalence has been reported at a rate of >5.0%* or if required by local standard of care, participants will be tested as follows:

1. At screening, HBsAg and HBcAb will be tested:
   a. If both tests are negative, the participant is eligible for study inclusion.
   b. If HBsAg is positive, the participant must be excluded from participation in the study.
   c. If HBsAg is negative and HBcAb is positive, HBsAb and HBVDNA reflex testing is required:
      i. If HBsAb is negative, the participant must be excluded from participation in the study;
      ii. If HBVDNA is detected, the participant must be excluded from participation in the study;
      iii. If HBsAb is positive and HBVDNA is undetectable, the participant is eligible for study inclusion. If the participant is included in the study, for subsequent visits HBVDNA testing must be performed according to the Schedule of Activities.

For participants in all other countries, participants will be tested as follows:

2. At screening, HBsAg and HBcAb will be tested:
   a. If both tests are negative, the participant is eligible for study inclusion.
   b. If HBsAg is positive, the participant must be excluded from participation in the study.
   c. If HBsAg is negative and HBcAb is positive, HBsAb reflex testing is required:
      i. If HBsAb is negative, the participant must be excluded from participation in the study;
      ii. If HBsAb is positive, the participant is eligible for study inclusion. If the participant is included in the study, for subsequent visits no hepatitis B testing is required.

* The Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383-403.

10.7. Appendix 7: Country-specific Requirements

10.7.1. Japan Specific Requirements for HBVDNA Testing

At screening, HBsAg, HBcAb and HBsAb will be tested for participants in Japan who are de novo participants or participants originating from Study B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7981015:

a. If all three tests are negative, the participant is eligible for study inclusion.

b. If HBsAg is positive, the participant must be excluded from participation in the study.

c. If HBsAg is negative, HBcAb is positive and HBsAb is negative, the participant must be excluded from participation in the study.

d. If HBsAg is negative, HBcAb is negative and HBsAb is positive, and prior hepatitis B virus (HBV) vaccination is unequivocally documented, the participant is eligible for the study and does not require HBVDNA monitoring during the study.

e. If HBsAg is negative, HBcAb is negative and HBsAb is positive, and no unequivocal documentation of prior HBV vaccination is available, the participant is required to undergo HBVDNA reflex testing:

    i. If HBVDNA is detected, the participant must be excluded from participation in the study;

    ii. If HBVDNA is undetectable, the participant is eligible for study inclusion. If the participant is included in the study, for subsequent visits HBVDNA testing must be performed according to the Schedule of Activities.

f. If HBsAg is negative, HBcAb is positive and HBsAb is positive, the participant is required to undergo HBVDNA reflex testing:

    i. If HBVDNA is detected, the participant must be excluded from participation in the study;

    ii. If HBVDNA is undetectable, the participant is eligible for study inclusion. If the participant is included in the study, for subsequent visits HBVDNA testing must be performed according to the Schedule of Activities.

10.7.2. China Specific Language for Section 8.5 Pharmacokinetics and Section 8.6 Pharmacodynamics

Section 8.5 Pharmacokinetics and Section 8.6 Pharmacodynamics are updated to remove exploratory analyses performed on pharmacokinetic and pharmacodynamic blood samples collected from participants at sites in China.

Section 8.5 Pharmacokinetics

During all study periods, blood samples (~2 mL) to provide plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K2EDTA) anticoagulant at times specified in the Schedule of Activities section of the protocol.

Blood will be collected at the time points identified in the Schedule of Activities section of the protocol. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. For each blood sample collection, the allowable windows are as follows for time post dose: 0.5 hr (±10 min), 1 hr (±15 min) and 3 hr (±30 min). The date and exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF), as well as the date and time of the previous dose. Samples obtained outside the windows specified in the Schedule of Activities will be considered a protocol deviation.

- The plasma will be stored in appropriately labeled screw capped polypropylene tubes at approximately -20°C or colder within 1 hour of collection.
- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

Section 8.6 Pharmacodynamics

Blood samples (~2.5 mL) will be collected for measurements of immunoglobulin (Ig) (IgA, IgG, IgM) and by fluorescence activated cell sorting (FACS) analysis to identify T cell, B cell, and natural killer (NK) cell subsets and at the time points listed in the Schedule of Activities.

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with applicable Pfizer standard operating procedures. The pharmacodynamic (PD) samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case by case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

10.8. Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in Study B7981032. Additional individual participant 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 participant may be withdrawn at any time at the discretion of the investigator.

For the purposes of safety monitoring and discontinuation, baseline values will be defined as follows:

- For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015:
    - Baseline values will be defined as the values from Day 1 of Study B7981032 (or from screening of Study B7981032 for evaluations not performed at Day 1).
- For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015:
    - Baseline values will be defined as the values from Day 1 of Study B7981015 (or from screening of Study B7981015 for evaluations not performed at Day 1).

10.8.1. Monitoring

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

The following laboratory abnormalities require re-testing until resolution or agreement with Pfizer:

Laboratory Variable	Laboratory Value	Re-testing Timeframe[c]
Hematology		
Absolute Neutrophil Count	<1000/mm^3 (<1.0 × 10^9/L)	Within 1 week
Hemoglobin	<10.0 g/dL (<6.21 mmol/L or <100 g/L)	Within 1 week
Platelet count	<100,000/mm^3 (<100 × 10^9/L)	Within 1 week
Absolute Lymphocyte Count[a]	<600/mm^3 (<0.6 × 10^9/L)	Within 1 week
Serum Chemistry		
Creatine kinase[b]	>3 × ULN	Within 1 week

Laboratory Variable	Laboratory Value	Re-testing Timeframe[c]
Aspartate aminotransferase	See section Appendix 5 for potential cases of drug-induced liver injury.	Within 48 hours
Alanine aminotransferase	See section Appendix 5 for potential cases of drug-induced liver injury.	Within 48 hours
Total bilirubin	See section Appendix 5 for potential cases of drug-induced liver injury.	Within 48 hours

a. After the screening visit, participants with absolute lymphocyte count <500/mm^3 (0.5 × 10^9/L) will be reflex-tested for FACS-TBNK until the absolute lymphocyte count resolves or stabilizes at a level acceptable to the investigator and sponsor.
b. In addition to re-testing creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN for visits on or before Month 36. For participants who have completed the Month 36 visit, creatine kinase and urine myoglobin will not be tested.
c. Based on awareness of the abnormal results.

In case of positive urine pregnancy test, the participant will have study intervention interrupted and a serum sample collected on the same day (or as soon as possible) and submitted to the central laboratory for pregnancy testing.

In the case of either a positive QFT-G, T-Spot, or PPD test result or chest x-ray indicative of active TB, the participant must have study intervention temporarily withheld until it is confirmed by a specialist (eg, pulmonologist or infectious disease specialist) whether the participant has active or latent TB. In the case of active TB, study intervention must be permanently withdrawn. If latent TB is diagnosed by the specialist, the participant may re-start study intervention only with approval by the Pfizer Medical Monitor as described in Section 8.2.8.1.2 and Section 10.14.

10.8.2. Discontinuation

Treatment will be discontinued and the participant withdrawn from this study following completion of the Early Termination visit and the Follow-up Visit (whenever possible) for:

Adverse Events:

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment or meeting other criteria that require the infection to be classified as serious adverse event;
- Treatment-related SAEs;
- Clinically meaningful, treatment-emergent declines in hearing from baseline (refer to Audiometry Study Guide for details) are to be discussed with the sponsor for possible withdrawal from study;

- Other serious or severe AEs, at the discretion of the investigator or sponsor.

ECG Findings (up to Month 36 Visit):

- Confirmed QTc_F >500 milliseconds;
- Confirmed increase from baseline in QTc_F of >60 milliseconds.

Study intervention Interruptions:

- Participants interrupting study intervention for more than 14 consecutive days are to be discussed with the sponsor for possible withdrawal from the study.

Laboratory Abnormalities:

All the following laboratory abnormalities **require discontinuation** if they are confirmed by retest. Refer to the re-testing timeframes for laboratory abnormalities in Section 10.8.1.

- Absolute Neutrophil Count <750/mm^3 (<0.75 × 10^9/L).
- Hemoglobin <9.0 g/dL (<5.59 mmol/L or <90 g/L) or a decrease of >30% from baseline (either criterion or both).
- Platelet count <75,000/mm^3 (<75.0 × 10^9/L).
- Absolute Lymphocyte Count <500/mm^3 (<0.5 × 10^9/L).

NOTE: After the screening visit, participants with absolute lymphocyte count <500/mm^3 (0.5 × 10^9/L) will be reflex tested for FACS-TBNK until the absolute lymphocyte count resolves or stabilizes at a level acceptable to the investigator and sponsor.

- Creatine kinase >10 × ULN (for visits on or before Month 36).

NOTE: In addition to re-testing creatine kinase >3 × ULN, urine myoglobin will be performed as reflex testing for any participant with creatine kinase >10 × ULN for visits on or before Month 36. For participants who have completed the Month 36 visit, creatine kinase and urine myoglobin will not be tested.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that meet ANY of the following:
  - >3 times the upper limit of normal with at least one total bilirubin value >2 times the ULN;
  - >3 times the upper limit of normal accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

- Two sequential AST or ALT elevations >5 times ULN, regardless of total bilirubin or accompanying signs or symptoms.

NOTE: In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the sponsor or designee.

Pregnancy:

- Female participants confirmed as pregnant during the study (see Section 8.3.5).

Prohibited Medications:

- Participants who are treated with any prohibited medication during the course of the study may require discontinuation. Participants who are administered a prohibited medication are to be discussed with the sponsor for possible withdrawal from the study.

Suicidal Ideation:

- Participants with suicidal ideation associated with actual intent and a method or plan in the past year: a "yes" answer on items 4, 5, or on any question in the suicidal behavior section of the C-SSRS must be discontinued. The participant must be referred to a mental health professional for appropriate evaluation and treatment or immediately referred to the Emergency Room at the investigator's judgement.

Discontinuation/End of Treatment Monitoring:

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

10.9. Appendix 9: Prohibited and Permitted Concomitant CYP3A Inducers and Substrates

Please note that this list addresses only CYP3A inducers and CYP3A substrates. Other prohibited medications for this trial are listed in Section 6.5.2. Refer to Section 6.5.1 for additional information regarding permitted medications for this trial, including CYP3A inhibitors.

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are moderate to potent CYP3A inducers or sensitive or moderate sensitive CYP3A substrates. If a medication is a sensitive or moderate sensitive CYP3A substrate and is not listed below as prohibited or permitted, consultation with the sponsor is required.

10.9.1. Prohibited Concomitant CYP3A Inducers and Substrates

Sensitive CYP3A Substrates[##]	Moderate Sensitive CYP3A Substrates[§]	Moderate to Potent CYP3A Inducers**
Dasatinib	Aprepitant	Avasimibe[#]
Dronedarone	Eliglustat	Bosentan
Ebastine	Pimozide	Barbiturates
Lomitapide	Rilpivirine	Carbamazepine[#]
Nisoldipine		Efavirenz
Sirolimus		Etravirine
Tacrolimus		Mitotane[#]
Tolvaptan		Modafinil
		Nafcillin
		Phenobarbital[#]
		Phenytoin[#]
		Rifabutin[#]
		Rifampin [#]
		St. John's Wort[#]
		Talviraline

** All prohibited drugs that are CYP3A inducers require at least a 28 day or 5 half-lives (whichever is longer) washout prior to the first dose of study intervention.
In a situation where appropriate medical care of a participant requires the use of a prohibited CYP3A inducer: Moderate to potent inducers of CYP3A are not permitted in the study EXCEPT in emergency situations. *Note: Mitotane is not permitted for any duration due to its long half-life; however, if necessary mitotane may be used in an emergency, however the participant will then be discontinued from the study*.
Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.
Notated as potent inducers.
Sensitive CYP3A substrates are drugs that demonstrate an increase in concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies.
§ Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

10.9.2. Permitted Concomitant CYP3A Substrates

Sensitive CYP3A Substrates[##]		**Moderate Sensitive CYP3A Substrates[§]**
Alfentanil	Midazolam	Alprazolam
Avanafil	Naloxegol	Atorvastatin
Buspirone	Quetiapine	Colchicine
Darifenacin	Sildenafil	Rivaroxaban
Eletriptan	Simvastatin	Tadalafil
Eplerenone	Ticagrelor	
Felodipine	Triazolam	
Lovastatin	Vardenafil	
Lurasidone		

Sensitive CYP3A substrates are drugs that demonstrate an increase in concentration-time curve (AUC) of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies.
Topical (including skin or mucous membranes) application of antimicrobial and antifungal medications is permitted.
§ Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

10.10. Appendix 10: Vaccine Sub-Study

Sub-Study Title:

A Study of Immune Responses Following Administration of Meningococcal and Tetanus Vaccines in Adult Participants with Alopecia Areata Receiving PF-06651600.

SUMMARY

The purpose of this sub-study is to evaluate the effect of PF-06651600 50 mg QD on primary immune responses to the meningococcal group C polysaccharide of a meningococcal (groups A, C, W-135 and Y [ACWY]) oligosaccharide diphtheria CRM_{197} conjugate vaccine, and on secondary (booster) immune responses to tetanus toxoid administered in a tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine in adult participants with AA. The effect of PF-06651600 treatment on the safety of meningococcal ACWY and Tdap vaccinations will also be evaluated. The participants can be enrolled to receive both vaccines or one of the two vaccines. Not all countries participating in the B7981032 study will be included in this sub-study. The vaccine sub-study will be performed at sites in the US, Canada, and Australia. Note: the vaccine sub-study will not be conducted at sites within the VHP countries in the EU (ie, Czech Republic, Germany, Hungary, Poland, and Spain).

Participants in this sub-study must have received at least 6 months of treatment with PF-06651600 50 mg QD in the main B7981032 study. They will continue to receive the study intervention (PF-06651600 50 mg QD) in the main B7981032 study while participating in the vaccine sub-study. The sub-study will be approximately 1 month (standardized 30 days) in duration and visits will occur at baseline and at Month 1. The sub-study baseline will occur at the same time as a scheduled main B7981032 study visit on or after Month 6 (for participants originating from Study B7931005 or B7981015) or after Month 7 (for de novo participants), and before or at Month 56 of the main B7981032 study.

SCHEDULE OF ACTIVITIES

Procedures to be performed in addition to activities described in Section 1.3.

Table 3. Vaccine Sub-Study Additional Procedures

Procedure	Sub-Study Baseline (Day 1)	Sub-Study Month 1 (Day 31)	Notes Baseline visit must occur at a scheduled study visit in the main B7981032 study.
Visit	1	2	
Window	None	+5 days	
Informed consent	X		Separate informed consent for vaccine sub-study required.
Review Inclusion and Exclusion criteria	X		
Collect pre-vaccination blood samples for titers[a]	X		
Administer Tdap and/or meningococcal ACWY vaccinations[b]	X		
Collect post-vaccination blood samples for titers[c]		X	
Physical Examination	X	X	For Day 1, targeted or full exam as per scheduled visit in main B7981032 study; for Month 1, targeted exam
Vital signs	X	X	For Day 1, as per scheduled visit in main B7981032 study
Laboratory testing: hematology & serum chemistry	X	X	For Day 1, as per scheduled visit in main B7981032 study
Adverse event monitoring	X	X	
Drug accountability	X	X	

Abbreviations: ACWY = groups A, C, W-135 and Y; Tdap = tetanus and diphtheria toxoids and acellular pertussis.

a. Pre-vaccination blood samples for titers will be collected based on the vaccine(s) to be administered to the participant on Day 1.

b. Participants may receive both vaccines, only Tdap vaccine, or only meningococcal ACWY vaccine.

c. Post-vaccination blood samples for titers will be collected based on the vaccine(s) received by the participant on Day 1.

INTRODUCTION

The United States Centers for Disease Control and Prevention (CDC) guidelines for vaccination recommend administration of various vaccines, including tetanus toxoid and meningococcal vaccines as well as boosters, over the lifetime of the individual.[1] PF-06651600 affects the signaling of several cytokines thought to be important in humoral and cellular immunity via blockade of the JAK3 enzyme. In addition, PF-06651600 inhibits members of the TEC family of kinases which may also contribute to its immunomodulatory properties. The effects of PF-06651600 on immunogenicity following vaccination has not been evaluated. Findings from the sub-study will inform whether vaccination during PF-06651600 treatment could affect generation of primary or secondary (ie, booster) immunogenicity responses. The sub-study findings will therefore be useful for informing clinical practice of PF-06651600 in patients with AA.

