Protocol Title: A PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY INVESTIGATING THE SAFETY OF RITLECITINIB (PF-06651600) IN ADULT PARTICIPANTS WITH ALOPECIA AREATA

Protocol Number: B7981037

Study Intervention Number: PF-06651600

Study Intervention Name: Ritlecitinib

Study Phase: Phase 2a

Short Title: PLACEBO-CONTROLLED SAFETY STUDY OF RITLECITINIB (PF-06651600) IN ADULTS 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	2020-001509-21

Approval Date: 28 April 2022

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Updated with full study title	This update was made to correct the omission in previous amendment.
Section 1.1 Synopsis Section 1.2 Schema; Section 1.3.2.1 Treatment periods 1 and 2 (TP1 and TP2): Day 1 through Month 15E; Section 1.3.2.2 Treatment Period 3 (TP3): Month 15E to Month 51E; Section 1.3.3. Early Termination and Follow-up; 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 6.1 Study Intervention; Section 8.2.13 Pregnancy Testing; Section 9.4.2 Efficacy Analysis; Section 9.4.3 Safety Analysis; Section 10.7.2 Discontinuation Section 10.9.3.1 Laboratory Testing (Usual Safety Assessments);	Study extension for all participants to continue to receive open-label 50 mg PF-06651600 QD. Study updated to have 2 active treatment periods in addition to placebo-controlled period (TP1). Treatment from Month 9 to Month 15E is TP2. TP3 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 TP3 for a maximum of an additional 36 months or until availability of commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first. Visit 11 Neurological Exam is removed from TP2 SoA. Updated with a table title [Home Pregnancy Test Schedule(in addition to clinic visits)]. 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). It was added to specify the unscheduled clinical visits separately than scheduled clinic visits.
Section 1.1 Synopsis; Section 3 Objectives, Estimands and Endpoints	New footnote is added to specify which safety endpoints apply to TP3. Added ECG analysis under safety endpoints at TP1 and TP2 phases only.	The endpoints were updated as a result of the study extension. ECG was missing in previous amendment for TP1 and TP2. No ECG will be recorded in TP3.

Section # and Name	Description of Change	Brief Rationale
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 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;	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).	Added in order to collect data in participants who have discontinued study intervention.
Section 1.3.2 Intervention Period; Section 1.3.3 Early Termination and Follow-up; Section 10.2 Appendix 2: Clinical Laboratory Tests; Section 10.7.1 Monitoring; Section 10.7.2 Discontinuation; Section 10.9.3.1 Laboratory Testing (Usual Safety Assessments); Section 10.9.3.3 Audiological and Neurological Specialist Evaluations; Section 10.9.3.4 Skin Biopsies; Section 10.9.6. Home Health Visits	Fasting Lipid Panel is not collected for participants who have completed the Month 15E Visit. For participants who have completed the Month 15E Visit, creatine kinase, urine myoglobin, skin biopsies and neurological testing will not be tested. Only audiological testing will be collected in TP3. For participants who have completed the Month 15E Visit, urinalysis and neurological testing will be performed only if considered clinically indicated by the investigator.	These changes were made for consistency with Section 1.3.2.2 in which fasting lipid panel, creatine kinase, urine myoglobin, urinalysis. skin biopsies, neurological testing are not collected after Month 15E Visit. Based on recent safety data analyses, it has been considered that measurements of fasting lipid panel, creatine kinase, urine myoglobin (reactive), skin biopsies, neurological testing and urinalysis are no longer warranted after Month 15E. Note that urinalysis and neurological evaluation can still be performed if considered clinically indicated by the investigator.
Section 1.3.3 Early Termination and Follow-up; Section 10.7.2 Discontinuation; Section 10.9.3.2 Electrocardiograms	12- lead ECG is not collected during ET visit for participants who have completed the Month 15E Visit.	These changes were made for consistency with Section 1.3.2.2 in which 12-lead ECG is not collected after Month 15E Visit.

Section # and Name	Description of Change	Brief Rationale
		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 2.2.1 Non-clinical Studies; Section 6.1 Study Intervention (s) Administered; Section 6.2 Preparation/Handling/ Storage/Accountability; Section 6.4 Study Intervention Compliance; Section 10.9.5. 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 and blister cards or bottles.	The study extension of up to an additional 36 months of treatment beyond Month 24 (15E Visit) may result in a transition of PF-06651600 dosage form from tablet to capsule and from blister cards to bottles.
Section 2.2.2 Clinical Experience Section 2.3. Benefit /Risk Assessment	Updated with the total numbers of participants from other Phase 2 and Phase 3 studies with PF-06651600. Phase 2b/3 B7981015 study information was added (Section 2.2.2.2). Updated with current benefit and risk information of PF-06651600 from study B7981015.	Update was made in alignment with Investigator Brochure version 8.0 December 2021, and also to clarify the safety of PF-06651600. Update was made to clarify the safety of PF-06651600.
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 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 no longer use abstinence as the selected contraception method" and "The contraception check for WOCBP will be performed during each	This update was made to provide additional clarification on the requirements and timing for contraception check.

Section # and Name	Description of Change	Brief Rationale
	study visit and monthly between study visits at time of the phone contact to check the at-home pregnancy test results."	
Section 6.3.1 Blinding	Added sections specifying the following: TP1 and initial 4 weeks of TP2 will be double-blinded. For the remainder of TP2, participants, investigators and site and sponsor staff are aware that active therapy is being provided; however, study intervention packaging may remain blinded. After all participants have completed TP2, the study will be fully unblinded to the initial treatment assignments, and TP3 will be fully unblinded.	This update was made to clarify the blinding approach in the study.
Section 8 Study Assessments and Procedures	Updated the amount of blood to be collected from each participant in Study B7981037.	This change was made to align with the extended Intervention Period for up to 36 additional months.
Section 8.2.5 Neurological Examination	Updated with the need of neurological evaluation by a neurologist during TP3 if medically indicated.	This change was made to align with the extended Intervention Period for up to an additional 36 months.
Section 8.2.11.1 Columbia Suicide Severity Rating Scale (C-SSRS); Section 10.7.2 Discontinuation	Added details on participants with suicidal ideation.	This update was made to provide details on participants with suicidal ideation and discontinuation criteria
Section 9.4.1 Timing of the Analyses; Section 9.4.2 Efficacy Analyses; Section 9.4.3 Safety Analyses	Added a new Section 9.4.1 explaining the scope of the efficacy and safety data to be included in the 3 analyses; Updated the efficacy and safety analyses tables, explaining details of the specific efficacy and safety analysis included in each of the three CSRs; added how to derive non-AA SALT score.	Updated to offer clarity in statistical analyses for additional 36 months extension period

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim Analyses	Clarified when an interim analysis may be needed eg, for study monitoring for internal decision making, due to regulatory requests, or to support regulatory submissions.	This update was made to specify the timing of interim analysis in this study.
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: Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	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 10.7.1 Monitoring	Updated hemoglobin values requiring re-testing in Table 3.	Based on a recent review of clinical safety data for PF-06651600 and a review of cases meeting the ⩾2 g/dL 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 absolute hemoglobin values <10.0 g/dL.
Section 10.9.2 Telehealth Visits	Updated language for WOCBP referencing Section 5.3.1. "Contraception".	This update was made for clarity and consistency with Section 5.3.1.
Section 10.9.3.1 Laboratory Testing (Usual Safety Assessments)	Updated with Tuberculosis testing Table 4 was updated with the additional visits in 36 months extension period. Visit days were corrected.	Updated to be consistent with the changes made for 36-month study extension.

Section # and Name	Description of Change	Brief Rationale
Section 10.11 Appendix 11: Protocol Amendment History	Moved table for Amendment 1 descriptions of changes and brief rationales to this appendix. The version date is corrected to April 23, 2021.	Following Pfizer's standard procedure for the common protocol template. The version date was revised based on the date of last sign-off date.
Throughout document	Other relatively minor administrative/typo/formatting/ Abbreviations updates.	Updated for grammatical correctness, clarity, consistency with Pfizer Global Style Guide and protocol template.

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

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY INVESTIGATING THE SAFETY OF RITLECITINIB (PF-06651600) IN ADULT PARTICIPANTS WITH ALOPECIA AREATA

Short Title: PLACEBO-CONTROLLED SAFETY STUDY OF RITLECITINIB (PF-06651600) IN ADULTS WITH ALOPECIA AREATA

Rationale:
PF-06651600 inhibits Janus kinase 3 (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). This study includes investigation of the clinical relevance of changes observed in non-clinical toxicity studies in dogs treated with PF-06651600. Specifically, in a 9-month dog study, axonal dystrophy (axonal swelling due to neurofilament accumulation without evidence of axonal degeneration) in the central and peripheral nervous systems at ≥20 mg/kg/day (a 12-fold exposure multiple relative to the clinical dose of 50 mg), and functional auditory deficits on 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) were observed. Consequently, this study is specifically designed to evaluate the safety, including assessment of BAEPs and intraepidermal nerve fiber (IENF) histology in skin punch biopsies, of PF-06651600 in adult participants with AA.

Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary – Safety	
• To assess I-V interwave latency on brainstem auditory evoked potentials (BAEPs) in adult participants with alopecia areata (AA) treated with PF-06651600.	• Change from baseline in I-V interwave latency on BAEP at a stimulus intensity of 80 decibels (dB) at Month 9.
Secondary – Safety	
• To assess I-V interwave latency on BAEPs in adult participants with AA treated with PF-06651600.	• Change from baseline in I-V interwave latency on BAEP at a stimulus intensity of 80dB at Months 6, 9E, and 15E.
• To assess axonal dystrophy in intraepidermal nerve endings over time in adult participants with AA treated with PF-06651600.	• Change from baseline in axonal dystrophy in skin punch biopsies at Month 9 and Month 15E.

Objectives	Endpoints
• To assess intraepidermal nerve fiber density (IENFD) over time in adult participants with AA treated with PF-06651600.	• Change from baseline in IENFD in skin punch biopsies at Month 9 and Month 15E.
• To assess wave V amplitude on BAEP over time in adult participants with AA treated with PF-06651600.	• Change from baseline in amplitude of wave V on BAEP at a stimulus intensity of 80dB at Months 6, 9, 9E, and 15E.
• To assess presence of wave V on BAEP over time in adult participants with AA treated with PF-06651600.	• Absence of wave V on BAEP at stimulus intensities ranging from 80dB to 40dB at Months 6, 9, 9E, and 15E.
• To evaluate the safety and tolerability of PF-06651600 in adult participants with AA.	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events (AEs) leading to discontinuation;[a] • Incidence of clinically significant abnormalities in vital signs and ECG; [a] • Incidence of clinically significant abnormalities in clinical laboratory values. [a]
Secondary – Efficacy TP1-TP2	
• To evaluate response to PF-06651600 measured by the Severity of Alopecia Tool (SALT) in adult participants with AA.	• Change from baseline in overall and AA SALT[b] score at Month 51E and other time points collected.
• To evaluate the response to PF-06651600 measured by the Patient's Global Impression of Change (PGI-C) tool in adult participants with AA.	• PGI-C score response defined as greatly improved or moderately improved at Month 9 and other time points collected.

a. Refer to Section 9.4.1 for specific safety summary included in each study report.
b. AA SALT is the amount of scalp hair loss due to AA.

Overall Design:
This study will investigate PF-06651600 in participants with AA. This is a Phase 2a, randomized, double-blind, placebo-controlled safety study designed to evaluate the safety

and tolerability of PF-06651600, including the assessments of BAEP and IENF, in adults 18 to ≤50 years of age with ≥25% scalp hair loss due to AA.

Disclosure Statement:
This is a Parallel Treatment study with 2 arms that is Investigator, Sponsor, and Participant blinded.

Number of Participants:
A total of approximately 60 participants will be randomized in the study.

Intervention Groups and Duration:
This study will have approximately 60 adults 18 to 50 years of age, randomized 1:1 to receive either PF-06651600 or placebo.

There will be three treatment periods, and an observation period as follows:

Treatment Period 1(TP1) and Treatment Period 2 (TP2):

The total duration of participation in TP1 plus TP2 is approximately 26 months. This includes up to a 5-week screening period, a 9-month placebo-controlled treatment phase (TP1), a 15-month active therapy extension phase (TP2), and a 4-week follow-up period (if not proceeding to TP3) (See Section 1.2). Screening will occur within 35 days prior to Day 1 of the study to confirm that selection criteria for the study are met. At Month 9, the placebo-controlled phase will end, and all participants may enter the active therapy extension phase of the study and receive PF-06651600.

At Month 6, any participant with a baseline overall SALT score ≤75 will have the option to enter the active therapy extension phase if the overall SALT score at Month 6 has increased from baseline by ≥25 points.

At the time of their Month 15E visit, participants will have the opportunity to enter TP3, as described below. In this case, the Follow-up visit will be completed at the end of their participation in TP3.

Treatment Period 3 (TP3):

- TP3 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 TP3 for a maximum of an additional 36 months or until availability of commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first.

- In TP3, participants will receive 50 mg QD of PF-06651600. The total duration of participation in TP3 is approximately 37 months, including up to 36 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:

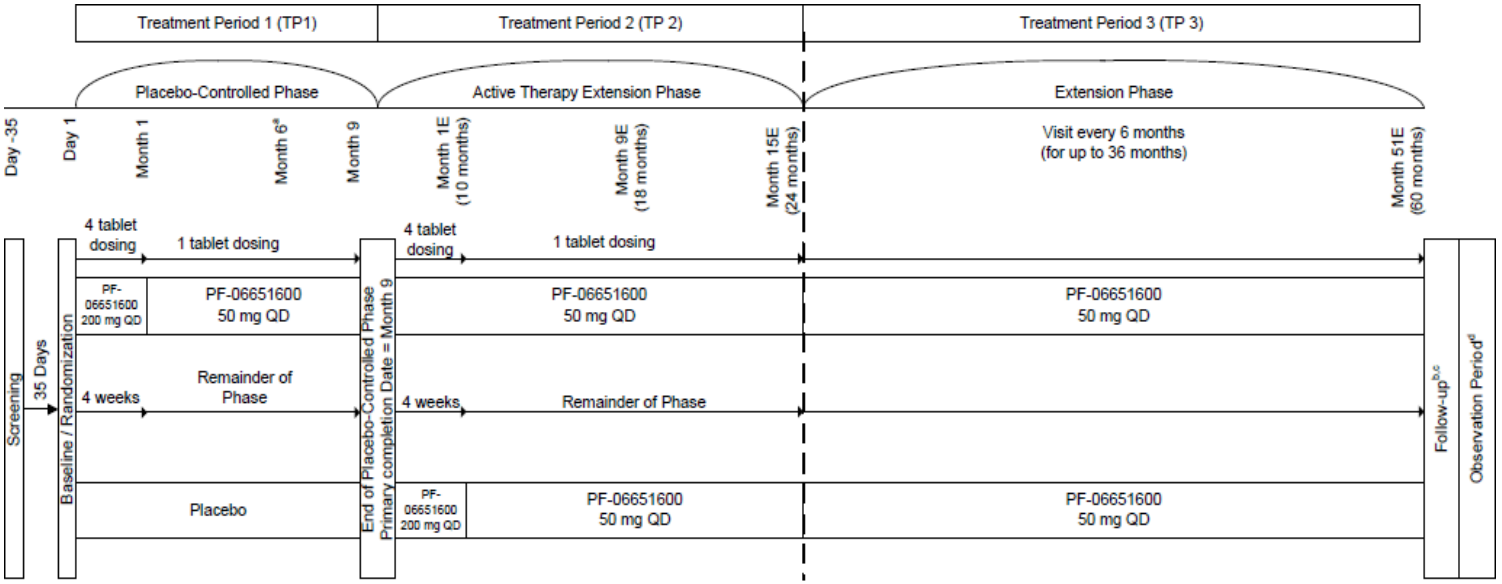
- If study intervention is permanently discontinued, the participant will be asked to remain in the study after the Follow-up visit without study intervention and continue to comply with study visit schedules for approximately 2 years after the last dose of study intervention or until study end, whichever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

Data Monitoring Committee: Yes

Statistical Methods

For the primary safety endpoint, there is no formal hypothesis testing. The analyses will be descriptive. Summary statistics for each group with 95% confidence intervals (CIs) will be provided. Estimands are not applicable since there is no formal statistical hypothesis testing for this study.

1.2. Schema



Abbreviations; E= active therapy extension phase; QD = once daily; TP = Treatment Period

a. Any participant with baseline overall SALT score ≤75 will be given the option to enter the active therapy extension phase at Month 6 if the overall SALT score at Month 6 has increased from baseline by ≥25 points.

b. After completion of TP2 (for participants not continuing to TP3) 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 24 visit will have the opportunity to enter TP3, of variable length for individual participants for a maximum of 36 months or until availability of commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first

c. In TP3, after completion or discontinuation of study intervention, a Follow-up period of 4 weeks will occur.

d. 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 or until study end, whichever occurs first.

Note: If a participant discontinues for neurological or audiological events at any time during the study, a follow-up period of 6 months will occur.

1.3. Schedule of Activities

1.3.1. Screening and Day 1

The Schedule of Activities (SoA) table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Some procedures conducted as part of the participant's routine clinical management (eg, chest radiograph [CXR] or other appropriate diagnostic imaging such as computed tomography or magnetic resonance imaging [MRI]) and obtained before signing the informed consent document (ICD) 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.