The sub-study will assess immunogenicity to tetanus (administered as Tdap) booster vaccination and meningococcal C polysaccharide (administered as meningococcal ACWY) primary vaccination in adult participants with AA undergoing treatment with PF-06651600 in Study B7981032.

Information for PF-06651600 is provided in the current version of the IB. More detailed information about the known and expected benefits and risks and reasonably expected AEs of the Tdap and meningococcal ACWY vaccinations may be found in the current versions of the US prescribing information (USPI) for Adacel[2] and MENVEO[3], respectively. The actual local product labels for the vaccinations used at each site should be referenced.

Sub-Study Rationale

Vaccination with Tdap allows evaluation of the effects of PF-06651600 on secondary (booster) immune response since tetanus is a common vaccination in children/adolescents and most adults should have received at least one primary tetanus immunization. CDC guidelines recommend one dose of Tdap and then boosters with tetanus and diphtheria toxoids (Td) vaccine every 10 years.[1]

Vaccination with meningococcal ACWY allows evaluation of the effects of PF-06651600 on primary immune responses. Meningococcal vaccination is currently uncommon in adults because routine meningococcal vaccination in the US started in 2005.[4-6] It is, however, recommended per CDC guidelines for administration to adolescents (and high susceptibility adults) to offer protection from meningococcal serogroups A, C, Y and W-135 disease. The immunologic correlate of clinical protection by meningococcal vaccines is serum bactericidal activity (SBA).[7,8] For assessment of the immune response to the meningococcal vaccine, functional antibodies will be analyzed in SBA assays using human complement with strains representing meningococcal serogroup C. The immunogenicity to serogroup C will be evaluated in this study as it has the most clinical relevance in North America.[9]

Immunogenicity for both Tdap and meningococcal ACWY reported in the product labels was evaluated approximately 1 month after administration (ie, at 28 days[2,3] post vaccination).

An effect of Tdap adsorbed vaccination or meningococcal ACWY vaccination on AA disease activity or disease course is not expected. It is therefore considered acceptable to add the vaccine sub-study to the main B7981032 study.

Risk/Benefit Assessment

The administration of tetanus vaccine as a booster in adults is consistent with vaccine guidelines worldwide. The response to booster vaccination with tetanus is expected to provide information on immunogenicity for secondary immune responses to a T-dependent antigen (as contained in Tdap) during treatment with PF-06651600. For adults, the administration of meningococcal ACWY vaccination as a primary vaccine has been recommended by CDC for individuals with additional risk factors or other special situations.[1] The response to meningococcal vaccination is expected to provide findings on immunogenicity for a primary immune response (in individuals previously not vaccinated or infected) during treatment with PF-06651600.

Administration of the vaccines during PF-06651600 treatment may potentially result in reduced immunogenicity to Tdap and meningococcal ACWY vaccinations. Concentrations of antibodies against specific vaccine antigens will be measured to evaluate the effect of PF-06651600 on immunogenicity.

In the Tdap adsorbed product information, the most frequent adverse reactions reported in >5% of adults following a second vaccination included: injection site reactions (including pain, swelling and erythema), myalgia, headache and malaise.[2] In the meningococcal groups A, C, W-135 and Y oligosaccharide diphtheria CRM_{197} conjugate vaccine product information, the most common adverse reactions reported in >5% of adults following primary vaccination included injection site reactions (including pain, erythema, and induration), headache, myalgia, malaise, nausea, and arthralgia.[3] Other than the risks described in the product information, no unique risks related to vaccination are expected.

Overall, the benefit-risk of the immunogenicity sub-study in B7981032 participants is considered favorable.

STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Evaluate immune response to Tdap vaccination in AA participants treated with PF-06651600.	• Proportion of participants achieving a booster response, defined as 1) ≥4-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the pre-vaccination concentration was ≤2.7 IU/mL; 2) ≥2-fold rise in anti-tetanus toxoid IgG antibody concentration at Month 1 if the

Objectives	Endpoints
	pre-vaccination concentration was >2.7 IU/mL.
Secondary	
• Evaluate immune response to meningococcal ACWY vaccination in AA participants treated with PF-06651600.	• Proportion of participants achieving ≥1:8 human serum bactericidal activity (hSBA) (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C.
• Evaluate immune responses to Tdap and meningococcal ACWY vaccinations based on other vaccine response endpoints in AA participants treated with PF-06651600.	Tdap vaccination: • Proportion of participants with anti-tetanus antibody level ≥1.0 IU/mL on Month 1. • Proportion of participants with anti-tetanus antibody level ≥0.1 IU/mL on Month 1. • Proportion of participants with ≥4× increase in anti-tetanus antibody level from baseline. • Fold increase in anti-tetanus levels above baseline values at Month 1. • Geometric mean concentrations (GMCs) of anti-tetanus antibody levels on Month 1. Meningococcal ACWY vaccination: • Proportion of participants achieving ≥1:4 hSBA (in participants with undetectable pre-vaccination assay titers) at Month 1 post-vaccination for serogroup C. • Geometric mean titers (GMTs) of antibodies for serogroup C at baseline and on Month 1.

Objectives	Endpoints
• Evaluate safety of tetanus and meningococcal ACWY vaccinations in AA participants treated with PF-06651600.	• Incidence of SAEs and AEs. • Incidence of SAEs and AEs leading to discontinuation.

STUDY DESIGN

This is a sub-study evaluating immunogenicity to vaccine antigens following Tdap and meningococcal ACWY vaccinations in adult participants with AA enrolled in the main B7981032 study. The participants can be enrolled to receive both vaccines or one of the two vaccines as follows:

- Participants who meet the eligibility criteria for both vaccines should be enrolled to receive both vaccines.
- Participants who meet the eligibility criteria only for Tdap vaccine should be enrolled to receive Tdap vaccine only.
- Participants who meet the eligibility criteria only for meningococcal ACWY vaccine should be enrolled to receive meningococcal ACWY vaccine only.

It is estimated that a total of approximately 60 participants eligible to receive the Tdap vaccine, with or without the meningococcal ACWY vaccine, will be enrolled in this sub-study. The sub-study participants will continue their participation and study treatment as assigned in the main B7981032 study. Study participants are required to provide a separate informed consent for the vaccine sub-study. All eligible participants participating in the sub-study must continue with all study assessments of the main study per the B7981032 Schedule of Activities.

PARTICIPANT SELECTION

The following eligibility criteria are designed to select participants for whom participation in the sub-study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this sub-study is suitable for a specific participant.

Sub-Study Inclusion Criteria for All Participants

B7981032 participants in select countries/sites only will be included in this sub-study. The vaccine sub-study will be performed at sites in the US, Canada and Australia. Note: the vaccine sub-study will not be conducted at sites within the VHP countries in the EU (ie, Czech Republic, Germany, Hungary, Poland, and Spain). Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's

study team before participants are included in the sub-study. Participants need to maintain eligibility to continue receiving study intervention (PF-06651600) in the main B7981032 study in order to participate in the sub-study. In addition, participants must meet all of the following inclusion criteria to be eligible for enrollment into the sub-study:

1. Male or female AA participants in B7981032 who, at the time of consent for this sub-study, are:

   - ≥18 to ≤55 years of age, if receiving **both** vaccines or **only** meningococcal ACWY vaccine;

   - ≥18 to ≤64 years of age, if receiving **only** Tdap vaccine.

2. Participants who have received PF-06651600 50 mg QD for ≥6 months in Study B7981032:

   a. For participants who received study intervention in study B7931005 or B7981015: ≥6 months after first dose of study intervention in study B7981032;

   b. For de novo participants: ≥7 months after first dose of study intervention in study B7981032.

3. In the preceding time in B7981032, participant is compliant with receiving study intervention described in Section 6.4. In addition, participant should not miss any dose of PF-06651600 for at least 7 consecutive days just prior to Day 1 of this sub-study.

4. Evidence of personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the sub-study. A separate informed consent for this sub-study is required (see Section 10.1.3 for informed consent process).

5. Participants who are willing and able to comply with scheduled procedures for this sub-study.

Additional Sub-Study Inclusion Criterion for Participants Receiving Tdap Vaccine (With or Without Meningococcal ACWY Vaccine)

6. Must have had prior tetanus vaccination ≥5 years before Day 1 of the sub-study.

Sub-Study Exclusion Criteria for All Participants

Excluded will be participants with:

1. History of any severe AE associated with any vaccination.

2. Safety concerns at time of vaccination, including anyone with unresolved laboratory abnormalities meeting monitoring criteria.

3. History of Guillain-Barre syndrome or brachial neuritis.

4. Presence of any unstable neurological conditions or history of seizures.

5. The following conditions are temporary or self-limiting and a participant may participate in the vaccine sub-study once the condition(s) has/have resolved, no other exclusion criteria are met, and following consultation with the Pfizer study clinician:

    a. Current febrile illness (oral temperature ≥38°C [100.4°F]) or other acute illness within 48 hours before sub-study vaccine administration.

    b. Receipt of antibiotic therapy for acute illness within 72 hours before sub-study vaccine administration.

6. Any other acute or chronic medical or psychiatric condition that may increase the risk associated with sub-study participation or vaccine administration or that may interfere with the interpretation of sub-study results and, in the judgment of the investigator or Pfizer (or designee), would make the participant inappropriate for entry into this sub-study.

Additional Sub-Study Exclusion Criteria for Participants Receiving Tdap Vaccine (With or Without Meningococcal ACWY Vaccine)

7. Hypersensitivity to any component of the Tdap vaccine.

8. History of Arthus-type hypersensitivity reactions after previous dose of tetanus vaccines.

9. Any condition that would make participant unsuitable for receiving the Tdap vaccine based upon product information.

Additional Sub-Study Exclusion Criteria for Participants Receiving Meningococcal ACWY Vaccine (With or Without Tdap Vaccine)

10. Prior history of meningococcal ACWY vaccination or history of meningococcal disease.

11. Hypersensitivity to any component of the meningococcal ACWY vaccine.

12. Any condition that would make participant unsuitable for receiving the meningococcal ACWY vaccine based upon product information.

STUDY INTERVENTION

Enrolled participants will either receive single doses of both Tdap and meningococcal ACWY vaccines, or a single dose of only one of the two vaccines, per the applicable product labels. Study treatment with PF-06651600 50 mg QD will continue as per the main B7981032 study.

Study Intervention Supplies

ARM Name	Tdap	Meningococcal ACWY
Intervention Name	Tetanus, diphtheria and pertussis vaccine	Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide Diphtheria CRM_{197} conjugate vaccine
Type	Vaccine	Vaccine
Dosage Form	Injectable	Injectable
Dose Strength	See local product information	See local product information
Dosage	See local product information	See local product information
Route of Administration	Intramuscular injection	Intramuscular injection
IMP or Non-IMP	Non-IMP	Non-IMP
Sourcing	Sourcing to be determined for each country in which the sub-study is run based on local requirements/guidelines	Sourcing to be determined for each country in which the sub-study is run based on local requirements/guidelines
Packaging and Labeling	Provided in commercial package	Provided in commercial package

Abbreviations: IMP = investigational medicinal product.

Administration

A single dose of Tdap vaccine will be administered to the participants who are eligible to receive the Tdap vaccine (ie, those who meet eligibility criteria for all participants and for those receiving Tdap vaccine) on Day 1 of the sub-study. A locally approved vaccine product containing tetanus, diphtheria and pertussis must be used. The Tdap vaccine must be administered by the intramuscular route. For complete instructions regarding storage and administration, please refer to the product label.

A single dose of meningococcal ACWY vaccine will be administered to the participants who are eligible to receive the meningococcal ACWY vaccine (ie, those who meet eligibility criteria for all participants and for those receiving meningococcal ACWY vaccine) on Day 1 of the sub-study. A locally approved vaccine product containing meningococcal (Groups A, C, W-135 and Y) oligosaccharide diphtheria CRM_{197} conjugate must be used. The meningococcal vaccine must be administered by the intramuscular route. For complete instructions regarding storage and administration, please refer to the product label.

In participants who receive both vaccines, the meningococcal ACWY vaccine may be given at the same time as the Tdap vaccination but in a separate injection site, preferably in a different limb. The two vaccines must not be mixed in the same syringe.

The participant should be observed for at least 30 minutes after vaccine administration to assess any acute reactions.

Compliance

Administration of both vaccines will be verified by review of source documents by the study monitor. Participants will continue with protocol-specified procedures in the main study.

ASSESSMENTS

Assessments are to be performed as described in Section 8 and according to the Schedule of Activities in the main B7981032 study protocol and the Schedule of Activities in the vaccine sub-study.

ADVERSE EVENT REPORTING

See Section 8.3 and Appendix 3 of the main B7981032 study.

STATISTICAL CONSIDERATIONS

Data analysis for the vaccine sub-study will be conducted when all enrolled participants have completed or withdrawn from this sub-study. Results from this analysis are considered final for the sub-study.

Methodologies for summary and statistical analyses of data collected in this sub-study are summarized here and further detailed in the statistical analysis plan (SAP) for this sub-study which will be dated and maintained by Pfizer.

Sample Size Determination

With 60 participants receiving the Tdap vaccine (with or without the meningococcal ACWY vaccine), assuming a similar observed immune response rate as reported in the product label (74.5% of participants achieving booster response as defined by anti-tetanus toxoid antibody levels pre-vaccination and on Month 1), the estimated half width of 95% confidence interval (CI) is 11% for the response rate to Tdap vaccination. The probability of observing at least 65% booster response rate for the tetanus vaccination is approximately 95.4%, assuming the booster response rate of 74.5%.

Analysis of Immunogenicity Endpoints

For the immunogenicity endpoints, two Full Analysis Sets (FAS) will be defined depending on the vaccine(s) received. The Full Analysis Set for Tdap (FAS-Tdap) is defined as all participants who receive the Tdap vaccine (with or without the meningococcal ACWY

vaccine); the Full Analysis Set for ACWY (FAS-ACWY) is defined as all participants who receive the meningococcal ACWY vaccine (with or without the Tdap vaccine).

The primary analysis will be descriptive in nature; there will be no formal hypothesis testing, although 95% two-sided CIs will be generated. The analyses for endpoints related to the Tdap vaccine will be based on the FAS-Tdap, whereas the analyses for endpoints related to the meningococcal ACWY vaccine will be based on the FAS-ACWY.

The number and percentage of participants who achieve the defined immune responses will be presented for the primary endpoint and binary secondary endpoints with 95% two-sided CIs based on Clopper-Pearson exact method.

For GMCs of anti-tetanus toxoid antibody concentrations, GMTs for meningococcal serogroup C antibody titers, and fold increases in anti-tetanus toxoid antibody levels above baseline values, geometric mean and 95% CI based on back transformation of the log-transformed data will be provided.

Safety Analysis

Safety analyses for this sub-study will be based on the Safety Analysis Set (SAS) defined as all participants from this sub-study who receive at least 1 dose of the vaccine (Tdap or meningococcal ACWY). All safety data from this sub-study will be reported using a similar approach and methods as the main study (see Section 9.4.3).

Interim Analysis

No interim analysis is planned for this sub-study.

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10.11. Appendix 11: Discontinuation Criteria for Worsening of Alopecia Areata for VHP Countries in the EU

Within the VHP countries in the EU, participants who meet the following criteria at Month 6 or any subsequent visit of Study B7981032 must be permanently discontinued from study intervention and complete the Early Termination visit and the Follow-up Visit (whenever possible). The VHP countries participating in this study are: Czech Republic, Germany, Hungary, Poland, and Spain.

Status at Baseline*	**Action at Month 6 or any subsequent visit**
AT/AU	Discontinuation not required
SALT AA >75	Discontinuation not required
SALT AA ≥25 to ≤75	Discontinuation required if AA "worsening", defined as change from baseline* in absolute SALT overall score ≥25 points

* Baseline values are defined as follows:

- For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015:
  - Baseline values will be defined as the values from Day 1 of Study B7981032 (or from screening of Study B7981032 for evaluations not performed at Day 1).
- For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015:
  - Baseline values will be defined as the values from Day 1 of Study B7981015 (or from screening of Study B7981015 for evaluations not performed at Day 1).