Procedure	Screening	Day 1	Notes
Visit Identifier	1	2	Day 1 (Visit 2) is the last day of screening and the first day of the placebo-controlled phase for eligible participants.
Day	-35 to -1	1	
Visit Window (±Days)	None	None	
Enrollment procedures			
Informed consent	X		Must be obtained before the participant is enrolled in the study per Section 10.1.3.
Inclusion and exclusion criteria	X	X	Pre-dose on Day 1. See Section 5.1 and Section 5.2.
Demography	X		
Medical and AA disease history	X	X	Pre-dose on Day 1. Refer to the CRF completion guidelines for specific information regarding medical history information to be collected for each group of participants per Section 8.2.1. Medical history includes neurological and audiological history per Section 8.2.5 and Section 8.2.6.
Smoking, drug, and alcohol history	X		See Section 8.2.1.
Medical procedures			
Full physical examination, including dermatological full body examination.	X	X	Pre-dose on Day 1. See Section 8.2.1 and Section 8.2.9.2.
Neurological evaluation by a neurologist	X		The examination will include the Neuropathy Assessment. Refer to the Manuals for General Neurological and Neuropathy Assessments for more information. See Section 8.2.5.
Audiological evaluation and history by an audiologist	X		Participants must have a full audiological assessment completed during screening prior to Day 1. Audiology and BAEP evaluations should be done on the same day, with

Procedure	Screening	Day 1	Notes
Visit Identifier	1	2	Day 1 (Visit 2) is the last day of screening and the first day of the placebo-controlled phase for eligible participants.
Day	-35 to -1	1	
Visit Window (±Days)	None	None	
			audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Audiology Study Guide for information on the auditory testing. Section 8.2.6.
Vital signs	X	X	Pre-dose on Day 1. Section 8.2.2.
12-lead ECG	X		Section 8.2.4.
Height	X		Section 8.2.1.
Weight	X	X	Section 8.2.1.
Chest radiograph	X		CXR or other appropriate diagnostic imaging, such as computed tomography or MRI, must be taken at screening if not performed within 3 months prior to the screening visit. Exclusion Criterion 21 in Section 5.2 and Section 8.2.3.
BAEP Evaluation	X		Audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Manual for BAEP Evaluation for additional information. See Section 8.2.7.
Laboratory			
Hematology and Serum Chemistry	X	X	Pre-dose on Day 1. See Section 8.2.10 and Section 10.2
Fasting Lipid Panel	X		See Section 8.2.10 and Section 10.2.
Urinalysis	X	X	Pre-dose on Day 1. See Section 8.2.9.2.2, Section 8.2.10 and Section 10.2
Serum FSH	X		To confirm postmenopausal status in female participants who have been amenorrheic for at least 12 consecutive months with no alternative pathological or physiological cause. See Section 10.2 and Section 10.4.
Pregnancy test (WOCBP only)	X	X	Pre-dose on Day 1. See Section 8.2.13, Section 10.2 and Section 10.4.
HbA1c testing	X		See Exclusion Criterion 8 and Section 10.2.
HIV testing	X		See Exclusion Criterion 15 and Section 10.2.
Hepatitis B and Hepatitis C Screening	X		See Exclusion Criterion 20, Section 10.2 and Section 10.6.
HBVDNA (applicable countries)	X		See Exclusion Criterion 20, Section 8.2.10.3, Section 10.2 and Section 10.6. Only for participants negative for HBsAg and positive for HBcAb in those regions for which hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care.
Skin punch biopsy for evaluation of axonal dystrophy and IENFD		X	Pre-dose. See Section 8.2.8.1.
Collection of blood sample for potential viral screen		X	Pre-dose. See Section 8.2.10.2, and Section 10.2.
Tuberculosis testing	X		See Exclusion Criterion 21, Section 8.2.10.1, and Section 10.2.

Procedure	Screening	Day 1	Notes
Visit Identifier	1	2	Day 1 (Visit 2) is the last day of screening and the first day of the placebo-controlled phase for eligible participants.
Day	-35 to -1	1	
Visit Window (±Days)	None	None	
Trial treatment			
IRT registration	X		
IRT study intervention assignment		X	Pre-dose.
Study intervention dispensing		X	Pre-dose. See Section 6.2.
Study intervention administration		X	See Section 6.1.
Clinical assessments			
SALT	X	X	See Section 8.1.2.1.
AA eligibility assessment	X		Scalp hair loss due to AA (AA SALT) to be assessed to verify eligibility. See Section 8.1.2.1.2.
C-SSRS	X	X	See Section 8.2.11.1.
Patient reported outcomes			
PHQ-8	X		See Section 8.2.12.
Other			
Prior and current concomitant medications and treatment(s) monitoring	X	X	See Section 6.5.
Adverse event monitoring	X	X	See Section 8.3 and Section 10.3.
Contraception check for WOCBP	X	X	See Section 5.3.1 and Section 10.4.

Abbreviations: AA = alopecia areata; BAEP = brainstem auditory evoked potential; CRF=case report form; C-SSRS = Columbia Suicide Severity Rating Scale; CXR = Chest radiograph; ECG = electrocardiogram; FSH = follicle stimulating hormone; HbA1c= hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBVDNA = hepatitis B viral deoxyribonucleic acid; HIV = human immunodeficiency virus; IENFD = intraepidermal nerve fiber density; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PHQ-8 = Patient Health Questionnaire – 8 items; SALT = Severity of Alopecia Tool; WOCBP = women of childbearing potential.

1.3.2. Intervention Period

1.3.2.1. Treatment Periods 1 and 2 (TP1 and TP2): Day 1 to Month 15E

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
Medical Procedures										
Full physical examination, including dermatological full body examination			X	X			X		X	See Section 8.2.1.
Targeted physical examination	X	X			X	X		X		See Section 8.2.1.

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
Neurological examination by a neurologist			X (see Note)	X			X			Neurological examination will include the Neuropathy Assessment. Refer to the Manuals for General Neurological and Neuropathy Assessments for more information. See Section 8.2.5. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
Vital signs	X	X	X	X	X	X	X	X	X	See Section 8.2.2.
12-lead ECG			X (see Note)	X					X	See Section 8.2.4. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
Weight			X (see Note)	X					X	**Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
Audiological Evaluation by an audiologist			X	X			X		X	At each intervention period, audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Audiology Study Guide for information on the auditory testing. See Section 8.2.6.
BAEP Evaluation			X	X			X		X	At each intervention period, audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Manual for BAEP Evaluation.

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
										See Section 8.2.7.
Laboratory										
Hematology and Serum Chemistry	X	X	X	X	X	X	X	X	X	See Section 8.2.10 and Section 10.2.
Fasting Lipid Panel			X (see Note)	X					X	See Section 8.2.10 and Section 10.2. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
Urinalysis	X	X	X	X	X	X	X	X	X	See Section 8.2.10 and Section 10.2.
Pregnancy test	X	X	X	X	X	X	X	X	X	For WOCBP only. Monthly urine pregnancy tests for home testing will be performed by the participant between scheduled study visits starting after the Month 1 visit through the 15E visit. Pregnancy tests for home testing will be

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
										provided for testing between visits. Site personnel will contact participants 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. See Section 8.2.13, Section 10.2, and Section 10.4.
HBVDNA (applicable countries)		X	X (see Note)	X	X	X	X	X	X	Only for participants who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care. Testing at additional time points may be performed as per the local standard of care. See Section 8.2.10.3, Section 10.2, and Section 10.6.

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
										Note: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
Skin punch biopsy for evaluation of axonal dystrophy and IENFD			X (see Note)	X					X	See Section 8.2.8.1. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1). **Note:** At the EOP visit (Month 6 or Month 9/EOP, as appropriate), the skin biopsy must be collected before the start of Active Therapy Extension Phase.
Tuberculosis testing			X (see Note)	X					X	See Section 8.2.10.1, Section 8.2.3, and Section 10.2. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
Trial Treatment										

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
IRT study intervention assignment			X (see Note)	X						IRT will be contacted at Month 9 for participants entering the active therapy extension phase for study intervention assignment. **Note**: IRT will be contacted at Month 6 for participants entering the active therapy extension phase at Month 6 for study intervention assignment.
Study intervention dispensing	X	X	X	X	X	X	X	X		At the Month 1 visit and each visit thereafter, the participant will return the package containing the study intervention which was dispensed at the previous visit for accountability. See Section 6.2. At the Month 6 visit (only for those eligible participants who enter the active therapy extension phase at Month 6 [see Section 4.1]) or 9/EOP visit, if the neurological or audiological/BAEP assessments have not yet been completed, double-blind therapy continues to be dispensed until the neurological and

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
										audiological/BAEP assessments (including the central read confirmation and any repeat assessments if deemed necessary by the central reader) are completed. Active therapy is dispensed (via on-site visit or shipping) only once all the above procedures are completed. Refer to the IRT reference manual for dispensing additional double-blind therapy.
Study intervention administration	X	X	X	X	X	X	X	X		See Section 6.1.
Study intervention accountability and compliance	X	X	X	X	X	X	X	X	X	See Section 6.2 and Section 6.4.
Clinical Assessments										

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
SALT		X	X	X	X	X	X	X	X	See Section 8.1.2.1. At Month 6, any participant with a baseline overall SALT score ≤75 will have the option to enter the active therapy extension phase if the overall SALT score at Month 6 has increased from baseline by ≥25 points.
Non-AA SALT			X (see Note)	X					X	Only participants with other known etiologies of scalp hair loss in addition to AA. See Section 8.1.2.1.1. **Note**: Assessment at Month 6 is required ***only*** for those eligible participants who enter the active therapy extension phase at Month 6 (See Section 4.1).
C-SSRS	X	X	X	X	X	X	X	X	X	See Section 8.2.11.1.
Patient reported outcomes										
PGI-C	X	X	X	X	X	X	X	X	X	See Section 8.1.3.1.