10.12. Appendix 12: Study Intervention Continuation Criteria for Adolescents

Adolescent participants ≥12 to <18 years of age at the time of the Day 1 visit (in B7981032 for de novo participants or in B7981015 for participants originating from Study B7981015) must meet the following criteria in Study B7981032 in order to continue study intervention. Adolescent participants who do not meet the following criteria must be permanently discontinued from study intervention and complete the Early Termination visit and the Follow-up Visit.

Table 4. Study B7981032 Study Intervention Continuation Criteria for Adolescents

Group	Criteria at Month 3 or any prior visit* in Study B7981032**	Criteria at Month 6 or any prior visit* in Study B7981032+
De novo participants	Not applicable	Absolute SALT score ≤20
Participants originating from Study B7981015	Improvement of ≥50% in absolute SALT score from the SALT score at Day 1 in Study B7981015. For example, a participant with a B7981015 Day 1 SALT score of 78 must have a SALT score of ≤39 at the B7981032 Month 3 or prior visit in order to continue study intervention.	Absolute SALT score ≤20

* For participants originating from Study B7981015 with ≤30 days between the last dose in B7981015 and the first visit in B7981032, prior visits include the B7981015 Week 48 or Early Termination visit.
** For participants who have completed the B7981032 Month 3 visit but not the Month 6 visit at the time of Protocol Amendment 4 approval for a site, only the Month 6 criteria will be checked at the scheduled Month 6 visit and will be based on achieving the SALT ≤20 score at the Month 6 visit or any prior visits.
\+ For participants who have already completed the B7981032 Month 6 visit at the time of Protocol Amendment 4 approval for a site, the Month 6 criteria must be checked at the next scheduled visit and will be based on achieving the SALT ≤20 score at that visit or any prior visits.

10.13. Appendix 13: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the coronavirus disease 2019 (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. **NOTE:** Any deviations from the Schedule of Activities or the protocol (eg, missed or partially completed procedures or assessments) must be reported to the sponsor in a timely manner and will be reported by the sponsor as a protocol deviation.

Procedures which are missed due to disruptions related to a public emergency, including the COVID-19 pandemic, are required to be performed at the next available opportunity, even if outside of a protocol-specified visit window.

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).

10.13.1. Eligibility

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) testing is not mandated for this study, local clinical practice standards for testing should be followed. A de novo patient or a participant originating from B7931005 and B7981015 with >30 days from the first study visit of Study B7981032 and the last dose in the index study should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. De novo patients and participants originating from B7931005 and B7981015 with >30 days from the first study visit of Study B7981032 and the last dose in the index study with active infections are excluded from study participation per Exclusion #17. When the infection resolves, the patient may be considered for re-screening.

For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit in Study B7981032 and the last dose in Study B7931005 or B7981015 and who are being considered for enrollment into Study B7981032:

- The participant must be able to perform all Screening and Day 1 procedures per the Schedule of Activities at the study site and/or designated ancillary facility (eg, for audiological evaluations and chest radiographs) in order to determine whether the participant meets eligibility criteria for Study B7981032. This includes collection and resulting of laboratory assessments through the central laboratory vendor.

- The participant must meet eligibility criteria for Study B7981032.

- It must be anticipated that the participant will be able to have the B7981032 Week 2 and Month 1 safety laboratory tests collected/performed at the study site or an alternative clinical laboratory facility according to the windows in Table 5 in Section 10.13.3.1.

- If a participant does not meet the criteria described above, the participant cannot be enrolled in the B7981032 study.

For participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015 and who are being considered for enrollment into Study B7981032:

- The participant must meet eligibility criteria for Study B7981032.
- The participant must be able to have safety laboratory tests collected at their final visit in Study B7981015 at the study site or an alternative clinical laboratory facility.
- The participant (if a WOCBP) must be able to have pregnancy testing performed at their final visit in Study B7981015 and the Day 1 visit in B7981032 (if applicable) at the study site, at an alternative clinical laboratory facility, or at the participant's home.
- The participant must be able to have the Day 1 tuberculosis test collected between the time of signing consent/assent for B7981032 and the Week 2 visit (inclusive) at the study site or an alternative clinical laboratory facility.
- It must be anticipated that the participant will be able to have the B7981032 Week 2 and Month 1 safety laboratory tests collected/performed at the study site or an alternative clinical laboratory facility according to the windows in Table 5 in Section 10.13.3.1.
- For participants who are not able to complete all required B7981015 Week 48 or Early Termination procedures and/or B7981032 Day 1 procedures per the respective protocol, these cases must be discussed with the Pfizer B7981032 study team prior to the final visit in Study B7981015 to obtain agreement that the participant may be suitable for entry into B7981032.
- If a participant does not meet the criteria described above, the participant cannot enter the B7981032 study.

10.13.2. 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. 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 (e.g., 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 dosing logs and record study intervention(s), including doses taken and any interruptions in intake of study intervention (ie, missed doses) since the last contact, and calculate compliance.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- For WOCBP: 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 Appendix 4, Section 10.4.4. Refer to Section 8.2.11 of the protocol and Section 10.13.3.1 of this appendix regarding pregnancy tests and to Section 5.3.1 of this protocol regarding contraception checks.
- For premenarchal female participants: Check for initiation of menarche per Section 8.2.12 of this protocol.
- Collection of updated audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation.
- Body temperature and collection method (eg, oral, tympanic, axillary, or temporal), and pulse rate (measured by study participant/caregiver).
- Administration of the C-SSRS performed by a qualified rater. Per Section 8.2.9.1, if there are "yes" answers on items 4 or 5 of the suicidal ideation section or on any question in the suicidal behavior section of the C-SSRS, the participant will be discontinued from the study and referred to a mental health professional for appropriate evaluation and treatment.
- **NOTE:** If the investigator determines that additional evaluation is warranted based on the information collected during the remote visit described above, follow-up is required to be performed, with results submitted to and reviewed by the investigator prior to shipping study intervention to the participant.

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

10.13.3. Alternative Facilities for Safety Assessments

10.13.3.1. Laboratory Testing

With the exceptions noted in Section 10.13.1 of this appendix for Screening and Day 1, 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. Collection of blood and urine samples may also be performed at the participant's home per Section 10.13.5 of this appendix. The following safety laboratory evaluations may be performed at a local laboratory or in the participant's home:

- Hematology
- Serum chemistry
- Lipid panel (for visits on or before Month 36)
- Urinalysis (for visits after Month 36, urinalysis will be performed only if considered clinically indicated by the investigator)
- Pregnancy testing (for WOCBP)
- Day 1 and annual tuberculosis testing
- Refer to the Schedule of Activities for visits at which these tests are required and to Appendix 2 for additional details regarding these tests.

If it is not possible for the participant to have the above tests completed within the visit window specified in the Schedule of Activities, an extended window may be allowed to collect samples for these laboratory tests, provided that the investigator has performed the remote visit as described above, assessed each case, and determined that it would not increase risk to a participant. The extended windows for laboratory sample collection for each study visit are noted in Table 5. These windows apply only to laboratory samples collected during interruptions due to public emergencies, including the COVID-19 pandemic, based upon written notification from Pfizer. If the laboratory samples are not collected within the specified extended window for the visit, the participant must temporarily withhold study intervention until the required laboratory samples can be collected.

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 and must be received and reviewed by the investigator within 14 days after they are collected in order to determine eligibility to continue dosing. In addition, laboratory test results from the previous visit must be available and reviewed by the investigator prior to shipping study intervention at the current visit. The local laboratory reports must be filed in the participant's source documents/medical records. Relevant data from the local laboratory report must be recorded on the CRF.

Special attention should be paid to ensure that laboratory results are checked against the Guidelines for Participant Safety Monitoring and Discontinuation in Appendix 8 and that required follow-up is performed as applicable.

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. Urine pregnancy test results may be collected based on information provided by the participant (or their legally authorized representative, if appropriate) during the remote visit. **The urine pregnancy test result must be available prior to dispensing or shipping study intervention to a participant.** The pregnancy test outcome must 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.

NOTE: Pregnancy testing (for WOCBP) between scheduled study visits and study site contact with participants to obtain pregnancy test results is required to continue as outlined in the Schedule of Activities and Section 8.2.11 of the protocol.

Table 5. Windows for Remote Visits and Laboratory Sample Collections if Required due to Public Emergencies, Including the COVID-19 Pandemic

Visit (Day in Study)	Remote Visit Window (Day in Study)[a]	Lab Collection Window (Day in Study)[b]
Week 2 (Day 15)	±3 days (Day 12-18)	±3 days (Day 12-18)
Month 1 (Day 31)	±3 days (Day 28-34)	-3 / +30 days (Day 28-61)
Month 3 (Day 91)	±7 days (Day 84-98)	-14 / +30 days (Day 77-121)
Month 6 (Day 181)	±7 days (Day 174-188)	-14 / +30 days (Day 167-211)
Month 9 (Day 271)	±7 days (Day 264-278)	-14 / +30 days (Day 257-301)
Month 12 (Day 361)	±7 days (Day 354-368)	-14 / +30 days (Day 347-391)
Month 15 (Day 451)	±7 days (Day 444-458)	-14 / +30 days (Day 437-481)
Month 18 (Day 541)	±7 days (Day 534-548)	-14 / +30 days (Day 527-571)
Month 21 (Day 631)	±7 days (Day 624-638)	-14 / +30 days (Day 617-661)
Month 24 (Day 721)	±7 days (Day 714-728)	-14 / +30 days (Day 707-751)
Month 28 (Day 841)	±7 days (Day 834-848)	-14 / +30 days (Day 827-871)
Month 32 (Day 961)	±7 days (Day 954-968)	-14 / +30 days (Day 947-991)
Month 36 (Day 1081)	±7 days (Day 1074-1088)	-14 / +30 days (Day 1067-1111)
Month 40 (Day 1201)	±7 days (Day 1194-1208)	-14 / +30 days (Day 1187-1231)
Month 44 (Day 1321)	±7 days (Day 1314-1328)	-14 / +30 days (Day 1307-1351)
Month 48 (Day 1441)	±7 days (Day 1434-1448)	-14 / +30 days (Day 1427-1471)
Month 52 (Day 1561)	±7 days (Day 1554-1568)	-14 / +30 days (Day 1547-1591)
Month 56 (Day 1681)	±7 days (Day 1674-1688)	-14 / +30 days (Day 1667-1711)
Month 60 (Day 1801)	±7 days (Day 1794-1808)	-14 / +30 days (Day 1787-1831)

a. These are the same as the windows in the protocol Schedule of Activities (Section 1.3.2).
b. Laboratory results must be received and reviewed by the investigator within 14 days after they are collected to determine eligibility to continue dosing. In addition, laboratory test results from the previous visit must be available and reviewed by the investigator prior to shipping study intervention at the current visit.

10.13.3.2. Chest Radiography

For de novo participants and participants with >30 days between the first visit in Study B7981032 and the last dose in Study B7931005 or B7981015, the Screening chest radiograph must be performed at the study site or designated ancillary center per Section 8.2.4.

If the participant requires a Day 1 (for participants with ≤30 days between the first visit in Study B7981032 and the last dose in Study B7981015) or annual chest radiograph (for all participants) per Section 8.2.4 and is unable to visit the study site or designated ancillary center for the chest radiograph, the participant may visit an alternative facility to have the chest radiograph performed. Qualified study site personnel must order, receive, and review results.

10.13.3.3. Electrocardiograms

For de novo participants and participants with >30 days between the first visit in Study B7981032 and the last dose in Study B7931005 or B7981015, the Screening and Day 1 ECG must be performed at the study site or designated ancillary center per Section 8.2.5. For ECGs after Day 1 (all participants), if the participant is unable to visit the study site for an ECG, the participant may visit an alternative facility to have the ECG performed according to the guidelines in Section 8.2.5. Qualified study site personnel must order, receive, and review results.

10.13.3.4. Audiological Evaluation

For de novo participants and participants with >30 days between the first visit in Study B7981032 and the last dose in Study B7931005 or B7981015, the Screening audiological evaluation must be performed at the study site or designated ancillary center per Section 8.2.6. For visits requiring audiological evaluations after Day 1 (all participants), if the participant is unable to visit the study site or designated ancillary center for an audiological evaluation, the audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) must be collected during the remote visit per Section 10.13.2 of this appendix (or home health visit per Section 10.13.5). The audiological evaluation must be performed per Section 8.2.6 at the next available opportunity, even if outside of a protocol-specified visit window.

10.13.4. Study Intervention

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 intervention must be considered.

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

If a third-party courier engaged by Pfizer or Pfizer's CRO **is used** for shipping the study intervention, written consent must be documented in the informed consent document prior to shipping study intervention. If a third-party courier engaged by Pfizer or Pfizer's CRO **is not used** for shipping the study intervention, consent must be verbally obtained (or per local guidelines/regulations) and documented in site's source documents prior to shipping study intervention.

Prior to shipping study intervention to a participant, 1) consent must be obtained and documented as described above, 2) all required safety information listed in Section 10.13.2 must have been collected and reviewed by the investigator, 3) the required laboratory tests from the previous visit must have been reviewed by the investigator, and 4) any additional evaluation (if requested based on investigator judgment) must have been performed, with results submitted to and reviewed by the investigator.

Study intervention cannot be shipped to the participant and must be temporarily discontinued if 1) the laboratory tests from the previous visit have not been reviewed by the investigator OR 2) after reviewing the required information (including that from a remote visit), the investigator cannot make an assessment of whether it is safe for the participant to continue study intervention. Refer to Section 6.4 regarding temporary withholding of study intervention.

The study site may deliver the study intervention to participants using an acceptable delivery method only if this is consistent with local laws and regulations and the site is able to ship the study intervention according to the guidelines provided by the sponsor in a separate document.

The amount of study intervention to be shipped should correspond to the amount dispensed per the Impala Quick Reference Guide at the specific study visit which is being conducted remotely. Dispensing and/or shipment of additional study intervention to extend the visit window is not permitted.

Participants should continue taking the current supply of study intervention until the new supply is received (unless temporary withholding of study intervention is required).

Dosing logs should be shipped with the study intervention.

Study sites should follow up with the participant once the study intervention is received by the participant to review when to start using the new blister cards or the new bottles, the dosing instructions, and completion of the dosing logs.

Participants should be instructed not to re-use or dispose of any blister cards or bottles dispensed at a previous visit (with the exception of the Week 2 visit).

All blister cards, or bottles, and dosing logs must be returned to the study site at the next on-site visit.

10.13.5. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities if operationally feasible and will be conducted according to local regulations. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site.

If a third-party engaged by Pfizer or Pfizer's CRO is used for home health visits, written consent must be documented in the informed consent document prior to conducting the first home health visit. If a third-party engaged by Pfizer or Pfizer's CRO is not used for home health visits, consent must be verbally obtained (or per local guidelines/regulations) and documented in site's source documents prior to conducting the first home health visit.

The following may be performed during a home health visit:

- Review dosing logs and record study intervention(s), including doses taken and any interruptions in intake of study intervention (ie, missed doses) since the last contact, and calculate compliance.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- For WOCBP: 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 Appendix 4, Section 10.4.4. Refer to Section 8.2.11 of the protocol and Section 10.13.3.1 of this appendix regarding pregnancy tests.
- For premenarchal female participants: Check for initiation of menarche.
- Collection of updated audiological history (Part 1 in the Audiometry Study Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation.
- Body temperature and collection method (eg, oral, tympanic, axillary, or temporal), pulse rate, and blood pressure.
- ECG per Section 8.2.5
- Hematology
- Serum chemistry
- Lipid panel (for visits on or before Month 36)

- Urinalysis (for visits after Month 36, urinalysis will be performed only if considered clinically indicated by the investigator)
- Pregnancy testing (for WOCBP)
- Day 1 and annual tuberculosis testing
- Physical examination

10.13.6. Adverse Events and Serious Adverse Events

If a participant has a confirmed or suspected COVID-19 infection during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. For non-serious COVID-19 infections, temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from the COVID-19 infection. If this is a serious infection (ie, requires parenteral antimicrobial therapy or hospitalization for treatment or meeting other criteria that require the infection to be classified as a serious adverse event), the participant must be permanently discontinued from study intervention per Appendix 8, Section 10.8.2 of the protocol.