Procedure	Intervention Period									Notes
Phase:	TP1: Placebo-controlled Phase			TP2: Active Therapy Extension Phase						
Visit Identifier	3	4	5	6	7	8	9	10	11	Visit 6 (Month 9/EOP), the last visit of the placebo-controlled phase, is also the first visit of the active therapy extension phase.
Visit (Months)	1	3	6	9 / EOP	3E	6E	9E	12E	15E	E=Active Therapy Extension Phase **Note**: Those participants who enter the active therapy extension phase at Month 6 (Visit 5) are to complete at that visit all Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E,
Day	31	91	181	271	91E	181E	271E	361E	451E	Day relative to the start of the study phase (ie, Day 1 = start of Placebo-controlled Phase; Day 1E = start of Active Therapy Extension Phase).
Visit Window (±Days)	±3	±7	±7 (See Note)	±7 (See Note)	±7	±7	±7	±7	±7	**Note:** For the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days.
Other										
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	X	X	X	X	X	X	See Section 6.5.
Adverse event monitoring	X	X	X	X	X	X	X	X	X	See Section 8.3 and Section 10.3.
Contraception check for WOCBP	X	X	X	X	X	X	X	X	X	See Section 5.3.1 and Section 10.4.

Abbreviations: AA = alopecia areata; BAEP = brainstem auditory evoked potential; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOP = End of placebo-controlled phase/ beginning of active therapy extension phase; EOT = End of Treatment; HBcAb = hepatitis B core antibody; HBVDNA = hepatitis B viral deoxyribonucleic acid; IENFD = intraepidermal nerve fiber density; IRT = Interactive Response Technology; PGI-C = Patient's global impression of change; SALT = Severity of Alopecia Tool; WOCBP = women of childbearing potential.

Home Pregnancy Test Schedule (in addition to clinic visits)

Procedure	Intervention Period													
Phase:	TP1: Placebo-controlled Phase					TP2: Active Therapy Extension Phase								
Month	2	4	5	7	8	1E	2E	5E	7E	8E	10E	11E	13E	14E
Home pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1.3.2.2. Treatment Period 3 (TP3)

Procedure	Intervention Period						Notes
Phase:	TP3: Extension Phase						
Visit Identifier	12	13	14	15	16	17/EOT	
Visit (Months)	21E	27E	33E	39E	45E	51E	**Note**: Those participants who enter Extension Phase TP3 at Month 15E (Visit 11) are to complete at that visit all Month 15E (Visit 11) assessments and then follow the schedule of visits in Extension Phase, starting with Month 21E (Visit 12).
Day	631E	811E	991E	1171E	1351E	1531E	Day relative to the start of the study phase (Day 1E = start of Active Therapy Extension Phase TP2)
Visit Window (±Days)	±7	±7	±7	±7	±7	±7	
Full physical examination, including dermatological full body examination		X		X		X	See Section 8.2.1.
Targeted physical examination	X		X		X		See Section 8.2.1.
Vital signs	X	X	X	X	X	X	See Section 8.2.2.
Weight		X		X		X	
Audiological Evaluation by an audiologist		X		X		X	Refer to the Audiometry Study Guide for information on the auditory testing. See Section 8.2.6.
Hematology and Serum Chemistry	X	X	X	X	X	X	For participants who have completed the Month 15E visit, creatine kinase will not be tested. See Section 8.2.10 and Section 10.2.

Procedure	Intervention Period						Notes
Phase:	TP3: Extension Phase						
Visit Identifier	12	13	14	15	16	17/EOT	
Visit (Months)	21E	27E	33E	39E	45E	51E	**Note**: Those participants who enter Extension Phase TP3 at Month 15E (Visit 11) are to complete at that visit all Month 15E (Visit 11) assessments and then follow the schedule of visits in Extension Phase, starting with Month 21E (Visit 12).
Day	631E	811E	991E	1171E	1351E	1531E	Day relative to the start of the study phase (Day 1E = start of Active Therapy Extension Phase TP2)
Visit Window (±Days)	±7	±7	±7	±7	±7	±7	
Urinalysis	X	X	X	X	X	X	For participants who have completed the Month 15E visit, urinalysis will be performed only if considered clinically indicated by the investigator. See Section 8.2.10 and Section 10.2.
Pregnancy test	X	X	X	X	X	X	For WOCBP only. * Monthly urine pregnancy tests for home testing will be performed by the participant between all scheduled study visits through to the 51E/EOT visit. Pregnancy tests for home testing will be provided for testing between visits. Site personnel will contact participants between study visits to obtain monthly pregnancy test results and ensure these contacts and the results of the pregnancy tests are recorded in participant source documentation and CRF.See Section 8.2.13, Section 10.2, and Section 10.4.
HBVDNA (applicable countries)	X	X	X(see Note)	X	X	X	Only for participants who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care. Testing at additional time points may be performed as per the local standard of care. See Section 8.2.10.3, Section 10.2, and Section 10.6.
Tuberculosis testing		X		X		X	See Section 8.2.10.1, Section 8.2.3, and Section 10.2.
IRT study intervention assignment							IRT will be contacted at Month 15E for participants entering Extension Phase TP3 for study intervention assignment.
Study intervention dispensing	X	X	X	X	X	X	The participant will return the package containing the study intervention which was dispensed at the previous visit for accountability.See Section 6.2.

Procedure	Intervention Period						Notes
Phase:	TP3: Extension Phase						
Visit Identifier	12	13	14	15	16	17/EOT	
Visit (Months)	21E	27E	33E	39E	45E	51E	**Note**: Those participants who enter Extension Phase TP3 at Month 15E (Visit 11) are to complete at that visit all Month 15E (Visit 11) assessments and then follow the schedule of visits in Extension Phase, starting with Month 21E (Visit 12).
Day	631E	811E	991E	1171E	1351E	1531E	Day relative to the start of the study phase (Day 1E = start of Active Therapy Extension Phase TP2)
Visit Window (±Days)	±7	±7	±7	±7	±7	±7	
Study intervention administration	X	X	X	X	X		See Section 6.1.
Study intervention accountability and compliance	X	X	X	X	X	X	See Section 6.2 and Section 6.4.
SALT	X	X	X	X	X	X	See Section 8.1.2.1.
Non-AA SALT						X	Only participants with other known etiologies of scalp hair loss in addition to AA. See Section 8.1.2.1.1.
C-SSRS	X	X	X	X	X	X	See Section 8.2.11.1.
PGI-C	X	X	X	X	X	X	See Section 8.1.3.1.
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	X	X	X	See Section 6.5.
Adverse event monitoring	X	X	X	X	X	X	See Section 8.3 and Section 10.3.
Contraception check for WOCBP	X	X	X	X	X	X	See Section 5.3.1 and Section 10.4.

Abbreviations: AA = alopecia areata; CK = creatine kinase; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; EOP = End of placebo-controlled phase/ beginning of active therapy extension phase; EOT = End of Treatment; HBcAb = hepatitis B core antibody; HBVDNA = hepatitis B viral deoxyribonucleic acid; IENFD = intraepidermal nerve fiber density; IRT = Interactive Response Technology; PGI-C = Patient's global impression of change; SALT = Severity of Alopecia Tool; WOCBP = women of childbearing potential.

Procedure	Intervention Period						Notes
Phase:	TP3: Extension Phase						
Visit Identifier	12	13	14	15	16	17/EOT	
Visit (Months)	21E	27E	33E	39E	45E	51E	**Note**: Those participants who enter Extension Phase TP3 at Month 15E (Visit 11) are to complete at that visit all Month 15E (Visit 11) assessments and then follow the schedule of visits in Extension Phase, starting with Month 21E (Visit 12).
Day	631E	811E	991E	1171E	1351E	1531E	Day relative to the start of the study phase (Day 1E = start of Active Therapy Extension Phase TP2)
Visit Window (±Days)	±7	±7	±7	±7	±7	±7	

Note: For participants, who have completed the Month 15E visit, neurological exam by neurologist, BAEP, skin punch biopsy, 12-Lead ECG, fasting lipid panel, CK, urine myoglobin,and urinalysis (unless clinically indicated) will not be tested in TP3.

*Home pregnancy test on all non-scheduled visit months during Observation Period (i.e., 16E-20E, 22E-26E, 28E-32E, 34E-38E, 40E-44E, 46E-50E)

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 or until study end, whichever occurs first. Refer to Section 4.1 for further details.

Procedure	ET	28-Day Follow-up	6-Month Follow-up	Notes
Visit Identifier	NA	18	19	
Day	NA	EOS 28 days after last dose	182 days after discontinuation for neurological or auditory adverse event	
Visit Window (±Days)	+7	±7	±30	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. 6-Month Follow-up visit occurs 6 months after the last dose of study intervention for any participant who discontinues the study due to a neurological or auditory adverse event (See Section 10.7).
Medical Procedures				
Full physical examination, including dermatological full body examination	X			See Section 8.2.1.
Targeted physical examination		X	X	See Section 8.2.1.
Neurological examination by a neurologist	X		X (see Note)	See Section 10.7.2 for follow-up assessment of participants who discontinue due to a neurological adverse event. Neurological examination will include the Neuropathy Assessment. Refer to the Manuals for General Neurological and Neuropathy Assessments for more information. See Section 8.2.5. Neurological examination not collected during ET visit for participants who have completed the Month 15E visit, unless these assessments are relevant to the reason for discontinuation. If neurological examination required, the same neurologist who saw the participant for the first 24 months should also do the consultation when possible.
Vital Signs	X	X	X	See Section 8.2.2.