10.13.7. Efficacy Assessments

Efficacy assessments listed in Section 8.1 are only to be collected during on-site visits. This includes SALT, ELA, EBA, fingernail assessment, CGI-AA, all patient reported outcomes, and the BRIEF®2. In addition, photographs described in Section 8.1.4 will only be collected during on-site visits.

10.14. Appendix 14: Management of Participants with a Positive Tuberculosis Test Result on Day 1 or Annual Tuberculosis Testing

The following evaluation process applies to participants WITHOUT either a positive QFT-G (or T-Spot or PPD, if applicable) test result during prior testing (including screening visits in Study B7931005, B7981015 or B7981032, as applicable) or a history of previous treatment for active or latent TB. For participants WITH either a positive TB test result during prior testing or a history of previous treatment for active or latent TB, refer to Section 8.2.8.1.2.

Per Section 8.2.8.1.2, participants with a positive QFT-G (or T-Spot or PPD, if applicable) test result must be evaluated to determine whether the participant has latent or active TB, and to determine whether study intervention may be re-started. **NOTE:** Repeat QFT-G (or T-Spot or PPD, if applicable) testing should not be performed unless specifically requested by the specialist (eg, pulmonologist or infectious disease specialist). The following process should be followed:

- Perform a chest radiograph or other appropriate diagnostic chest imaging (ie, computed tomography or MRI).
- Once the chest radiograph results are available, have the participant referred to a specialist (eg, infectious disease specialist or pulmonologist). The results of the recent chest radiograph, TB test (ie, QFT-G, T-SPOT, or PPD) and any other relevant information should be provided to the specialist.
- If the specialist diagnoses active TB, the participant is required to be permanently withdrawn from study intervention.
- If the specialist diagnoses latent TB:
    - The specialist should establish a treatment plan for latent TB based on the participant's best interest and local standard of care, taking into account that the participant would be receiving an immunosuppressive study intervention in B7981032. The local incidence rates of TB and multi-drug resistant TB should be considered.
    - Once the treatment plan for latent TB is established, the PI should provide to the sponsor the English translation of the specialist's report, the treatment plan recommended by the specialist, and local incidence rate of multi-drug resistant TB infection.
    - Upon review of the relevant documentation, the sponsor's Medical Monitor may give approval to re-start study intervention.
        - Depending on the time off study intervention, the participant may be required to complete an on-site visit prior to re-starting study intervention.

- Note that the only latent TB treatment that will be considered for concomitant use with study intervention is INH. Participants taking INH concomitantly with study intervention should also receive vitamin B6 supplementation for the duration of INH treatment (as appropriate per opinion of the treating physician).

- If study intervention is permitted to be re-started, at the next annual visit (ie, Month 12, 24, 36, 48 or 60), a chest radiograph is required to be performed (a QFT-G, T-SPOT, or PPD test need not be obtained).

- If the specialist determines that the participant does not have latent or active TB in spite of a positive QFT-G (or T-Spot or PPD, if applicable) test result:

  - The specialist must provide the following:

    - An unequivocal documented diagnosis that the participant does not have latent or active TB. A rationale for this medical opinion, which takes into consideration local incidence rates of TB and multi-drug resistant TB, must also be provided.

    - A statement as to whether treatment for latent TB should be instituted.

    - A statement as to whether it is safe for the participant to receive the immunosuppressive study intervention in B7981032.

  - The English translation of the specialist's report must be forwarded to the sponsor for review.

  - If the sponsor's Medical Monitor grants approval then study intervention may be re-started.

    - Depending on the time off study intervention, the participant may be required to complete an on-site visit prior to re-starting study intervention.

  - If study intervention is permitted to be re-started, QFT-G testing (or T-SPOT or PPD, if applicable) will be required at the next visit per the protocol Schedule of Activities (ie, Month 12, 24, 36, 48 or 60); in this case the recent test has been effectively deemed a 'false positive' by the specialist and the participant is considered to be WITHOUT a true positive QFT-G (or T-Spot or PPD, if applicable) test result at this visit.

10.15. Appendix 15: Abbreviations

Abbreviation	Term
5-ARI	5α-Reductase inhibitors
AA	Alopecia areata
AA SALT	Severity of Alopecia Tool alopecia areata (used interchangeably with SALT AA)
AAPPO	Alopecia areata patient priority outcomes
AARU	Alopecia areata resource utilization
ACWY	groups A, C, W-135 and Y
AE	Adverse event
AESI	adverse event of special interest
AGA	androgenetic alopecia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Alopecia totalis
ATP	Adenosine triphosphate
AU	Alopecia universalis
AUC	Area under the concentration-time curve
BAEP	brainstem auditory evoked potentials
BCR	B cell receptor
BMX	Bone marrow tyrosine kinase on chromosome X
BP	Blood pressure
BRI	Behavior Regulation Index
BRIEF®2	Behavior Rating Inventory of Executive Function®, Second Edition
BTK	Bruton's tyrosine kinase
C_{avg}	Average steady state drug concentration
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CFB	Change from baseline
CFP-10	Culture filtrate protein 10 kiloDalton
CFR	Code of Federal Regulations
CGI-AA	Clinician Global Impression - Alopecia Areata
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CRF	Case report form
CRI	Cognitive Regulation Index
CRO	Contract research organization
CRU	Clinical research unit
CSR	Clinical study report

Abbreviation	Term
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Clinical Trial
CTA	Clinical trial application
CYP450	Cytochrome P450
CYP3A	Cytochrome P450, family 3, subfamily A
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DNCB	1-chloro-2,4-dinitrobenzene
DPCP	Diphenylcyclopropenone
EBA	Eyebrow Assessment
EBV	Epstein Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
E-DMC	External data monitoring committee
EDP	Exposure during pregnancy
eGFR	Estimated glomerular filtration rate
ELA	Eyelash assessment
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQoL 5 dimensions
EQ-5D-Y	EuroQoL 5 Dimensions—Youth
ERI	Emotional Regulation Index
ESAT-6	Early secreted antigenic target of 6 kiloDalton
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS-TBNK	Fluorescence-activated cell sorting for T-cells, B-cells, and natural killer (NK) cells
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMC	geometric mean concentrations
GMT	geometric mean titers
GPSP	Good Post Marketing Surveillance Practices
HADS	Hospital Anxiety and Depression Scale
HBcAb	Hepatitis B core antibody

Abbreviation	Term
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBVDNA	Hepatitis B virus deoxyribonucleic acid
HCRU	Healthcare resource utilization
HCVAb	Hepatitis C antibody
HCV RNA	Hepatitis C virus ribonucleic acid
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
hSBA	human serum bactericidal activity
HTA	Health technologies assessment
IB	Investigator's brochure
ICF	Informed consent document
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IgA	Immunoglobin A antibody
IgG	Immunoglobulin G antibody
IgM	Immunoglobin M antibody
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug application
INH	isoniazid
INR	International normalized ratio
IP	Investigational product
IP-10	Interferon gamma-induced protein 10
IRB	Institutional review board
IRT	Interactive response technology
ITK	Interleukin 2 inducible T cell kinase
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVRS	Interactive voice response system
IWRS	Interactive web response system
JAK	Janus kinase
J-NDA	Japan New Drug Application
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
LFT	Liver function test
LOAEL	Lowest observed adverse effect level

Abbreviation	Term
MHLW,	Ministry of Health, Labour and Welfare
MMF	Mycophenolate mofetil
MMR	Measles, mumps, rubella
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imaging
MTX	Methotrexate
NK	Natural killer
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
ObsRO	observer reported outcomes
PACL	Protocol administrative change letter
PCD	Primary completion date
PD	Pharmacodynamic
PGI-C	Patient's global impression of change
PHQ-8	Patient health questionnaire – 8 items
PI	Principal investigator
PK	Pharmacokinetic
PPD	Purified protein derivative
PRO	Patient reported outcome
P-Sat	Patient's Satisfaction with Hair Growth
PT	Prothrombin time
PUVA	Psoralen ultraviolet A
QD	Once daily
QFT-G	QuantiFERON®-TB Gold In–tube test
QoL	Quality of life
QT interval	Time from the beginning of the QRS complex to the end of the T wave
QTc_F	QT corrected using Fridericia's correction factor
RA	Rheumatoid Arthritis
RNA	Ribonucleic acid
SADBE	Squaric acid dibutylester
SAE	Serious adverse event
SALT	Severity of Alopecia Tool
SALT ≤10	Response based on achieving absolute Severity of Alopecia Tool (SALT) score ≤10, for overall and AA SALT score
SALT ≤20	Response based on achieving absolute SALT score ≤20, for overall and AA SALT score
SALT50	50% improvement in SALT score from baseline
SALT75	75% improvement in SALT score from baseline
SALT AA	Severity of Alopecia Tool alopecia areata (used interchangeably with AA SALT)
SALT AGA	Severity of Alopecia Tool androgenetic alopecia

Abbreviation	Term
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SBA	serum bactericidal activity
SF-36v2 Acute	36-Item Short Form Health Survey version 2 Acute
SoA	Schedule of Activities
SOP	Standard operating procedure
SRSD	Single reference safety document
STAT	Signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TBili	Total bilirubin
TCR	T cell receptor
Td	tetanus and diphtheria toxoids
Tdap	tetanus and diphtheria toxoids and acellular pertussis
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse event
TEC	Tyrosine kinase expressed in hepatocellular carcinoma
TH1	Type 1 helper
TP1	Treatment Period 1
TP2	Treatment Period 2
T-Spot test	T-SPOT®.*TB*
TYK2	Tyrosine kinase 2
TXK	tyrosine kinase expressed in T cells
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
ULN	Upper limit of normal
UTI	Urinary Tract Infection
UVB	Ultraviolet B
VHP	Voluntary Harmonisation Procedure
VZV	Varicella zoster virus
VZV IgG Ab	Varicella zoster virus immunoglobulin G antibody
WOCBP	Woman of childbearing potential
WPAI:AA	Work productivity and activity impairment: alopecia areata

10.16. Appendix 16: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5 (23 April 2021)

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis, Section 1.2: Schema; Section 1.3: Schedule of Activities; Section 4.1: Overall Design; Section 4.2; Scientific Rationale for Study Design; Section 4.3: Justification for Dose	Study extension for all participants (de novo or originating from Study B7981015 or B7931005) to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36.	Study extended to 36 months based on regulatory feedback to obtain longer-term safety and efficacy data from adolescent participants with alopecia areata (AA) receiving PF-06651600 and based on sponsor decision to also extend the study duration for adult participants.
Section 1.3.2: Intervention Period	Added that the contraception check will also be performed monthly between study visits at the time of the phone contact to check the at-home pregnancy test results.	This was made for consistency with the Protocol Deviation Alert Letter (dated 12Nov2020).
Section 1.3.2: Intervention Period; Section 8.2.11: Pregnancy Testing	Added clarification that the site contact to check pregnancy test results between visits will occur via telephone contact.	This was made for consistency with the Protocol Deviation Alert Letter (dated 12Nov2020) and with the case report form (CRF) collection for this study.
Section 1.3.2: Intervention Period	Added clarification for timing of pharmacokinetic (PK) sampling.	Added as PK may be skipped at visits under the alternative measures during public emergencies, including the COVID-19 pandemic, as outlined in Appendix 21.
Section 1.3.2: Intervention Period; Section 1.3.3: Early Termination and Follow-up; Section 8.6: Pharmacodynamics; and Section 10.2, Appendix 2: Clinical Laboratory Tests; Section 10.8, Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation.	Clarified timing for collection of samples for reflex testing of fluorescence activated cell sorting (FACS) analysis of samples for T cell, B cell, and natural killer cell (TBNK) subsets, and that separate blood samples will be collected for FACS TBNK samples.	These changes were made to be consistent with the central laboratory manual, which requires a separate 5 mL collection tube for FACS TBNK samples.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2: Intervention Period	Created subsection (Section 1.3.2.2) for intervention period for receipt of open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36, to distinguish from Schedule of Activities for intervention period through Month 24. Updated subsection for Week 2 to Month 24 (Section 1.3.2.1) to reference study procedures from Month 28 through Month 36/EOT.	These changes were made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36.
Section 1.3.2.1: Intervention Period: Week 2 to Month 24	Removed 12-lead ECG procedure for Month 18 visit.	Reduced the frequency of ECG assessments to occur yearly after the Month 12 visit, as the sponsor has performed an analysis of applicable nonclinical and clinical data that indicate that the risk for PF-06651600 to cause clinically meaningful QT prolongation in humans is low.
Section 1.3.3: Early Termination and Follow-Up	Added statements to clarify the patient reported outcomes (PROs) that will not be reported at the Early Termination visit for participants who have completed the Month 24 visit: 36 Item Short Form Health Survey version 2 (SF36v2), EuroQoL 5 Dimensions (EQ-5D-5L), EuroQoL 5 Dimensions Youth (EQ-5D-Y), Alopecia Areata Resource Utilization (AARU), and WPAI:AA (Work Productivity and Activity Impairment: Alopecia Areata).	These changes were made for consistency with Section 1.3.2 in which select PROs are not collected after Month 24.
Section 1.3.3: Early Termination and Follow-up; Section 7.1: Discontinuation of Study Intervention	Added statement for study visit continuation for participants that discontinue study intervention.	Added in order to collect data in participants who have discontinued study intervention.
Section 1.3: Schedule of Activities; Section 8.1: Efficacy Assessments; Section 8.2: Safety Assessments; Section 10:	Removed Section 10 appendices for copyrighted instruments (Severity of Alopecia Tool [SALT], Columbia Suicide Severity Rating Scale [C-SSRS], Hospital Anxiety and	Updated per current practice not to include copyrighted instruments in protocol appendices.