Procedure	ET	28-Day Follow-up	6-Month Follow-up	Notes
Visit Identifier	NA	18	19	
Day	NA	EOS 28 days after last dose	182 days after discontinuation for neurological or auditory adverse event	
Visit Window (±Days)	+7	±7	±30	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. 6-Month Follow-up visit occurs 6 months after the last dose of study intervention for any participant who discontinues the study due to a neurological or auditory adverse event (See Section 10.7).
12-lead ECG	X			See Section 8.2.4. 12-lead ECG is not to be collected during ET visit for participants who have completed the Month 15E visit.
Weight	X			See Section 8.2.1.
Audiological Evaluation	X		X (see Note)	Audiology and, if applicable, BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Audiology Study Guide for information on the auditory testing. Section 8.2.6. See Section 10.7.2 for follow-up assessment of participants who discontinue due to an auditory adverse event. **Note**: Assessments as relevant to the reason for discontinuation

Procedure	ET	28-Day Follow-up	6-Month Follow-up	Notes
Visit Identifier	NA	18	19	
Day	NA	EOS 28 days after last dose	182 days after discontinuation for neurological or auditory adverse event	
Visit Window (±Days)	+7	±7	±30	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. 6-Month Follow-up visit occurs 6 months after the last dose of study intervention for any participant who discontinues the study due to a neurological or auditory adverse event (See Section 10.7).
BAEP Evaluation	X		X (see Note)	Audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. Refer to the Manual for BAEP Evaluation. Section 8.2.7. See Section 10.7.2 for follow-up assessment of participants who discontinue due to an auditory adverse event. **Note**: Assessments as relevant to the reason for discontinuation. BAEP evaluation not collected during ET visit for participants who have completed the Month 15E visit, unless these assessments are relevant to the reason for discontinuation.
Laboratory				
Hematology and Serum Chemistry	X	X		For participants who have completed the Month 15E visit, creatine kinase will not be tested. Section 8.2.10 and Section 10.2.
Fasting Lipid Panel	X			Fasting lipid panel is not to be collected during ET visit for participants who have completed the Month 15E visit. Section 8.2.10 and Section 10.2.
Urinalysis	X	X		For participants who have completed the Month 15E visit, urinalysis will be performed only if considered clinically indicated by the investigator during ET and Follow-up visits. See Section 8.2.10 and Section 10.2.

Procedure	ET	28-Day Follow-up	6-Month Follow-up	Notes
Visit Identifier	NA	18	19	
Day	NA	EOS 28 days after last dose	182 days after discontinuation for neurological or auditory adverse event	
Visit Window (±Days)	+7	±7	±30	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. 6-Month Follow-up visit occurs 6 months after the last dose of study intervention for any participant who discontinues the study due to a neurological or auditory adverse event (See Section 10.7).
Pregnancy test (WOCBP only)	X	X		See Section 8.2.13, Section 10.2 and Section 10.4.
HBVDNA (applicable countries)	X			Only for participants who were enrolled with a positive HBcAb and a negative HBVDNA in those regions for which hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care. See Section 8.2.10.3 and Section 10.6.
Skin punch biopsy for evaluation of axonal dystrophy and IENFD	X		X (see Note)	See Section 8.2.8.1. See Section 10.7.2 for follow-up assessment of participants who discontinue due to a neurological adverse event. **Note**: Assessments as relevant to the reason for discontinuation. Skin punch biopsies will not be collected during ET visit for participants who have completed the Month 24 visit.
Trial treatment				
Study intervention accountability and compliance	X			See Section 6.2 and Section 6.4.
Clinical assessments				
SALT	X			See Section 8.1.2.1.
Non-AA SALT	X			Only participants with other known etiologies of scalp hair loss in addition to AA. See Section 8.1.2.1.1.
C-SSRS	X			See Section 8.2.11.1.

Procedure	ET	28-Day Follow-up	6-Month Follow-up	Notes
Visit Identifier	NA	18	19	
Day	NA	EOS 28 days after last dose	182 days after discontinuation for neurological or auditory adverse event	
Visit Window (±Days)	+7	±7	±30	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. 6-Month Follow-up visit occurs 6 months after the last dose of study intervention for any participant who discontinues the study due to a neurological or auditory adverse event (See Section 10.7).
Patient reported outcomes				
PGI-C	X			See Section 8.1.3.1.
Other				
Prior and current concomitant medication(s) and treatment(s) monitoring	X	X	X	See Section 6.5.
Adverse event monitoring	X	X	X	See Section 8.3 and Section 10.3.
Contraception check for WOCBP	X	X		See Section 5.3.1 and Section 10.4.

Abbreviations: AA = alopecia areata; BAEP = brainstem auditory evoked potential; ECG = electrocardiogram; EOS=end of study; ET = Early Termination; HBcAb = hepatitis B core antibody; HBVDNA = hepatitis B viral deoxyribonucleic acid; IENFD = intraepidermal nerve fiber density; PGI-C = Patient's global impression of change; SALT = Severity of Alopecia Tool; WOCBP = women of childbearing potential.

2. INTRODUCTION

2.1. Study Rationale

PF-06651600 is being developed as an oral treatment for patients with alopecia areata (AA) based on its mechanism of action and the clinical results obtained in Phase 1 and Phase 2 studies. This study is specifically designed to evaluate the safety of PF-06651600 in adult participants with AA. This includes assessments of brainstem auditory evoked potentials (BAEPs) and intraepidermal nerve fiber (IENF) histology. The BAEP and IENF assessments are being performed to investigate the clinical relevance of changes observed in non-clinical toxicity studies in dogs treated with PF-06651600 (see Section 4.2).

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.[1, 2] AA is associated with other immune diseases including asthma, allergic rhinitis, atopic dermatitis, and autoimmune diseases such as thyroiditis and vitiligo.[2]

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 and body (alopecia universalis [AU]).[3] 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.[4] It is estimated that AA affects as many as 6 to 7 million individuals in the United States (US)[2] and 147 million worldwide.[5]

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.[6, 7] 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,[8-12] problems with social relations,[13] decreased health-related quality of life (HRQoL) and general quality of life (QoL), as well as the QoL of their families.[5, 14-21]

No drugs have been approved for the treatment of AA in most countries/regions, including the US 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.[22-26]

CD8+ T cells, natural killer (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).[27, 28] Mouse models have shown that interleukin (IL)-2 and IL-15 play a

role in the initiation of auto-reactive $CD8^+$ cells that attack hair follicles. IL-12 and IL-23 may also play a role in the pathogenesis of AA.[29]

The cytokine signaling pathways of IFNγ and IL-15, among others, can be blocked via Janus kinase (JAK) inhibition, supporting the rationale of a JAK inhibitor in the treatment of AA.[30] Indeed, treatment with the JAK inhibitors tofacitinib and ruxolitinib is reported to reverse AA in a mouse model.[31] Clinically, there are case reports and case series reporting that these JAK inhibitors demonstrate efficacy in AA.[31-39]

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 (IL)-2 inducible T cell kinase [ITK], TEC and tyrosine kinase expressed in T cells [TXK]), primarily expressed in hematopoietic cells.[40, 41] 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.[42] Since $CD8^+$ T cells, NK cells, and mast cells have all been implicated in the pathophysiology of AA,[28, 31, 43, 44] inhibition of TEC kinases has the potential to contribute to efficacy in this disease by modulating the functional activity of these pathogenic effector cells.

PF-06651600 is a covalent and irreversible inhibitor of Janus kinase 3 (JAK3) with high selectivity over the other three JAK isoforms (JAK1, JAK2, and tyrosine kinase 2 [TYK2]). PF-06651600 also inhibits irreversibly the TEC family kinases with selectivity over the broader human kinome. Treatment with PF-06651600 is expected to inhibit the inflammatory pathways mediated by IL-7, IL-15, and IL-21, all implicated in AA. Moreover, due to lack of activity against the other JAK isoforms, PF-06651600 is expected to spare immunoregulatory cytokines such as IL-10, IL-27 and IL-35, which are critical to the maintenance of immunosuppressive functions and immune homeostasis.

2.2.1. Nonclinical Studies

Data from nonclinical studies support the planned clinical trials with PF-06651600; these studies are described in the Investigator's Brochure (IB).

In the first 9-month study of PF-06651600 in dogs, bilateral axonal dystrophy (not axonal degeneration) in the olivary nuclei of the brainstem was observed in males and females administered ≥20 mg/kg/day. Auditory testing (BAEP) performed on recovery control and high dose animals during the last 2 weeks of the 3-month recovery period showed BAEP waveform defects. There was partial recovery in the brainstem microscopic lesions at the end of the 3-month recovery period. The no observed adverse effect level (NOAEL) was the lowest dose tested of 5 mg/kg/day, based on the adverse finding of axonal dystrophy in the brainstem and associated waveform defects in males and females administered ≥20 mg/kg/day.

In the second 9-month study in dogs, PF-06651600-related, minimal to moderate axonal dystrophy (axonal swelling due to neurofilament accumulation without evidence of axonal degeneration) in the brainstem, minimal axonal dystrophy in the sciatic nerve and branches of the vagus nerve, and an increased severity (from minimal to mild) of axonal dystrophy in the spinal cord were observed at ≥20 mg/kg/day (a 12-fold exposure multiple relative to the clinical dose of 50 mg). Minimal to mild axonal dystrophy was also observed in the white matter of the rostral vermis of the cerebellum at ≥10 mg/kg/day. Adverse BAEP findings were noted in 1 male and 1 female administered 40 mg/kg/day (a 29-fold exposure multiple relative to the clinical dose of 50 mg) at 7 and/or 9 months of dosing, and these findings completely recovered at the end of the 6-month recovery in the animal that continued into the recovery phase. The auditory deficits observed were consistent with a central, not peripheral, effect on auditory function.

The NOAEL was 10 mg/kg/day, based on adverse over-immunosuppression and axonal dystrophy in the central and peripheral nervous system at ≥20 mg/kg/day and accompanied by auditory deficits (BAEP) at the highest dose of 40 mg/kg/day. The area under the concentration-time curve (AUC) exposure margins in this study at the NOAEL at study end were approximately 1.5x and 6.5x relative to the predicted exposure at the 200 mg and 50 mg clinical QD doses, respectively (Table 1).

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

For a complete description of these studies please refer to the current version of the IB.

2.2.2. Clinical Experience

Data from Phase 1 clinical studies, including pharmacokinetics, bioavailability, and food effect, support the planned clinical trials with PF-06651600; these studies are described in the IB.

There are completed and ongoing Phase 2 and 3 studies with PF-06651600 (N=1557) in a number of disease indications including rheumatoid arthritis (RA), AA, ulcerative colitis, vitiligo, and Crohn's disease. Forty-two (42) participants with rheumatoid arthritis (RA) were exposed to PF-06651600 in the Phase 2a Study B7981006. One hundred and fifty (150) participants with ulcerative colitis were exposed to PF-06651600 in the Phase 2b Study B7981005. Three hundred and sixty-four (364) and 238 participants with vitiligo were exposed to PF-06651600 in the dose-ranging period and in the extension period, respectively, of Phase 2b study B7981019. Forty-eight (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 results presented below. There are ongoing studies in participants with Crohn's disease and AA (Phase 2a Study B7981007 and Phase 3 Study B7981032 AA LTE).

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

2.2.2.1. Phase 2a Study in Alopecia Areata

Study B7931005 was a Phase 2a study evaluating the safety, tolerability, pharmacokinetics (PK), and efficacy of 2 investigational JAK inhibitors, PF-06700841 and PF-06651600, in adult participants with AA (restricted to those with ≥50% scalp hair loss without evidence of hair regrowth within the previous 6 months; current episode of hair loss ≤7 years). The study included 3 periods: an initial 24-week double-blind treatment period, an up to 48-week single-blind extension (SBE) period, and a 24-week cross-over open label extension period.

During the initial 24-week double-blind treatment period, participants received an induction dose of 200 mg QD for 4 weeks, followed by maintenance dosing of 50 mg QD for 20 weeks of PF-06651600; an induction dose of 60 mg QD for 4 weeks, followed by maintenance dosing of 30 mg QD for 20 weeks of PF-06700841; or a matching placebo for 24 weeks. This was followed by an SBE period including a withdrawal/re-treatment period for responders and a treatment period for non-responders. After the SBE phase eligible participants could enter an open-label cross-over period for non-responders.

PF-06651600 achieved the primary endpoint, SALT change from baseline, at Week 24. PF-06651600 was efficacious compared to placebo as measured by proportion of subjects achieving ≥30% and ≥90% improvement from baseline in SALT score (SALT30 and SALT90).

PF-06651600 showed continued improvements in the proportion of participants achieving various percent improvements from baseline in SALT score (SALT30, SALT50, SALT75, SALT90, and SALT100) during the initial 24-week treatment period showing significant responses compared to placebo group starting from Week 6 for SALT30, SALT50 and SALT 75, Week 12 for SALT90, and at Week 24 for SALT100.

The proportion of subjects achieving at least 1 grade improvement in both eyelash assessment (ELA) and eyebrow assessment (EBA) for PF-06651600 continued to increase over the initial double-blind treatment period, significantly differentiating from placebo as early as Week 4 for ELA and as early as Week 6 for EBA.

Participants who received placebo in the initial treatment period followed by PF-06651600 in the SBE period had a response consistent with the responses of participants who received PF-06651600 during the initial treatment period. There was a loss of efficacy based on SALT30 compared to the response in the initial treatment period, as SALT30 was only achieved by 57% of subjects receiving PF-06651600 who had previously responded in the initial treatment period. Non-responders who continued treatment for another 24 weeks were unlikely to respond during the SBE period.

Blood samples for PK were collected predose at each visit from baseline to Week 24 as well as at 0.5 hours post dose on Weeks 8 and 20; 0.5 and 1 hour post dose on Week 12; and 0.5, 1, 2, and 4 hours post dose on Weeks 4 and 24. The observed mean $C_{max,ss}$ and mean AUC_{tau} for 200 mg QD in the AA population were 1601 ng/mL and 6353 ng*hr/mL, respectively, slightly higher than the $C_{max,ss}$ and AUC_{tau} for 200 mg QD observed in the healthy population, 1422 ng/mL and 4069 ng*hr/mL, respectively.

PF-06651600 had an acceptable safety profile and was well tolerated. No participants in the PF-06651600 group experienced an SAE. During the initial treatment period, the number of AEs in the placebo group (105) was higher than in the PF-06651600 group (82), although the number of subjects reporting AEs was similar in the placebo and PF-06651600 groups (35 [74.5%] subjects and 30 [66.7%] subjects, respectively). Two participants in the PF-06651600 group discontinued from treatment in the initial treatment period due to an AE (angioedema and elevated creatine kinase level, both of which resolved), but continued in the study. One active non-responder who received PF-06651600 discontinued from the SBE period due to a treatment-emergent adverse event (TEAE) of abnormal liver function test; the laboratory values did not reach the criteria for Hy's Law.

The most common (≥5%) AEs during the initial treatment period in the PF-06651600 group were in the Infections and Infestations (upper respiratory tract infections, nasopharyngitis, folliculitis), Gastrointestinal Disorders (nausea, diarrhea), and the Skin and Subcutaneous Tissue Disorders (acne, atopic dermatitis) categories, and the majority of events were mild. No serious infections or cases of herpes zoster or herpes simplex were reported in the PF-06651600 group during the initial treatment period; 1 AE of herpes simplex was reported in the PF-06651600 group during the SBE period.

During the initial treatment period, absolute lymphocyte and platelet counts showed a slight decrease from baseline in PF-06651600 treatment group. The mean (90% CI) percent CFB absolute neutrophil count in the PF-06651600 treatment group at Week 2 and Week 24 was 17.30% (23.12%, -11.47%) and -8.44% (15.59%, -1.29%), respectively. In the PF-06651600 treatment group, platelet counts remained slightly lower than baseline value with mean (90% CI) percent CFB of -17.89% (-21.32%, -14.47%) and -9.61% (13.87%, 5.35%) at Week 2 and Week 24, respectively. There was a decrease in absolute lymphocyte count in the PF-06651600 treatment group during the COE period but there was no consistent trend in lymphocyte or platelet count during the SBE period.

There were no clinically significant auditory changes in the active treatment groups. A mild TEAE of neurosensory deafness was reported in 1 participant in the placebo group during the initial 24-week treatment period. There were no clinically significant findings in electrocardiograms (ECG) or vital signs, except increased diastolic blood pressure >20 mmHg in 1 participant each on placebo and PF-06651600.

There were no increased safety risks with re-exposure to PF-06651600 or after cross-over to treatment with either PF-06651600 or PF-06700841. The final study results, including the results of the two extension periods, are described in the current version of the PF-06651600 IB.

2.2.2.2. 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 for participants who did not roll over

into the open label long-term Study B7981037. 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, 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.

All SAEs were considered by the investigator as unrelated to study drug, except in 3 participants (sepsis and empyema, breast cancer, eczema). There were no deaths reported in the study.

Treatment with PF-06651600 was associated with changes in hematological parameters, some of which were dose dependent. From Week 4 onward, 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. Up to Week 24, 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.

2.2.2.3. Phase 2a Study in Rheumatoid Arthritis

The completed Phase 2a study B7981006 was an 8-week randomized, double-blind, placebo-controlled, parallel-group, multi-center study in participants with moderate-to-severe active rheumatoid arthritis (RA) with an inadequate response to methotrexate. A total of 70 participants were randomized to study treatment; 28 participants received placebo and 42 participants received PF-06651600.

PF-06651600 was determined to be safe and well tolerated in this study. There were no deaths or SAEs. The TEAEs reported in more than 5% of participants with RA receiving PF-06651600 were influenza and lymphopenia. There were no clinically relevant changes in vital signs, ECG, or audiometric assessments. For more details, including effects on laboratory parameters, please refer to the current version of the IB.