Section # and Name	Description of Change	Brief Rationale
Supporting Documentation and Operational Considerations	Depression Scale [HADS], EuroQol 5 Dimensions [EQ-5D-5L], EuroQol 5 Dimensions – Youth [EQ-5D-Y], Patient Health Questionnaire – 8 Items [PHQ-8], 36-Item Short Form Health Survey Version 2 Acute [SF-36v2 Acute], and Tanner Stages of Development) as well as cross-references to the deleted appendices.	
Section 3: Objectives, Estimands and Endpoints	Added clarification for timing of endpoints.	These changes were made to provide clarification for the timing of each endpoint, to account for a potential extension of the study duration beyond Month 36 (eg, in the event of a regulatory authority request).
Section 4.4: End of Study Definition	Added definition for primary completion date (PCD).	These changes were made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36, and in the event the study duration is extended beyond Month 36 (eg, per a regulatory authority request).
Section 4.4.1: Expanded Study Duration	Language added to provide the option for study extension (eg, per a regulatory authority request).	This change was made to allow for participants to continue to receive study intervention beyond Month 36 (eg, if requested by a regulatory authority.)
Section 5.2: Exclusion Criteria; Section 6.5.2: Prohibited Concomitant Medications	Removed restrictions for medications that cause QT prolongation.	Sponsor has performed an analysis of applicable nonclinical and clinical data, which indicate that the risk for PF-06651600 to cause clinically meaningful QT prolongation in humans is low. Prohibition of these medications is no longer required.
Section 5.3.1: Contraception;	Updated text to clarify the time period, including the time after last	These changes were made as some participants may

Section # and Name	Description of Change	Brief Rationale
Section 5.3.2: Cosmetic Treatments/Applications; Section 5.3.5: Elective Surgery; Section 6.5.2: Prohibited Concomitant Medications; Section 6.5.3: Vaccinations; Section 6.5.4: Surgery	dose, under which the restrictions apply.	remain in the study without study intervention per updates in Section 7.1.
Section 6.5.3: Vaccinations	Added text to clarify that vaccines (including COVID-19 vaccines) that are not live attenuated are permitted.	Added to provide affirmatory clarity given the widespread use of COVID-19 vaccines in the setting of the COVID-19 pandemic.
Section 8: Study Assessments	Updated maximum amount of blood to be collected from a participant over the duration of the study.	This change was made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36 and with clarifications regarding FACS TBNK sample collection in Sections 1.3.2, 1.3.3, 8.6, and 10.2.
Section 8: Study Assessments	Added statement regarding handling of participant medical records if requested by the sponsor.	This change was made to align text for handling of participant medical records in Section 10.3.3.
Section 8.1.2.1.1: Androgenetic Alopecia SALT Score; Section 8.1.3.5: EQ-5D-5L and EQ-5D-Y; Section 8.1.3.9: Behavior Rating Inventory of Executive Function®, Second Edition (BRIEF®2); Section 8.2.11: Pregnancy Testing; Section 9.4.1: Efficacy Analyses	Updated assessment timing for participants that receive open-label 50 mg PF-06651600 QD through Month 36.	These changes were made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36.
Section 8.2.3: Vital Signs; Section 10.13.2: Telehealth visits; Section 10.13.5: Home Health Visits	Respiratory rate has been removed from the vital sign measurements.	Respiratory rate is considered to have little utility for safety monitoring or reporting purposes.
Section 8.2.8.1.2; Appendix 22, Section 10.22	Added clarification of the process (included in Appendix 22) for	Clarification added, which is consistent with updates

Section # and Name	Description of Change	Brief Rationale
	participants with a positive tuberculosis (TB) test result during the study.	made in B7981032 Protocol Amendment 4.
Section 8.3.5.1: Exposure During Pregnancy	Updated language to include reporting of pregnancies in female partners of male participants and to add the routes of exposure to study intervention.	To correct an error made in Protocol Amendment 4 when updating for consistency with the protocol template.
Section 9.3: Populations for Analyses; Appendix 22, Section 10.22: List of Abbreviations	Updated efficacy analysis population to define Full Analysis Set (FAS) and added the definition of the PK population.	FAS definition added for consistency with updates made in Study B7981015, per regulatory agency request, and PK population definition added for consistency with Section 9.4.4.
Section 9.4.1: Timing of the Analyses	Added specification for PCD analysis and potential for supplemental analysis in the event of study duration extension beyond Month 36 (eg, due to regulatory authority request).	These changes were made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36, and to include a supplemental analysis if participants continue to receive study intervention beyond Month 36 (eg, upon request by a regulatory authority).
Appendix 1, Section 10.1.5.2: Adjudication/Review Committee Submission	Added language for sponsor review of source documents to support event adjudication by the Adjudication/Review Committee.	This change was made for consistency with language in the March 2021 protocol template, Section 4.2.3 Adjudication Committee.
Appendix 4, Section 10.4.3: Women of Childbearing Potential	Added language regarding use of contraception if a participant's childbearing potential or risk of pregnancy changes after the start of the study.	This change was made for consistency with Sections 5.3.1 and 8.2.12.
Appendix 10, Section 10.10: Summary	Updated timing for which participants from the main B7981032 study can participate in the vaccine sub-study.	This change was made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36.

Section # and Name	Description of Change	Brief Rationale
Appendix 10, Section 10.10: Summary; Schedule of Activities; Study Design, Participant Selection; Study Intervention	Updated vaccine sub-study to allow participants to either receive both meningococcal ACWY and Tdap vaccines or just one of the two vaccines, and to match age requirements in Tdap label for participants who receive only Tdap vaccine.	Increased flexibility of vaccine sub-study vaccine requirement to allow enrollment of participants eligible to receive only one of the vaccines.
Appendix 10, Section 10.10: Introduction, References for Vaccine Sub-Study	Updated information for the Tdap and meningococcal ACWY vaccines to reference the US prescribing information (USPI). References to single reference source documents (SRSD) for the vaccines in the sub-study were also removed as these are non-IMP.	These updates were made for clarification and consistency with the change made in the Study Intervention section of the sub-study, which specifies these as non-IMP.
Appendix 10, Section 10.10: Study Objectives and Endpoints	Updated primary endpoint to only include immune response to Tdap vaccination; immune response to meningococcal ACWY vaccination moved to a secondary endpoint.	These updates were made due to the expectation that only a smaller number of participants is likely to be eligible for receiving the meningococcal ACWY vaccine.
Appendix 10, Section 10.10: Study Intervention	Updated table for study intervention supplies to include a row that specifies whether each study intervention (vaccine) is an investigational medicinal product (IMP) or non-IMP.	Added clarification that the Tdap and meningococcal ACWY vaccines are considered non-IMPs in the United States, Canada, and Australia, where the vaccine sub-study is planned to be conducted.
Appendix 10, Section 10.10: Statistical Considerations	Updated vaccine sub-study sample size to be based on the number of participants who receive the Tdap vaccine (with or without meningococcal ACWY vaccine).	These changes were made to align with the changes to allow vaccine sub-study participants to either receive both meningococcal ACWY and Tdap vaccines or just one of the two vaccines, and due to the expectation that more participants are likely to be eligible for Tdap vaccine than for meningococcal ACWY vaccine.
Appendix 10, Section 10.10: Statistical Considerations	Defined vaccine sub-study Full Analysis Sets (FAS) and Safety Analysis Set (SAS).	These changes were made to align with the changes to allow vaccine sub-study participants to either receive both meningococcal

Section # and Name	Description of Change	Brief Rationale
		ACWY and Tdap vaccines or just one of the two vaccines, and due to the expectation that more participants are likely to be eligible for Tdap vaccine than for meningococcal ACWY vaccine.
Appendix 10, Section 10.10: Summary, Participant Selection	Added Australia as a country location for the vaccine sub-study.	Updated to clarify that the vaccine sub-study will also be conducted at site(s) in Australia.
Appendix 13, Section 10.13.3.1	Specified windows for remote visits and laboratory sample collections for participants that receive open-label 50 mg PF-06651600 QD through Month 36.	These changes were made to align with the changes for participants to continue to receive open-label 50 mg PF-06651600 QD for 12 additional months, through Month 36.
Appendix 16, Section 10.16: Protocol Amendment History	Moved table for Amendment 4 descriptions of changes and brief rationales to this appendix.	Following Pfizer's standard procedure for the common protocol template.
Throughout document.	Other relatively minor administrative/typo/formatting updates.	Updated for grammatical correctness, clarity, consistency with Pfizer Global Style Guide and protocol template.

Amendment 4 (31 August 2020)

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Updates were made to the Objectives and Endpoints table.	These changes were made to align with changes made to the Objectives and Endpoints table in Section 3.
Section 1.1: Synopsis; Section 4.1: Study Design, Overall Design; Section 4.2: Scientific Rationale for Study Design; Section 9.2: Sample Size Determination	The number of de novo participants was updated, with a corresponding update to the total sample size, and reference to the number of participants from the index studies B7931005 and B7981015 was removed. In addition, the number of sites was updated.	Updated the total sample size to more accurately reflect the actual number of participants expected to be enrolled. Reference to number of participants from Study B7931005 and B7981015 was removed considering the uncertainty regarding the number of participants willing and eligible to be enrolled in Study B7981032 from each of the index studies. The number of sites was updated to more accurately reflect the actual number of sites expected to participate in this study.
Section 1.3: Schedule of Activities, table footnotes; Section 8.1.3.3: Patient's Satisfaction with Hair Growth (P-Sat); Appendix 22: Abbreviations	For Patient's Satisfaction with Hair Growth (P-Sat), "(3-items)" was removed from the title of the instrument.	Updated for consistency with the title of the instrument, which does not include a description of the number of items.
Section 1.3: Schedule of Activities; Section 4.1: Study Design, Overall Design	Reference to Appendix 21, Alternative Measures During Public Emergencies, was added.	This change has been made to clarify alternative measures to accommodate study procedures during the public emergencies, including the COVID-19 pandemic. This change is consistent with the protocol administrative change letter dated 05 June 2020.
Section 1.3.1: Schedule of Activities, Screening and Day 1	Under the Laboratory Section, Serum FSH, added a reference to Section 10.4.3 and clarifying text.	This change was added to provide clarity regarding FSH testing in postmenopausal women and to instruct that this testing will not be performed in WOCBP.
Section 1.3.1: Schedule of Activities, Screening and Day 1	Under Patient Reported Outcomes section, AARU, second paragraph in the Notes	This update was made to clarify which visit was referred to for this PRO.

Section # and Name	Description of Change	Brief Rationale
	column: "first visit" was updated to "Day 1 visit"	
Section 1.3.2: Schedule of Activities, Intervention Period	Under Clinical Assessments section, Photography: in the Notes column, Section 8.1.3.9 was changed to Section 8.1.4.	This change was made to update the Section header to its correct number.
Section 1.3.2: Schedule of Activities, Intervention Period	Under Observer Reported Outcomes Section, BRIEF®2: the shading in columns for Months 1 and 3 was removed.	Updated for clarification as BRIEF®2 is not administered at these timepoints.
Section 1.3.2, Schedule of Activities, Intervention Period	Under Other Section: Added a row titled, "Check for study intervention continuation criteria for adolescents" and timepoints at Months 3 and 6. A Section reference and notes were added to the Notes column.	This addition was made to align with updates made in Appendix 10.8.2.
Section 2.2.2: Nonclinical and Phase 1 Efficacy and Safety Data	The text related to exposure margins was updated.	These changes have been made to provide updated information to sites.
Section 2.2.3: Clinical Experience; Section 2.2.3.1: Phase 2a Study in Alopecia	Information was updated to include new ongoing studies with PF-06651600. In addition, a statement was added to indicate that the final results of the Phase 2a study in participants with alopecia areata (B7931005) are now available in the Investigator's Brochure. The header title of Section 2.2.3.1 was updated to Phase 2a Study in Alopecia Areata.	These changes have been made to provide updated information now available in the January 2020 Investigator's Brochure. The header title was updated to include the full name of the study intervention indication.
Section 3: Objectives, Estimands and Endpoints	The following secondary endpoints were moved to tertiary endpoints: -Absolute SALT scores at all time points collected, for overall and AA SALT score -Response based on achieving at least 50% improvement in SALT (SALT50) from baseline at all time points	These changes were made to align with regulatory feedback for the B7981015 protocol to reduce the number of secondary endpoints.

Section # and Name	Description of Change	Brief Rationale
	collected, for overall and AA SALT score - Change from baseline in 36-Item Short Form Health Survey version 2 Acute (SF36v2 Acute) at all time points collected	
Section 3: Objectives, Estimands and Endpoints	The following secondary endpoint was removed: - Absolute score of Patient's Global Impression of Change (PGI-C) at all time points collected; The definition for the secondary endpoint of PGI-C response was updated to the following: - PGI-C response defined as a PGI-C score of "moderately improved or greatly improved" at all timepoints collected. The following tertiary endpoint was added: - Improvement on PGI-C defined as "slightly improved", moderately improved", or "greatly improved" at all time points collected	These changes have been made to align with regulatory agency feedback for the B7981015 protocol to report on multiple aspects of this patient reported outcome.
Section 3: Objectives, Estimands and Endpoints	The tertiary endpoint for the P-Sat was revised from a continuous score to a categorical assessment to accurately indicate a participants categorical improvement at the item level.	These changes have been made because the scaling and scoring for this patient reported outcome is still in the process of being established.

Section # and Name	Description of Change	Brief Rationale
Section 3: Objectives, Estimands and Endpoints	Reference to the specific domain scores were removed from the secondary endpoint evaluating a change from baseline in the AAPPO. The scales are now described in section 8.1.3.1.	These changes have been made because the validation for this patient reported outcome has now been completed to reflect the correct domains.
Section 3: Objectives, Estimands and Endpoints	The secondary endpoint evaluating a change from baseline in the HADS was split into two separate endpoints to clarify that the depression and anxiety subscales will be analyzed separately. In addition, the secondary endpoint assessing participants with baseline HADS subscale scores indicative of depression or anxiety were revised and split into 2 separate endpoints.	These changes have been made to align with feedback from the developer's scoring manual and clinical experts in AA to analyze depression and anxiety separately and to measure a change in individual subscales.
Section 4.1: Overall Design	The text describing de novo participant characteristics was updated.	Update made for consistency with revisions to inclusion #1 in Section 5.1.1.
Section 4.3: Justification for Dose	Minor revisions were made to this section and data were updated in Table 1.	Revisions were made to provide updated study information.
Section 5: Study Population	The text regarding participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose of the index study was updated.	Updated for consistency with revisions made in Exclusion Criterion #1.
Section 5.1.1: Inclusion Criteria for De Novo Participants and Those Originating From B7931005 or B7981015 with ≥ 30 Days Between the Index Study and Study B7981032	Inclusion Criterion #1 was updated to require ≥50% terminal scalp hair loss (previously ≥25%) for de novo participants ≥12 to <18 years of age at the time of signing informed consent/assent.	To address regulatory agency feedback, Pfizer modified the Study B7981032 inclusion criteria to require that de novo adolescent participants at the time of the B7981032 Day 1 visit have ≥50% (changed from ≥25%) terminal scalp hair loss due to AA (including

Section # and Name	Description of Change	Brief Rationale
		AT and AU) at both the screening and Day 1 visits.
Section 5.1.3: Inclusion Criteria for All Participants	The following text was added to Inclusion Criterion #4: "Within the UK, participants must be 18 years of age or older."	Added per request of MHRA (Medicines and Healthcare Products Regulatory Agency) to clarify that within the UK, participants below the age of 18 years are not permitted.
Section 5.1.3: Inclusion Criteria for All Participants	References to sections in Appendix 4 were added.	Appendix 4 was updated to align with the latest version of the Pfizer protocol template.
Section 5.2.1: Exclusion Criteria for Participants Originating from B7981015 with ≤30 Days between Studies	Exclusion Criterion #1 was updated to: "During Study B7981015 or in the period between the index study and Study B7981032, presence of safety events meeting discontinuation criteria in Appendix 8, Section 10.8.2 (eg, serious infections, laboratory results, ECG results)"	For clarity, the VHP country specific Discontinuation Criteria for Worsening of AA was moved from Appendix 8, Section 10.8.2 to the separate Appendix 19. Consequently, the section reference was updated to refer specifically to Section 10.8.2. As such, reference to the discontinuation criteria for worsening AA was removed from this criterion as it is not applicable in the context of Exclusion criterion #1.
Section 5.2.2: Exclusion Criteria for De Novo Participants and Those Originating From B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032	In Criterion #11, "Exclusion Criterion 21" was updated to "Exclusion Criterion 19".	Update was made because the numbering for this criterion had changed. The content of the criterion did not change.
Section 5.2.3: Exclusion Criteria for all Participants	The following text was added to Exclusion Criterion #16: "This criterion is not applicable to sites where enrollment of adolescent participants is not permitted (see Inclusion #4)."	Added for clarification
Section 5.2.3: Exclusion Criteria for all Participants	Exclusion Criterion #25, item d, was updated to refer to immunosuppressants instead of immune suppressants.	Updated for consistency with Section 6.5.2.
Section 5.2.3: Exclusion Criteria for all Participants	Exclusion Criterion #25, item i, was updated to state that psychiatric drugs and antihypertensives are prohibited unless allowed by	Updated for clarification

Section # and Name	Description of Change	Brief Rationale
	the sponsor (changed from "may be acceptable if approved" to "prohibited unless approved"	
Section 5.3.1: Contraception	The text in this section was updated.	This change was made to align with the current version of the Pfizer protocol template.
Section 5.3.1: Contraception	The following text was deleted: "Participants who are WOCBP must agree to use one highly effective method of contraception (as specified in Appendix 4), as applicable." Text was added to include consultation with the participant's parent/legal guardian (if required for adolescent participants).	This change was made to align with the current version of the Pfizer protocol template. This text was added to account for adolescent participants in the study.
Section 6.5.2: Prohibited Concomitant Medications	Text was updated to state that psychiatric drugs and antihypertensives are prohibited unless allowed by the sponsor (changed from "may be acceptable if approved" to "prohibited unless approved"	This change was made to align to changes made to Exclusion Criterion #25 in Section 5.2.3: Exclusion Criteria for All Participants.
Section 7: Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal	References added to Appendix 8, Appendix 19, and Appendix 20.	Updated based on changes made in Appendix 8 and the addition of Appendix 19 and Appendix 20.
Section 8: Study Assessments and Procedures	Text regarding the following was added: • Completion of screening evaluations • Completion of protocol-required tests and procedures • Information regarding provision of instructions for samples being collected and shipped.	These changes were made to align with the current version of the Pfizer protocol template.
Section 8: Study Assessments and Procedures	Added that all Day 1 evaluations must be	This text was added for clarification.