2.3. Benefit/Risk Assessment

The preliminary clinical data indicate that PF-06651600 has a favorable benefit:risk profile. It provided clinical benefit (scalp hair regrowth) in patients with AA and was determined to be well tolerated and to have an acceptable safety profile in the clinical studies to date. 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. PF-06651600 is an immunomodulator and, like others in this class, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation. The risk of infection will be monitored in this study.

In animal studies, PF-06651600 administration was associated with effects on fetal development, including skeletal and visceral organ malformations and lower fetal body weights. In the fertility and early embryonic development study in rats, PF-06651600-related

higher incidence of preimplantation loss was noted in non-dosed females mated with males administered PF-06651600, without effects on sperm or other features of male reproduction.

When PF-06651600 was administered to healthy women together with an oral contraceptive containing ethinyl estradiol and levonorgestrel, the level of ethinyl estradiol in the blood was decreased; the clinical significance of this decrease is unknown, however the efficacy of estrogen-containing contraceptives may be decreased.

In the Phase 2b/3 pivotal, dose-ranging Study B7981015 in adult and adolescent participants with AA, PF-06651600 was evaluated for 48 weeks. PF-06651600 dose regimens of 200/50 mg (200 mg QD for 4 weeks followed by 50 mg QD through Week 48), 200/30 mg (200 mg QD for 4 weeks followed by 30 mg QD through Week 48), 50 mg (50 mg QD for 4 weeks and through Week 48), and 30 mg (30 mg QD for 4 weeks and through Week 48) were significantly superior to placebo on clinician-assessed and patient-reported endpoints, including SALT ⩽10, SALT⩽20, and PGI-C response. PF-06651600 was safe and well-tolerated in participants treated for up to 48 weeks. No deaths were reported. There were no dose-dependent trends in overall SAEs, severe TEAEs, or TEAEs leading to discontinuation. There were few serious infections and no opportunistic infections. All TEAEs of herpes zoster were mild to moderate and occurred in participants treated with PF-06651600. Dose regimens with a 200 mg loading dose had a higher incidence of some TEAEs (eg, folliculitis, urticaria, dizziness, influenza, upper respiratory tract infection and urinary tract infection) compared to their respective maintenance dose (50 mg or 30 mg) and larger decreases in some hematological parameters (such as lymphocytes and lymphocyte subsets). There were mild and mostly transient changes in hematological parameters, some of which were dose dependent.

These preliminary clinical data indicate that PF-06651600 at doses up to 200 mg QD for 4 weeks followed by 50 mg QD for 20 weeks, 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.

It is not known whether PF-06651600 is secreted into human milk.

Because of the above and 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 blood levels.

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-06651600		
Reductions in platelet counts and lymphocyte counts.	In Study B7931005, reductions in platelet counts and lymphocyte counts were observed during treatment with PF-06651600 200 mg QD but were not considered clinically meaningful and improved after switching to 50 mg QD.	In participants receiving PF-06651600, a 200 mg QD dose will be used only for 4 weeks after which they will receive 50 mg QD. Clinical laboratory test results will be monitored and there are pre-specified discontinuation criteria based on laboratory test results (Section 10.7).
Potential risk of infections.	PF-06651600 is an immunomodulator and, as such, can be associated with the potential risk of infections (including serious infections), opportunistic infections, and viral reactivation.	Participants with infection history will be excluded (See Section 5.2), the risk of infection will be monitored in the study, and there are discontinuation criteria for serious infections (Section 10.7).
Potential fetal risk.	In animals, PF-06651600 was associated with fetal changes in bones and some internal organs, and lower fetal body weights.	WOCBP who are unwilling or unable to use contraception as defined in the study protocol will be excluded (See Section 5.3.1 and Section 10.4). WOCBP will routinely have pregnancy tests and will follow discontinuation requirements if pregnant (Section 8.2.13).
Potential risk of secreting into human milk.	It is not known whether PF-06651600 is secreted into human milk.	Breastfeeding women are not eligible to participate in the study. PF-06651600 should not be administered to breastfeeding women and exposure during breastfeeding should be reported to Pfizer Safety (See Section 8.3.5.2).

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary - Safety	
• To assess I-V interwave latency on brainstem auditory evoked potentials (BAEPs) in adult participants with alopecia areata (AA) treated with PF-06651600.	• Change from baseline in I-V interwave latency on BAEP at a stimulus intensity of 80 decibels (dB) at Month 9.
Secondary - Safety	
• To assess I-V interwave latency on BAEPs in adult participants with AA treated with PF-06651600.	• Change from baseline in I-V interwave latency on BAEP at a stimulus intensity of 80dB at Months 6, 9E, and 15E.
• To assess axonal dystrophy in intraepidermal nerve endings over time in adult participants with AA treated with PF-06651600.	• Change from baseline in axonal dystrophy in skin punch biopsies at Month 9 and Month 15E.
• To assess intraepidermal nerve fiber density (IENFD) over time in adult participants with AA treated with PF-06651600.	• Change from baseline in IENFD in skin punch biopsies at Month 9 and Month 15E.
• To assess wave V amplitude on BAEP over time in adult participants with AA treated with PF-06651600.	• Change from baseline in amplitude of wave V on BAEP at a stimulus intensity of 80dB at Months 6, 9, 9E, and 15E.
• To assess presence of wave V on BAEP over time in adult participants with AA treated with PF-06651600.	• Absence of wave V on BAEP at stimulus intensities ranging from 80dB to 40dB at Months 6, 9, 9E, and 15E.
• To evaluate the safety and tolerability of PF-06651600 in adult participants with AA.	• Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events (AEs) leading to discontinuation;[a] • Incidence of clinically significant abnormalities in vital signs and ECG;[a]

Objectives	Endpoints
	• Incidence of clinically significant abnormalities in clinical laboratory values.[a]
Secondary- Efficacy TP1-TP2	
• To evaluate response to PF-06651600 measured by the Severity of Alopecia Tool (SALT) in adult participants with AA.	• Change from baseline in overall and AA SALT[b] score at Month 9 and other time points collected.
• To evaluate the response to PF-06651600 measured by the Patient's Global Impression of Change (PGI-C) tool in adult participants with AA.	• PGI-C score response defined as greatly improved or moderately improved at Month 9 and other time points collected.
Tertiary/Exploratory-Efficacy TP3	
• To evaluate long-term response to PF-06651600 measured by the Severity of Alopecia Tool (SALT) in adult participants with AA.	• Change from baseline in overall and AA SALT[b] score at Month 51E and other time points collected.
• To evaluate the long-term response to PF-06651600 measured by the Patient's Global Impression of Change (PGI-C) tool in adult participants with AA.	• PGI-C score response defined as greatly improved or moderately improved at Month 51E and other time points collected.

a. Refer to Section 9.4.1 for specific safety summary included in each study report.
b. AA SALT is the amount of scalp hair loss due to AA.

4. STUDY DESIGN

4.1. Overall Design

Study B7981037 is a Phase 2a, randomized, double-blind, parallel group, placebo-controlled safety study designed to evaluate the safety and tolerability of PF-06651600, including the assessment of BAEP and IENF, in adults with ≥25% scalp hair loss due to AA.

Approximately 60 adults 18 to 50 years of age will be randomized 1:1 to receive either PF-06651600 or placebo. If there are issues related to the integrity of some peripheral nerve punch biopsy samples, up to an additional 20 participants may be added at the discretion of the Sponsor to ensure adequate numbers of participants with interpretable biopsies.

Treatment Period 1 (TP1) and Treatment Period 2 (TP2):

The total duration of participation in the study for TP1 and TP2 will be approximately 26 months.

This includes up to a 5-week screening period, a 9-month placebo-controlled treatment phase, a 15-month active therapy extension phase, and a 4-week follow-up period [for participants not continuing to TP3 or discontinuation of study intervention (see Schema Section 1.2)]. Screening will occur within 35 days prior to Day 1 of the study to confirm that selection criteria for the study are met. At Month 9, the placebo-controlled phase will end, and all participants may enter the active therapy extension phase of the study and receive PF-06651600. For any participant discontinued for a neurological or auditory adverse event, the participant will be evaluated again at 6 months after discontinuation; the maximum duration of participation in the study for such participants could be approximately 32 months if the event occurred at the last visit.

At Month 6, any participant with a baseline overall SALT score ≤75 will have the option to enter the active therapy extension phase if their overall SALT score at Month 6 has increased from baseline by ≥25 points. Those participants who enter the active therapy extension phase at Month 6 are to complete at that visit all the Month 6 (Visit 5) assessments and then follow the schedule of visits in the active therapy extension phase starting with Month 3E skipping the Month 9 (Visit 6).

BAEPs will be measured at screening and at Months 6, 9, 9E, and 15E, or early termination for all participants. IENF will be assessed at Day 1, Month 9, and Month 15E, or early termination. Participants who enter the active therapy extension phase at Month 6 will have a skin punch biopsy taken at Month 6 for IENF assessments instead of at Month 9. The skin biopsy must be collected before the start of Active Therapy Extension Phase.

Participants who discontinue the study due to a neurological or auditory AE will have assessments performed at the time of discontinuation and repeated at 6 months after the last dose of study intervention (see Section 10.7).

Treatment Period 3 (TP3):

The total duration for TP3 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 TP3 for a maximum of an additional 36 months or until availability of commercial product in their country, or until the Sponsor terminates the study in that country, whichever occurs first.