Section # and Name	Description of Change	Brief Rationale
	completed and reviewed to confirm that potential de novo participants and participants originating from B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and the last dose in Study B7931005 or B7981015 meet all eligibility criteria prior to randomizing the participant in Impala.	
Section 8: Study Assessments and Procedures	References to the following appendices were added: Appendix 19, Discontinuation criteria for Worsening AA in VHP countries in the EU. Appendix 20, Study Intervention Continuation Criteria for adolescents. Appendix 21, Alternative Measures During Public Emergencies,	 These criteria were moved from Appendix 8 as they are not safety discontinuation criteria. This change has been made to address regulatory agency feedback regarding discontinuation criteria for adolescents without adequate clinical response to limit their total exposure to chronic study treatment. Based on this, Pfizer modified the B7981032 protocol in order to minimize the time that non-responder adolescent participants are exposed to PF-06651600 treatment in Study B7981032. This change has been made to clarify alternative measures to accommodate study procedures during the public emergencies, including the COVID-19 pandemic. This change was previously communicated to sites in the protocol administrative change letter dated 05 June 2020.
Section 8.1.3.1: Alopecia Areata Patient Priority Outcomes (AAPPO)	Language was added to this section providing information on the anchor-based methodology to be used for	This change has been made for clarification.

Section # and Name	Description of Change	Brief Rationale
	the interpretation of the AAPPO.	
Section 8.1.3.4: Hospital Anxiety and Depression Scale (HADS)	Language was updated to correct the description of the subscales for the HADS.	This change has been to limit any observer bias at sites.
Section 8.2: Safety Assessments	Text regarding unscheduled clinical laboratory assessments was added.	This change was made to align with the current version of the Pfizer protocol template.
Section 8.2.3: Vital Signs	Language was updated to allow for the use of temporal artery temperature measurements.	This change has been made to reflect current clinical practice for temperature measurement.
Section 8.2.7.2.2: Drug-Related Rash	Header title updated to Potential Drug-Related Rash and Unexplained Rash.	This update was made for clarity.
Section 8.2.8: Clinical Safety Laboratory Assessments	Text regarding protocol-required laboratory assessments and a reference to Appendix 6 for DILI were added.	These changes were made to align with the current version of the Pfizer protocol template.
Section 8.2.8.1.2: Day 1 and Annual Tuberculosis Testing	• Text was added regarding withholding of study intervention for participants with a positive TB result or a chest radiograph indicative of active TB. Minor edits were also made to this section to align with the above additions.	This text was added to provide clarification for study intervention administration for participants with positive TB test results.
Section 8.3: Adverse Events and Serious Adverse Events	Text was added regarding the questioning about the occurrence of AEs.	This change was made to align with the current version of the Pfizer protocol template.
Section 8.3.4: Regulatory Reporting Requirements for SAEs	Minor edits were made to this section.	These changes were made to align with the current version of the Pfizer protocol template.
Section 8.3.5.1: Exposure During Pregnancy	The original text was deleted and replaced with alternate text.	This change was made to align with the current version of the Pfizer protocol template.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.5.2: Exposure During Breastfeeding	The original text was deleted and replaced with alternate text.	This change was made to align with the current version of the Pfizer protocol template.
Section 8.3.5.3: Occupational Exposure	Minor edits were made to this section.	These changes were made to align with the current version of the Pfizer protocol template.
Section Headers 8.3.6 -8.3.9	Headers were added. Text was added to Section 8.3.8: "Refer to Section 8.2.7". Header for Section 8.3.8.1. Lack of Efficacy (Not Applicable) was added with accompanying text.	Added headers to align with the current version of the Pfizer protocol template. Reference was added for clarity. Updated to align with the current version of the Pfizer protocol template.
Section 8.3.6: Medication ErrorsHeader re-numbered to 8.3.10Header was re-numbered since additional headers were added.Sections 8.3.10: Medication Errors, and Section 8.4, Treatment of Overdose	Updated text to clarify that in the event of a medication dosing error, the sponsor should be notified within 24 hours.	Updated to align with the current version of the Pfizer protocol template.
Section 8.4: Treatment of Overdose	Updated the instruction regarding monitoring of events of overdose.	This change was made to align with the current version of the Pfizer protocol template.
Section 8.5: Pharmacokinetics, and Section 8.6, Pharmacodynamics	The following text was added: "These additional exploratory analyses will not be performed on samples collected from participants at sites in China; refer to Section 10.7.2." Updated text to: "Samples will be analyzed using fit for purpose or validated analytical methods in compliance with applicable Pfizer standard operating procedures."	This text was added to provide reference to the new Section 10.7.2. Updated to correct a typo.

Section # and Name	Description of Change	Brief Rationale
Section 9.2: Sample Size Determination	Text was updated to align with changes made in Section 4.1: Overall Design.	Refer to rationale for changes made in Section 4.1: Overall Design.
Appendix 1, Section 10.1.3: Informed Consent Process	Text was added regarding giving participants sufficient time to ask questions before deciding to participate in the trial. Text was added regarding informed consent procedures for minor participants. In addition, text was added to include consultation with the participant's parent/legal guardian.	This revision was made to align with the current version of the Pfizer protocol template. These additions were added from the template pediatric library to address informed consent for adolescent participants in the study. This text was added to account for adolescent participants in the study.
Appendix 1, Section 10.1.3: Informed Consent Process	• Text regarding the use of remaining mandatory samples for optional exploratory research was deleted.	This change is in accordance with the PACL dated 21 Feb 2020 to correct an error in the protocol as banked biospecimen samples will not be collected for this study.
Appendix 1, Section 10.1.5.2: Adjudication/Review Committee Submission	• The following statement was added: "Additional types of events for review and adjudication may be identified by Pfizer."	This statement was added to allow for additional types of events to be requested for review and adjudication.
Appendix 1, Section 10.1.6: Dissemination of Clinical Study DataMinor revisions were made to this section.These revisions were made to align with the current version of the Pfizer protocol template. Appendix 1, Section 10.1.9: Study and Site Closure	Text regarding premature termination or suspension of the study was added.	This revision was made to align with the current version of the Pfizer protocol template.
Appendix 2 (Section 10.2): Clinical Laboratory Tests	Footnotes #2, #6, and #13 in Table 2 were updated.	Footnote #2 was updated to fix a typo. Footnote #6 was updated and a reference to Section 10.4.3 was added for clarity.

Section # and Name	Description of Change	Brief Rationale
		Footnote #13 was corrected to add hyphens for the QFT-G and T-Spot tests.
Appendix 3 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting)	Minor edits were made to this appendix overall.	The revisions were made to align with the current version of the Pfizer protocol template.
Appendix 3, Section 10.3.1: Definition of AE (Events Meeting the AE Definition)	Text regarding abnormal laboratory test results was added.	These revisions were made to align with the current version of the Pfizer protocol template.
Appendix 3, Section 10.3.1: Definition of AE (Events Meeting the AE Definition)	Text regarding lack of efficacy was deleted.	The deleted text does not pertain to this study.
Appendix 3, Section 10.3.2: Definition of SAE (f. Other situations)	A bullet was added regarding SAE reporting for suspected transmission of an infectious agent via a Pfizer Product.	The revision was made to align with the current version of the Pfizer protocol template.
Appendix 3, Section 10.3.3: Recording/Reporting and Follow-Up of AE and/or SAE	Updated table to provide additional clarity.	The revisions were made to align with the current version of the Pfizer protocol template.
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	This section was retitled, updated with third-level headers, and updated with template text.	These changes were made to align this Appendix with the current version of the protocol template. No changes to contraceptive requirements were made.
Appendix 7, Section 10.7.2: China Specific Language For Section 8.5 Pharmacokinetics and Section 8.6 Pharmacodynamics	This section was added to the protocol. The following text was also added: “Section 8.5 Pharmacokinetics and Section 8.6 Pharmacodynamics are updated to remove exploratory analyses performed on pharmacokinetic and pharmacodynamic blood samples collected from participants at sites in China.”	The section added is in accordance with the PACL dated 06 Apr 2020 in order to document that exploratory analyses will not be performed on these samples collected from participants at sites in China. The additional text was added for clarification.

Section # and Name	Description of Change	Brief Rationale
Appendix 8, Section 10.8.1: Monitoring	Text regarding withholding of study intervention in participants with a positive TB result was added. A footnote was added to the table in this section.	This text was added to provide clarification for study intervention administration for participants with positive TB test results, in alignment with updates made to Section 8.2.8.1.2.The footnote was added to the table to provide clarification regarding the timelines for re-testing of laboratory values.
Appendix 8, Section 10.8.2: Discontinuation	Under Laboratory Abnormalities, text was added to indicate that test abnormalities require discontinuation if they are confirmed by retest, and a reference to Section 10.8.1 was added for laboratory abnormalities re-testing timeframes. The VHP country specific Discontinuation Criteria for Worsening of AA was moved from Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation, Section 10.8.2. Discontinuation to the separate Appendix 19.	This text and section reference were added to provide clarification concerning re-testing regarding laboratory abnormalities. These criteria were moved as they are not safety discontinuation criteria.
Appendix 18: Vaccine Sub-Study	A day was added to the Study Day for the sub-study Month 1 visit in the Schedule of Activities. In addition, the timeframe for the vaccine sub-study endpoints was updated in the Study Objectives and Endpoints table and the Statistical Considerations sections of the sub-study appendix.	The update to the Study Day was made to correct a typographic error. The timeframe for the vaccine sub-study endpoints was updated for consistency with the visit name in the Schedule of Activities
Appendix 18: Vaccine Sub-Study	Inclusion Criterion #3 was updated with the additional	Inclusion criterion #3 of the sub-study is being clarified so

Section # and Name	Description of Change	Brief Rationale
	text: "In addition, participant should not miss any dose of PF-06651600 for at least seven consecutive days just prior to Day 1 of this sub-study."	that the baseline antibody levels are evaluated during uninterrupted PF-06651600 treatment and to ensure that the response to vaccination reflects uninterrupted exposure to study intervention. This change was made according to the PACL dated 13-May-2020.
	In the section titled Administration, the following text was added: "The participant should be observed for at least 30 minutes after vaccine administration to assess any acute reactions."	The text to the Administration section was added in accordance with the PACL dated 13-May-2020 in order to add observations of participants to assess any acute reactions following administration of vaccines.
	The following text was added to the Summary and Sub-Study Inclusion Criteria Sections: "The vaccine sub-study will be performed at sites in the US and Canada."	The additional text was added to the Summary and Sub-Study Inclusion Criteria sections for clarity.
Appendix 19: Discontinuation Criteria for Worsening of Alopecia Areata	The VHP country specific Discontinuation Criteria for Worsening of AA was moved from Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation, Section 10.8.2. Discontinuation to the separate Appendix 19.	These criteria were moved as they are not safety discontinuation criteria.
Appendix 20: Study Intervention Continuation Criteria for Adolescents	New text and table were added under the heading "Study Intervention Continuation Criteria for Adolescents."	This change has been made to address regulatory agency feedback regarding discontinuation criteria for adolescents without adequate clinical response to limit their total exposure to chronic study treatment. Based on this, Pfizer modified the B7981032 protocol in order to minimize the time that non-responder adolescent participants are

Section # and Name	Description of Change	Brief Rationale
		exposed to PF-06651600 treatment in Study B7981032.
Appendix 21: Alternative Measures During Public Emergencies	This appendix was added.	These changes have been made to clarify alternative measures to accommodate study procedures during public emergencies, including the COVID-19 pandemic. These changes were previously communicated to sites in the protocol administrative change letter dated 05 June 2020.
Appendix 22: Abbreviations	This appendix was renumbered to Appendix 22 from Appendix 19 after the addition of 3 new Appendices. Additional definitions were added as needed to align with added text.	This is a change resulting from an additional 3 appendices being added. Additional text resulted in additional abbreviations; those abbreviations and definitions were added to this section.
Appendix 23: Protocol Amendment History	This appendix was renumbered to Appendix 23 from Appendix 20 after the addition of 3 new Appendices. The information for Protocol Amendment 3 was moved from the beginning of the document to this section.	This is a change resulting from an additional 3 appendices being added. Protocol amendment 3 information was moved to this section since only the current amendment information (protocol amendment 4) should be placed at the beginning of the document.

Amendment 3 (28 April 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Appendix 18: Vaccine Sub-Study	The following was added to the Summary and Inclusion Criteria sections of the appendix describing the vaccine sub-study: The vaccine sub-study will not be conducted at sites within the VHP countries in the EU (ie, Czech Republic, Germany, Hungary, Poland, and Spain).	Added per VHP request to clarify that sites in VHP countries will not participate in the sub-study.
Appendix 20: Protocol Amendment History	Moved table for Amendment 2 descriptions of changes and brief rationales to this appendix.	Following Pfizer's standard procedure for the common protocol template.

Amendment 2 (05 February 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis; Section 1.3 Schedule of Activities; Section 2 Introduction; Section 2.1 Study Rationale; Section 2.3 Benefit/Risk Assessment; Section 3 Study Objectives and Endpoints; Section 4.1 Overall Design; Section 5 Study Population; Section 6 Study Intervention; Section 9 Statistical Considerations	Added references to the vaccine sub-study in Appendix 18.	Updated to reflect sections for which corresponding information for the vaccine sub-study can be found in Appendix 18.
Section 1.3.1 Schedule of Activities, Screening and Day 1	Removed the Hamilton-Norwood Scale	Updated for consistency with revisions to Inclusion #1, in which the requirement regarding degree of androgenetic alopecia in male participants was removed.
Section 1.3.1 Schedule of Activities, Screening and Day 1; Section 1.3.2 Schedule of Activities, Intervention Period; Section 1.3.3 Schedule of Activities, Early Termination and Follow-up; Section 3 Study Objectives and Endpoints; Section 8.1.3.9 BRIEF®2	Added BRIEF®2 to the Schedule of Activities. Added BRIEF®2 endpoint to Section 3. Added BRIEF®2 information to Section 8.	Added questionnaire to assess neuropsychological development and executive functioning in adolescents.
Section 1.3.1 Schedule of Activities, Screening and Day 1	The following was updated for the notes for the AARU: "For participants originating from Study B7981015 with <3 months between the Day 1 visit of Study B7981032 and the last visit at which the AARU was performed in Study B7981015, the AARU will not be collected until the Month 3 visit (ie, the AARU will not be collected at the Day 1 visit for this group)."	This was updated as Day 1 is the first visit at which the AARU is collected in Study B7981032.
Section 1.3.1 Schedule of Activities, Screening and	Language regarding varicella zoster virus immunoglobulin G	Updates made based on revisions to Exclusion #16

Section # and Name	Description of Change	Brief Rationale
Day 1; Section 8.2.8.3. Varicella Zoster Virus Immunoglobulin G Antibody (VZV IgG Ab) Testing; Section 10.2. Appendix 2: Clinical Laboratory Tests, Table 1 footnote12	antibody (VZV IgG Ab) testing was updated to the following: "Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses) per Exclusion #16."	
Section 1.3.1 Schedule of Activities, Screening and Day 1; Section 8.2.8.3. Varicella Zoster Virus Immunoglobulin G Antibody (VZV IgG Ab) Testing; Section 10.2. Appendix 2: Clinical Laboratory Tests, Table 1 footnote 12	Language regarding varicella zoster virus immunoglobulin G antibody (VZV IgG Ab) testing was updated to the following: "Serological testing must be performed for VZV IgG Ab only in the absence of documented evidence of having received varicella vaccination (2 doses) per Exclusion #16."	Updates made based on revisions to Exclusion #16
Section 1.3.2 Schedule of Activities, Intervention Period; Schedule 1.3.3 Schedule of Activities, Early Termination and Follow up; Section 8.2.2 Tanner Stages of Development	The following statement was added: "For participants with AU (ie, total loss of hair on the scalp, face and body) at the Day 1 visit and for whom the stage for pubic hair cannot be reliably assessed, the Tanner stages will be collected at visit(s) after the Day 1 visit only until the participant has reached a score of 5 on the remaining applicable domain (ie, breasts for females and genitalia for males)."	This clarification was added as the Tanner stage for pubic hair will not be able to be reliably assessed in participants with AU.
Section 2.2	The definition for AU was updated to include total hair loss on the face.	Updated for clarification.
Section 2.2.2 Nonclinical and Phase 1 Efficacy and Safety Data	The following statement was added: "The potential for PF-06651600 to be involved in drug-drug interactions (DDI) is	Updated for clarification regarding the process for removing excluded prior or concomitant medications from the protocol based on

Section # and Name	Description of Change	Brief Rationale
	being investigated. If results exclude a clinically meaningful DDI (eg, relative to AUC) between PF-65551600 and a perpetrator or victim drug then that perpetrator or victim drug will no longer be prohibited as a prior or concomitant medication based on DDI; this information will be communicated via an administrative letter. Refer to Exclusion Criterion 25, Section 6.5.2, and Section 10.9.1 for medications prohibited to be used prior to and during the study."	PF-06651600 drug-drug interaction (DDI) studies.
Section 1. Protocol Summary; Section 3. Objectives, Estimands and Endpoints	The following secondary endpoints were added: • "Response based on achieving absolute SALT score ≤20 at all time points collected, for overall and AA SALT score; • Change from baseline in SALT score at all timepoints collected, for overall and AA SALT score; • PGI-C response defined as PGI-C score of moderately or greatly improved; • Shift from baseline (among participants with abnormal scores at baseline) in the category for each of the depression and anxiety sub-scales of the Hospital Anxiety and Depression Scale (HADS) at all time points collected." The following secondary endpoint was removed: • "Response based on achieving at least 90% improvement in SALT	These changes have been made to align with scientific advice interactions with regulatory agencies and from clinical experts in alopecia areata.

Section # and Name	Description of Change	Brief Rationale
	(SALT90) from baseline at all time points collected, for overall and AA SALT score" The following secondary endpoint was revised: • "Change from baseline of the total score for each of the depression and anxiety sub-scales of the Hospital Anxiety and Depression Scale (HADS) at all time points collected" The following endpoint was moved from tertiary to secondary: • "Absolute score of Patient's Global Impression of Change (PGI-C) at all time points collected" The following tertiary endpoint was removed: • "Response based on improvement status in PGI-C at all timepoints collected"	
Section 4.1 Overall Design	The following sentence was removed from the 4th paragraph: "For these participants, scalp photographs will be taken at the screening visit to verify eligibility."	Updated for consistency with revisions to Inclusion #1, in which the requirement for central photography review to verify study entry criteria was removed.
Section 5.1.1 Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032	Inclusion #1 was updated to the following: "Participants must meet the following AA criteria; • Have a clinical diagnosis of AA with no other etiology of hair loss (including, but not limited to traction and scarring alopecia, telogen effluvium). Androgenetic alopecia coexistent with	Updated to remove requirements regarding the degree of hair loss due to androgenetic alopecia in male participants and for central photography review to verify study entry criteria.

Section # and Name	Description of Change	Brief Rationale
	AA is allowed provided that the following criteria are met; • ≥25% terminal scalp hair loss due to AA (including AT and AU), as measured by SALT, at both the screening and Day 1 visits which, in the opinion of the investigator, is appropriate for systemic therapy; • Hair loss must be carefully reviewed to verify that ≥25% terminal scalp hair loss is due to AA (ie, SALT (AA) score is ≥25%). If, in cases of concomitant AA and androgenetic alopecia, it cannot be verified that SALT (AA) score is ≥25%, then the participant must be excluded from the study. • No evidence of terminal scalp hair regrowth in areas affected by AA within 6 months of both the screening and Day 1 visits (for de novo participants only); • Current episode of terminal scalp hair loss due to AA ≤10 years (for de novo participants only)."	
Section 5.1.1 Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032	Inclusion #1 was updated to include the following description of current episode of hair loss: "When determining the duration of "current episode of terminal scalp hair loss", the initiation of the current episode	Update made for clarification.

Section # and Name	Description of Change	Brief Rationale
	should be the last time when the patient had substantial scalp hair (regardless of whether that hair growth occurred spontaneously or was the result of interventional treatment)."	
Section 5.1.1 Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032; Section 4.1 Overall Design; Section 4.2 Scientific Rationale for Study Design	Inclusion 1 was updated to include reference to terminal scalp hair loss. Section 4.1 and 4.2 updated to reference terminal scalp hair loss due to change in Inclusion 1.	This clarification was added to differentiate between terminal hair versus indeterminate or vellus hair.
Section 5.2.1 Exclusion Criteria for Participants Originating from B7981015 with ≤30 Days between Studies	Exclusion #1 was updated to the following: "During Study B7981015 or in the period between the index study and Study B7981032, presence of events meeting criteria in the Discontinuation section of Appendix 8 (eg, serious infections, laboratory results, ECG results) other than discontinuation criteria for worsening of AA."	Updated to clarify that the criterion regarding worsening of AA is not exclusionary for participants continuing from Study B7981015.
Section 5.2.2 Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and B7981032.	Exclusion #16 was updated to the following: "Adolescent participants 12 to <18 years of age without one of the following: • Documented evidence of having received the varicella vaccine (2 doses); or • Evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (ie, a positive VZV immunoglobulin G antibody [VZV IgG Ab] result) at screening. Note: Serological testing must be performed for VZV IgG Ab only in the absence of	Updated to allow adolescent participants with documented evidence of varicella vaccine (2 doses) to participate regardless of results of serological VZV testing.

Section # and Name	Description of Change	Brief Rationale
	documented evidence of having received varicella vaccination (2 doses). If serological testing is performed in the presence of documented evidence of having received varicella vaccination (2 doses), participants are eligible to enter the study regardless of the result of serological testing."	
Section 5.2.2 Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and B7981032.	Exclusion #17 was updated to the following: "Active acute or chronic infection requiring treatment with oral antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to Day 1 or any active infection not meeting other exclusion criteria within 1 week prior to Day 1. NOTE: participants may be rescreened after the infection resolves."	Updated to include any active infection, not only skin infections.
Section 5.2.2 Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and B7981032.	Corrected Exclusion #21c to reference Exclusion #25i instead of Exclusion #27h.	Corrected a typographical error in the number and updated to reflect correct letter.
Section 5.2.2 Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and B7981032.	Exclusion #21b: Added abbreviation for first use of Torsades de Pointes (TdP).	For document consistency.
Section 5.2.3 Exclusion Criteria for All Participants	Added Exclusion #25a: "At any time: previous use of any non-B-cell selective lymphocyte-depleting agent (eg, alefacept, alemtuzumab)." Subsequent exclusion criterion numbers were also updated.	Added for consistency with the B7981015 protocol, which also specifically excludes any previous use of B-cell selective lymphocyte-depleting agents.

Section # and Name	Description of Change	Brief Rationale
Section 5.2.3 Exclusion Criteria for All Participants	Added everolimus and ibritunib to the second bullet of Exclusion #25d: "**Within 8 weeks** of first dose of study intervention or within 5 half-lives (if known), whichever is longer: • Other systemic treatments that could affect AA including: • Immune suppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib)."	Updated to clarify that while everolimus and ibritunib are no longer prohibited CYP3A substrates, they are still prohibited as they are immune suppressants.
Section 5.2.3 Exclusion Criteria for All Participants; Section 6.5.2 Prohibited Medications	Added clarification to Exclusion #25i and in the corresponding bullet in Section 6.5.2 regarding medications that prolong the QT interval.	Updated for clarification.
Section 5.2.3 Exclusion Criteria for All Participants	Removed the following bullet from Exclusion #25j: "Prohibited CYP3A inhibitors as described in Appendix 9 (within 7 days or 5 half lives, whichever is longer)."	Changes to restrictions regarding prior and concomitant CYP3A inhibitors were made based on the results of the PF-06651600 drug-drug interaction (DDI) studies.
Section 5.4 Screen Failures	The last paragraph was updated to the following: "De novo participants and participants originating from B7931005 or B7981015 with >30 days prior to enrolling in Study B7981032 who do not meet the criteria for participation in this study (screen failure) may be rescreened (with a new screening number) following an agreement with the sponsor."	The restriction for re-screening participants only once was removed. However, sponsor agreement is still required before a participant can be re-screened.
Section 6.5.1 Permitted Concomitant Medications	The following statement was added after the second paragraph:	Changes to restrictions regarding prior and concomitant CYP3A inhibitors and sensitive and moderate

Section # and Name	Description of Change	Brief Rationale
	"With the exception of those medications prohibited for use in Section 6.5.2, CYP3A inhibitors are permitted to be used during the study. Sensitive and moderate sensitive CYP3A substrates permitted to be used during the study are listed in Section 10.9.2."	sensitive CYP3A substrates were made based on the results of the PF-06651600 drug-drug interaction (DDI) studies.
Section 6.5.2 Prohibited Concomitant Medications	Under 'Medications that could affect AA', the 2nd bullet was updated to the following: "• Immunosuppressants (eg, cyclosporine A, azathioprine, methotrexate [MTX], sulfasalazine, mycophenolate mofetil [MMF], everolimus, ibrutinib)." Under 'Medications with potential drug-drug interactions or potential safety concerns', the 5th and 6th bullets were updated to the following: "• Moderate to potent CYP3A inducers (See Appendix 9.1). • Specific sensitive to moderate sensitive CYP3A substrates as listed in Appendix 9.1."	Changes to restrictions regarding prior and concomitant CYP3A inhibitors and sensitive and moderate sensitive CYP3A substrates were made based on the results of the PF-06651600 drug-drug interaction (DDI) studies.
Section 7 Discontinuation of Study Intervention and Participant Withdrawal; Section 7.1.1 Temporary Discontinuation; Section 7.2 Participant Discontinuation/Withdrawal From Study, Section 7.2.1 Withdrawal of Consent;	Updated sections to be consistent with new mandatory template language (05 Dec 2019 version).	Updated sections to be consistent with new mandatory template language (05 Dec 2019 version).
Section 8 Study Assessments and Procedures	The 8th bullet was updated to remove reference to verification of screening SALT scores.	Updated for consistency with revisions to Inclusion #1, in which the requirement for central photography review to verify study entry criteria was removed.

Section # and Name	Description of Change	Brief Rationale
Section 8 Study Assessments and Procedures	Added reference to observer reported outcomes to the 11th bullet.	Updated due to the addition of the BRIEF®2.
Section 8.1.1 Rater Qualifications	Removed reference to rater qualifications for the Hamilton-Norwood scale.	Updated for consistency with revisions to Inclusion #1, in which the requirement regarding degree of androgenetic alopecia in male participants was removed.
Section 8.1.2.2 Hamilton-Norwood Scale for Androgenetic Alopecia in Males	This section was removed.	Updated for consistency with revisions to Inclusion #1, in which the requirement regarding degree of androgenetic alopecia in male participants was removed.
Section 8.1.3 Patient Reported Outcomes	Updated title to include observer reported outcomes. Added information on observer reported outcomes.	Updated due to the addition of the BRIEF®2.
Section 8.1.4 Photography	Removed 2nd paragraph regarding central review of screening photographs.	Updated for consistency with revisions to Inclusion #1, in which the requirement for central photography review to verify study entry criteria was removed.
Section 8.2.1 Medical History, Physical Examinations, Height, and Weight	The description of information on substance use collected for medical history was revised from "Smoking status and average weekly alcohol consumption (units/week) will…" to "Smoking status and alcohol consumption will…".	This change has been made to correct an inconsistency between the protocol and the case report forms (CRFs).
Section 8.2.6 Audiological Evaluation	Added "All procedures must be performed according to the Audiological Evaluation Study Guide".	Added for clarity.
Section 8.2.9.1 Columbia Suicide Severity Rating Scale (C-SSRS)	The 3rd paragraph was updated to the following: "For de novo participants and participants originating from Study B7931005 or B7981015 with >30 days between the first visit of Study B7981032 and	This was updated to include instructions regarding which version of the C-SSRS should be used and to refer to the specific exclusion criterion related to the C-SSRS.

Section # and Name	Description of Change	Brief Rationale
	the last dose in Study B7931005 or B7981015: At the screening or Day 1 visits, the C-SSRS for screening and Day 1 visits will be used and the results must be evaluated against Exclusion criterion 5."	
Section 9.4.1 Efficacy Analyses	The table for Endpoints and Statistical Analysis Methods was updated to indicate that there are no primary efficacy endpoints.	Updated for consistency with the endpoints listed in Section 3.
Section 9.4.1 Efficacy Analyses	The Statistical Analysis Methods for the Secondary Endpoint was updated to the following: "Efficacy analyses are descriptive in nature (such as number and percent, mean, standard deviation) at each visit where measured…"	Analysis by quartiles was removed for consistency with the statistical analysis plan.
Section 9.4.1 Efficacy Analyses	The Statistical Analysis Methods for the Exploratory Endpoint was updated to the following: "Will be described in the statistical analysis plan."	As this is a long-term open-label study, the statement regarding the statistical analysis plan has been updated for consistency with Section 9.5, which states that interim analyses may be performed for internal decision making, due to regulatory requests, or to support regulatory submissions.
Section 9.4.2 Safety Analyses	The Statistical Analysis Methods for the Primary Endpoint was updated to the following: "The primary endpoints of incidence of TEAEs, SAEs, and AEs leading to discontinuation, clinically significant abnormalities in vital signs, and clinically significant abnormalities in laboratory values will be summarized using descriptive	This clarification was added for consistency with the endpoints listed in Section 3.

Section # and Name	Description of Change	Brief Rationale
	measures such as numbers and percentages."	
Section 9.4.2 Safety Analyses	The table for Endpoints and Statistical Analysis Methods was updated to indicate that there are no secondary or exploratory safety endpoints.	Updated for consistency with the endpoints listed in Section 3.
Section 9.4.3 Other Analyses	The following was added to this section: "Analyses of pharmacodynamic and disease-related biomarkers will be described in the statistical analysis plan."	Added for consistency with the endpoints listed in Section 3.
Appendix 2: Clinical Laboratory Tests; Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation	Updated from creatinine kinase to creatine kinase	Updated for consistency throughout the protocol.
Appendix 4: Contraceptive Guidance and Collection of Pregnancy information	Added bilateral tubal ligation to the list of highly effective contraceptive measures.	This clarification was added as the term "bilateral tubal occlusion" was intended to encompass the procedures for both bilateral tubal occlusion and bilateral tubal ligation since both of these prevent ova from moving through the fallopian tubes, thereby preventing contact with sperm.
Appendix 6: Hepatitis B Testing Algorithm and Full Eligibility Criteria	The reference for the testing algorithm was updated to the following: "The Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383-403."	Updated to provide the complete reference
Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation, Section 10.8.2. Discontinuation	Revised the 2nd bullet under ECG findings to the following: "Confirmed increase from baseline in QTcF of >60 milliseconds."	Updated for clarification regarding discontinuation criteria for ECG findings.

Section # and Name	Description of Change	Brief Rationale
Appendix 9: Prohibited Concomitant Medications	The following changes were made to this section: - The title of this Appendix was updated to the following: "Appendix 9 Prohibited and Permitted Concomitant CYP3A Inducers and Substrates." - The instructional paragraphs were updated to the following: "Please note that this list addresses only CYP3A inducers and CYP3A substrates. Other prohibited medications for this trial are listed in Section 6.5.2. Refer to Section 6.5.1 for additional information regarding permitted medications for this trial, including CYP3A inhibitors. This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are moderate to potent CYP3A inducers or sensitive or moderate sensitive CYP3A substrates. If a medication is a sensitive or moderate sensitive CYP3A substrate and is not listed below as prohibited or permitted, consultation with the sponsor is required. The list of prohibited concomitant CYP3A inhibitors, inducers and substrates was revised to include only the updated list of prohibited concomitant CYP3A inducers and substrates and a separate section for permitted concomitant CYP3A substrates was added.	Changes to restrictions regarding prior and concomitant CYP3A inhibitors and sensitive and moderate sensitive CYP3A substrates were made based on the results of the PF-06651600 drug-drug interaction (DDI) studies.

Section # and Name	Description of Change	Brief Rationale
Appendix 17: Hamilton-Norwood Scale for Androgenetic Alopecia Males	This appendix was removed.	Updated for consistency with revisions to Inclusion #1, in which the requirement regarding degree of androgenetic alopecia in male participants was removed.
Appendix 18: Vaccine Sub-Study	This appendix was added to provide details for the newly added vaccine sub-study.	The vaccine substudy was added to assess immunogenicity to tetanus booster vaccination and meningococcal primary vaccination in adult participants with AA undergoing treatment with PF-06651600 in Study B7981032.
Appendix 19: Abbreviations	The following abbreviations were added: BRI, BRIEF®2, CDC, CI, CRI, ERI, GMC, GMT, hSBA, IgG, ObsRO, SAP, SBA, Td, TdP, Tdap, USPI. Updated to ensure abbreviations are in alphabetical order.	Updated to include new abbreviations and to list abbreviations alphabetically.
Appendix 21: Protocol Amendment History	Added appendix and moved table for Amendment 1 descriptions of changes and brief rationales to this appendix.	Following standard procedure for the common protocol template.
Section 11 References	Added 2 references for the BRIEF®2.	Updated due to the addition of the BRIEF®2.
Section 11 References	Added references for the HADS.	Updated based on addition of categorical HADS endpoints.

Amendment 1 (15 October 2019)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.2: Schema	Day 14 updated to Week 2	This clarification was made for consistency with showing monthly visits as opposed to the specific study days after Day 1 in the Schema.
Section 1.2: Schema; Section 1.3. SoA; Section 1.31.: Screening and Day 1; Section 1.32.: Intervention Period; Section 1.33.: Early Termination and Follow-up; Section 5: Study Population; Section 5.2.1: Exclusion Criteria for Participants Originating from B7931005 or B7981015 with ≤ 30 Days between Studies; Section 8.2: Safety Assessments; Section 8.2.8.1.2: Day 1 and Annual Tuberculosis Testing Section 8.2.8.5: Hepatitis B DNA Testing; Section 8.2.9.1:	For groups with ≤30 days between the first visit of Study B7981032 and the last dose in the index study, reference to study B7931005 was removed.	This clarification was made as the last dose in Study B7931005 was achieved on 13 April 2019. Based on the projected first study visit for Study B7981032, all participants enrolling from Study B7981005 will have >30 days between the first visit of Study B7981032 and the last dose in Study B7931005.

Section # and Name	Description of Change	Brief Rationale
Columbia Suicide Severity Rating Scale; Appendix 8: Guidelines for Participant Safety Monitoring and Discontinuation		
Section 1.3.1: SoA, Screening and Day 1 (Hamilton-Norwood Scale); Section 5.1.1. Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032, Inclusion #1; Section 8.1.1: Rater Qualifications; Section 8.1.2.2: Hamilton Norwood Scale for Androgenetic Alopecia; Appendix 17: Hamilton Norwood Scale for Androgenetic Alopecia	Updates were made to add the word "Male or Males" when referring to the Hamilton-Norwood Scale for Androgenetic Alopecia	This clarification was made to align with the literature references for the assessment to indicate that the Hamilton-Norwood Scale for Androgenetic Alopecia should be used for males and not for females and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.
Section 1.3.1: SoA, Screening and Day 1 (Audiological Evaluation)	In the SoA, Evaluation at Day 1 for Group E and the note "Participants originating from Study B7931005 with ≤30 days between the first visit of Study B7981032 and the last dose in	This clarification was made as the last dose in Study B7931005 was achieved on 13 April 2019. Based on the projected first study visit for Study B7981032, all participants enrolling from Study B7981005 will have >30 days between

Section # and Name	Description of Change	Brief Rationale
	Study B7931005 must have a full audiological evaluation performed at the Day 1 visit and results available at the Month 1 visit (but preferably at the Week 2 visit, if possible)" were removed.	the first visit of Study B7981032 and the last dose in Study B7931005. Therefore, all participants from Study B7931005 will have the evaluation performed at the Screening visit.
Section 1.3.1: SoA, Screening and Day 1 (SALT); Section 1.3.2: SoA, Intervention Period; Section 8.1.2.1.1: Androgenetic Alopecia SALT Score	For participants with known androgenetic alopecia, a separate assessment of scalp hair loss due to androgenetic alopecia (ie, androgenetic alopecia SALT score) was removed from the Screening, Day 1, and all Intervention Period visits with the exception of the Month 24 and Early Termination visits.	Per updates to Section 9.4.1, the final (ie, Month 24 or Early Termination) androgenetic alopecia SALT score will be used to derive the SALT AA score at all study visits, as appropriate. Therefore, androgenetic alopecia SALT score was removed from the other visits.
Section 1.3.2: SoA, Intervention Period.	A day was added to each of the Study Days in the Schedule of Activities for Week 2 through Month 24/EOT. For example, Day 14 was updated to Day 15, Day 30 was updated to Day 31, etc.	This clarification was made to correct a typographic error and was previously communicated in the protocol administrative change letter dated 22-May-2019.
Sections 1.3.2: SoA, Intervention Period; Section 8.2.11. Pregnancy Testing; Section 8.2.12: Check for Initiation of Menarche	Monthly pregnancy testing was changed to start after the Month 1 visit.	This change was made to align with a request from the Voluntary Harmonisation Procedure (VHP) for Study B7981015 to include more frequent pregnancy testing for females of childbearing potential in the VHP countries in the EU. In study B7981032, monthly pregnancy testing between the Month 1 and Month 3 visits was added as a global update as monthly pregnancy testing after Month 3 was included in the original protocol.
Sections 1.3.2: SoA, Intervention Period; Section 8.2.11: Pregnancy Testing	The following statement was added: "The pregnancy testing between visits may occur outside of the study site".	This clarification was made to indicate that pregnancy testing between visits is not required to be performed at the study site.
Section 1.3.3: Early	Early Termination and Follow-up visit timeframe was clarified.	This update was made to clarify the Early Termination and Follow-up visit timing.

Section # and Name	Description of Change	Brief Rationale
Termination and Follow-up		
Section 4.1 Overall Design	The second sentence in the third paragraph of this section was updated to the following: "In addition, participants enrolling from Study B7931005 must have taken their last dose of PF 06700841 (a TYK2/JAK1 inhibitor) in Study B7931005 >12 weeks prior to the B7981032 Day 1 visit."	This change was made for alignment with the update to Inclusion #2 in Section 5.1.2 noted below.
Section 5: Study Population	The following statement was added: "NOTE: There are certain eligibility requirements specific to subjects within Voluntary Harmonisation Procedure (VHP) countries in the EU. The VHP countries participating in this study are: Czech Republic, Germany, Hungary, Poland, and Spain."	This change was made to align with the update for age in Section 5.1.3 and to include the list of participating VHP countries.
Section 5.1.1: Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032	Inclusion #1 was updated to the following: "No evidence of terminal scalp hair regrowth in areas affected by AA within 6 months of both the screening and Day 1 visits (for de novo participants only)."	This clarification was made to indicate more explicitly that evidence of terminal hair regrowth is prohibited at <u>both</u> the Screening <u>and</u> Day 1 visits. In addition, this was updated to clarify that this only refers to regrowth of hair affected by AA and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.
Section 5.1.1: Inclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the	Inclusion #1 was updated to the following: "Current episode of hair loss due to AA ≤10 years (for de novo participants only)"	This clarification was made to indicate that the current episode of hair loss only refers to loss of hair due to AA and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.

Section # and Name	Description of Change	Brief Rationale
Index Study and Study B7981032		
Section 5.1.2: Inclusion Criteria for All Participants Originating from B7931005 or B7981015	Inclusion #2 was updated to the following: "Taken the last dose of PF 06700841 (a TYK2/JAK1 inhibitor) in Study B7931005 >12 weeks prior to the Study B7981032 Day 1 visit."	This update was made for consistency with exclusion #25b and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.
Section 5.1.3: Inclusion Criteria for All Participants	The following was added to Inclusion #4: "Within the VHP countries in the EU, de novo participants must be aged 18 through 74 years at the time of informed consent (see Section 5 for a list of VHP countries participating in this study)."	This change was made to align with a request from the VHP for Study B7981015 to exclude participants age 75 years and older in VHP countries in the EU.
Section 5.2.1: Exclusion Criteria for Participants Originating from B7981015 with ≤30 Days between Studies	Exclusion #2 was updated to the following: "Discontinuation from Study B7981015 for safety related events. Participants discontinued from Study B7981015 due to issues other than safety-related events must be discussed with the sponsor prior to enrollment in Study B7981032."	This change was made to indicate that all discontinuations from the index studies other than for safety-related events must be discussed with the sponsor prior to enrollment in Study B7981032.
Section 5.2.2. Exclusion Criteria for De Novo Participants and Those Originating from B7931005 or B7981015 with >30 Days between the Index Study and Study B7981032	Exclusion #23 was updated to: "Discontinuation from Study B7931005 or B7981015 for safety-related events. Participants discontinued from Study B7931005 or B7981015 due to issues other than safety-related events must be discussed with the sponsor prior to enrollment in Study B7981032".	This was added for consistency with Exclusion #2 in Section 5.2.1.
Section 5.2.3: Exclusion Criteria for All Participants	Exclusion #25g was updated to remove the following from the end of the criteria: "that could affect AA unless used for androgenetic alopecia"	This update was made for consistency with exclusion #26 and Section 6.5.1 Permitted Concomitant Medications and was previously communicated in the protocol administrative change letter dated 11-Sep-2019

Section # and Name	Description of Change	Brief Rationale
Section 5.2.3: Exclusion Criteria for All Participants	Exclusion #25 h was updated to add a reference for the website www.CredibleMeds.org. Subsequent references were renumbered as appropriate.	This clarification was made to correct a typographic error and was previously communicated in the protocol administrative change letter dated 22-May-2019.
Section 8.2.6: Audiological Evaluation	The following statement was removed: "Participants originating from Study B7931005 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7931005 must have a full audiological evaluation performed at the Day 1 visit and results available at the Month 1 visit (but preferably at the Week 2 visit, if possible). Audiological testing is not required at the Day 1 visit for participants originating from Study B7981015 with ≤30 days between the first visit of Study B7981032 and the last dose in Study B7981015".	This was updated for consistency with changes in Section 1.3.1. SoA, Screening and Day 1; Audiological Evaluation.
Section 8.2.8.2: Purified Protein Derivative (PPD) Test	A typographic error in paragraph 2 was corrected to reflect that the test should be performed and interpreted as "negative" (not "positive") according to local standards.	This clarification was made to correct a typographic error and was previously communicated in the protocol administrative change letter dated 22-May-2019
Section 8.2.12: Check for Initiation of Menarche (for Premenarchal Females Only)	The language was updated to indicate that pregnancy tests should be performed "according to the Schedule of Activities" instead of "at every visit".	This change was made to ensure consistency with the Schedule of Activities.
Section 8.5: Pharmacokinetics	The first paragraph was updated to the following: "During all study periods, blood samples (~2 mL) to provide plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K2EDTA) anticoagulant at times specified in the (Schedule of	This update was made for consistency with the final required blood volumes from the central laboratory for this sample and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.

Section # and Name	Description of Change	Brief Rationale
	Activities) section of the protocol."	
Section 9.3: Populations for Analysis	The "Description" in the table for the safety and efficacy populations was updated to the following: "All participants who take at least 1 dose of study intervention."	This change was made to remove the requirement that participants must be assigned study intervention in order to be included in the analysis population as the sponsor's intent is to analyze all participants who take at least 1 dose of study intervention. Wording regarding how the population would be analyzed was also removed as this is not appropriate to be included in this section.
Section 9.4.1. Efficacy Analyses	The Statistical Analysis Methods in the table for the primary endpoint was updated to the following: "Efficacy analyses are descriptive in nature; such as number and percent, mean, standard deviation and quartiles at each visit where measured; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported. Displays using by stratification by roll-over and de-novo participants (ie, those who did not receive study intervention in either Study B7931005 or B7981015) and participants originating from Study B7931005 or B7981015 (ie, those who received study intervention in either Study B7931005 or B7981015) will also be included."	This change was made to clarify the descriptions of de novo participants and participants originating from Study B7931005 or B7981015.
Section 9.4.1. Efficacy Analyses	The following was added: The secondary endpoints for SALT include both the SALT overall and SALT AA scores. The SALT overall score includes hair loss regardless of etiology (eg, including scalp hair loss due to both androgenetic alopecia and AA). The SALT androgenetic alopecia (SALT AGA) score only takes into account scalp hair loss due to androgenetic alopecia and	This change was made to define how the SALT AA endpoint will be derived.

Section # and Name	Description of Change	Brief Rationale
	is required to be assessed only at the Month 24 or Early Termination visit (as appropriate). The SALT AA score at each visit will be calculated as follows using the SALT AGA score collected at the Month 24 or Early Termination visit (as appropriate): SALT AA score = SALT overall score – SALT AGA score.	
Section 9.4.2: Safety Analyses	The first paragraph was updated to read as follows: "All safety analyses will be performed on the Safety Population. For the purpose of analysis of safety measures for the participants with ≤30 days between the first visit of Study B7981032 and the last dose of study intervention in the index studies, the baseline values are defined as the Day 1 values from Study B7981015 or B7931005."	This typographical error was corrected for consistency with the baseline definitions in Section 8.2 Safety Assessments and was previously communicated in the protocol administrative change letter dated 11-Sep-2019.
Section 9.4.2: Safety Analyses	The Statistical Analysis Methods in the table for the primary endpoint was updated to the following: "The primary endpoints of incidence of TEAEs, SAEs, and AEs leading to discontinuation, clinically significant abnormalities in vital signs, and abnormalities in laboratory values will be summarized using descriptive measures such as numbers and percentages. The safety summaries will be reported for all participants, as well as by de novo participants (ie, those who did not receive study intervention in either Study B7931005 or B7981015) and participants originating from Study B7931005 or B7981015 (ie, those who received study intervention in either Study B7931005 or B7981015).	This change was made for consistency with the Primary Endpoints in Section 3 and to align with a request from the VHP to provide additional details regarding the safety analysis methods, including analysis by de novo participants and those originating from Study B7931005 or B7981015.

Section # and Name	Description of Change	Brief Rationale
	No formal statistical hypotheses will be tested. Further details will be specified in the Statistical Analysis Plan."	
Appendix 2: Table 1, Protocol-Required Safety Laboratory Assessments	A typographic error in the laboratory assessment for %Reticulocytes was corrected to remove "%".	This clarification was made to correct a typographic error to indicate that both % and absolute reticulocytes will be assessed and is consistent with the update previously communicated the protocol administrative change letter dated 22-May-2019.
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information:	Bullet 3 (Postmenopausal female) was updated to the following: • "A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range must also be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT)." The requirement for follicle stimulating hormone (FSH) testing has not changed.	This change was made to align with a request from the VHP for Study B7981015 to update the definition of "postmenopausal state".
Appendix 8: Guidelines for Subject Safety Monitoring and Discontinuation	A typographic error in the monitoring criteria for hemoglobin was corrected to reflect that a decrease greater than or equal to 2.0 g/dL (not just a decrease of 2.0 g/dL) requires additional monitoring activities.	This clarification was made to correct a typographic error and was previously communicated in the protocol administrative change letter dated 22-May-2019.
Appendix 8: Guidelines for Subject Safety Monitoring and Discontinuation	Discontinuation criteria for worsening alopecia areata were added for the VHP countries.	This change was made to align with a request from the VHP to add discontinuation criteria for worsening alopecia areata.

Section # and Name	Description of Change	Brief Rationale
Appendix 10: Severity of Alopecia Tool (SALT)	Typographic errors were corrected in the calculations shown for the first example.	This clarification was made to correct a typographic error and was previously communicated in the protocol administrative change letter dated 22-May-2019.
Appendix 19: Abbreviations	AGA: Androgenetic alopecia VHP: Voluntary Harmonisation Procedure abbreviations added.	This was updated to add new abbreviations.

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Document Approval Record

Document Name:	Protocol Amendment_ B7981032 Amendment 6_clean
Document Title:	Protocol Amendment_ B7981032 Amendment 6_clean

Signed By:	Date(GMT)	Signing Capacity
PPD	28-Mar-2022 18:27:12	Final Approval
PPD	28-Mar-2022 18:39:18	Final Approval