In TP3, participants will receive 50 mg QD PF-06651600. The total duration of participation in TP3 is approximately 37 months, including up to 36 months 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.

4.2. Scientific Rationale for Study Design

Because the dog toxicity study BAEP finding was considered a central auditory effect, BAEP interwave I-V latency will be the primary endpoint for this study, since generally, the interwave latencies are used for diagnosis of brainstem effect in humans.[45] High-intensity stimulation (eg, 80dB) is used in humans for differential diagnosis of cochlear versus retro-cochlear lesions.[45]

The total duration of the study is approximately 62 months (26 months [TP1 + TP2] + 36-month extension [TP3]), though this duration could be longer for any participant who discontinues due to a neurological or auditory AE and needs to return for follow-up in 6 months. This includes a 9-month placebo-controlled phase that will evaluate the effect of PF-06651600 during the same time frame in which axonal dystrophy was observed in the 9-month dog toxicity study (ie, axonal dystrophy in the dog studies presented at 9 months and a functional correlate [BAEP threshold and waveform abnormality] was evident at 7 and 9 months). Following the placebo-controlled phase, there will be a 15-month active therapy extension phase TP2. The extension phase is included to collect longer-term safety information.

In this study, BAEP will be measured at screening, 6 months, 9 months (the end of the placebo-controlled phase), Month 9E, and Month 15E or end of treatment for early discontinuation and potentially at a 6-Month Follow-Up. The timepoints for BAEP (not measured in TP3) were chosen for the placebo-controlled phase based on the timing of findings in the dog toxicity study. The additional 2 measurements during active therapy extension phase TP2 are intended to provide longer-term assessment.

Axonal dystrophy and IENFD will be evaluated in peripheral skin biopsies (TP1 and TP2 only). The technique allows direct assessments of both morphological features (such as axonal dystrophy) as well as IENFD in nerve endings.[46-48] IENFD directly evaluates the loss of axons (as an index of axonal degeneration) and its assessment in peripheral skin punch biopsies is an established technique used in clinical evaluations of patients with peripheral neuropathies. For example, an IENFD study evaluating the structural and functional integrity of small autonomic nerve fibers in E46KSNCA (a biomarker for an aggressive Lewy body brain disease), carriers showed small fiber neurodegeneration in the skin. In another study, distal leg IENFD was shown to detect axonal loss in patients with oxaliplatin-induced neuropathy.[49] Also, in a study of patients with diabetic small fiber neuropathy, impaired glucose tolerance neuropathy and idiopathic small fiber neuropathy, IENFD loss was seen at

three sites (proximal thigh, distal thigh, distal leg) whereas there was no significant change in IENFD in healthy controls over 2 to 3 years.[50]

The distal part of lower extremities will be selected for skin punch biopsies because distal portions of long axons are typically more susceptible to axonal dystrophy than proximal portions. Axonal dystrophy and IENFD will be measured at Day 1, Month 9, Month 15E, or end of treatment for early discontinuation (TP1 and TP2 only), and potentially at 6-Month Follow-Up, reflecting the timing of findings in the dog toxicity studies and for longer-term assessment.

Inclusion of patients with ≥25% scalp hair loss due to AA, which the investigator has additionally determined to be appropriate for systemic therapy, is considered to be justified. The threshold of ≥25% scalp hair loss due to AA is also currently being used in the long-term safety study B7981032. 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 severe hair loss.[51]

4.3. Justification for Dose

This study will evaluate PF-06651600 administered at a dose of 200 mg QD for 4 weeks followed by a dose of 50 mg QD for up to 60 months for participants proceeding to TP3. This dose regimen was selected as it is the highest dose regimen being evaluated in the Phase 3 development program in AA.

Exposure margins of the proposed clinical doses relative to the nonclinical 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 Human 50 mg QD Dose in AA patients				
Dog 2-month toxicology (Study 1)	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 & TP2, including follow-up visit and does not continue to TP3 due to local commercial availability of PF-06651600 for AA; OR
- If participant has completed all phases of TP3, including Follow-up Visit; OR
- If participant discontinued from the study during TP3 due to local commercial availability of PF 06651600 for AA.

The end of the study is defined as the date of the last visit of the last participant in the study.

The primary completion date (PCD) is defined as the date when the last participant completes the Month 9 Visit of the Placebo-Controlled Phase.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Participants must meet the following AA criteria:
    - Have a clinical diagnosis of AA. Other etiologies of hair loss coexistent with AA are allowed.
    - ≥25% scalp hair loss due to AA (including AT and AU) measured by SALT at screening 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 other etiologies of alopecia, it cannot be verified that SALT (AA) score is ≥25, then the participant must be excluded from the study.

Hearing and Neurological Assessments at Screening

2. Participants must have normal hearing and BAEP assessed by the audiology professional and confirmed by the central reader.
3. Participants must have a normal neurological examination by a neurologist and absence of peripheral neuropathy by history, symptoms, and the neuropathy assessment. Participants with stable unilateral carpal tunnel syndrome or stable unilateral ulnar entrapment on neurological examination or history are allowed in the study.

Age

4. All participants must be 18 to 50 years of age at the time they sign the informed consent.

Sex

5. Male or Female

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

The study protocol requirements regarding contraception are as follows:

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 Section 10.4.

OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 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 (Section 10.2) pregnancy test (urine or serum as required by local regulations) at screening and 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 as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.
7. All participants must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Prior/Concomitant Therapy

8. If receiving permitted concomitant medications, 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:

Medical Conditions

1. Other medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study. 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 8.2.11).

    b. Suicidal behavior in the past year: a "Yes" answer on any question in the suicidal behavior section of the C-SSRS.

    c. For participants who had previous history of suicidal behaviors in the past >1 year: (a "Yes" answer to any of the suicidal behavior items of the C-SSRS), 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.

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

e. Clinically significant depression as indicated by a Patient Health Questionnaire-8 Items (PHQ-8) total score ≥15 (Section 8.2.12).

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.

2. Any current hearing loss or current disease that can affect hearing, including disorders associated with progressive hearing loss in adults, e.g. Meniere's disease, otosclerosis, superior semicircular canal dehiscence or labyrinthitis.
3. Occupational or recreational noise exposure sufficient to place the participant at risk for noise-induced hearing loss without proper ear protection as determined by the audiology professional performing the screening audiological evaluation.
4. Current or history of clinically significant central or peripheral neurological disease regardless of etiology or any other neurologic disease that could impact study results in the judgement of the investigator or the examining neurologist.
5. First degree family history of hereditary neuropathy.
6. Any history of peripheral neuropathy (PN), including diabetic PN, chemotherapy-induced PN, drug-induced PN, genetic PN, idiopathic PN, etc.
7. Cognitive or behavioral conditions which could prevent the participant from cooperating with the investigator or audiology/neurology professionals performing the evaluations or procedures.
8. HbA1c ≥7.5% at screening.
9. 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 and parathyroid disease, which can be associated with hair loss), pulmonary, cardiovascular, psychiatric, immunologic (other than AA), rheumatologic, dermatologic 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).

10. 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.
11. History of any lymphoproliferative disorder such as Epstein Barr virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs and symptoms suggestive of current lymphatic or lymphoid disease.
12. History of disseminated herpes zoster or disseminated herpes simplex, or recurrent (more than one episode of) localized, dermatomal herpes zoster.
13. 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 21).
14. Known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.
15. History of human immunodeficiency virus (HIV) or positive serology for HIV) at screening.
16. Significant trauma or major surgery within 1 month of the first dose of study intervention.
17. Significant trauma, surgery, or clinical condition at the skin biopsy site(s) which could interfere with the collection or interpretation of the punch biopsy specimens.
18. Considered in imminent need for surgery. Participants with elective surgery scheduled can only be enrolled with the approval of the sponsor.
19. 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. Long-term antibiotic treatment for acne is not exclusionary but should be approved by the Sponsor.
20. 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). Additional reflex testing for hepatitis B virus deoxyribonucleic acid

(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 Section 8.2.10.3 and Section 10.6 for testing algorithm, reflex testing, and full eligibility criteria.

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.

21. 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 (CXR) (posterior-anterior and lateral views are recommended; however local guidelines should be followed) (Section 8.2.3) or other appropriate diagnostic imaging such as computed tomography or magnetic resonance imaging (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 (INH) 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, CXR 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 8.2.3). 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 or latent TB infection must be excluded from the study.

Prohibited Prior/Concomitant Therapy

22. Receipt of (in the timeframes outlined below), or anticipated treatment with (during the course of the study), the following prohibited prior/concomitant medication(s) or treatment regimens (and those listed in Section 10.8):

a. At any time:

- Previous use of PF-06651600 in any disease indication.
- 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 systemic JAK inhibitor for use in any disease indication.
- Other immunomodulatory biologic agents.

Note: Discontinuation of any JAK inhibitor due to a treatment-related safety event is exclusionary. Topical use of any JAK inhibitor during the course of the study is prohibited.

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 be immunosuppressive including:
  - Cyclosporine A, azathioprine, methotrexate (MTX), mycophenolate mofetil (MMF), everolimus, ibrutinib.
  - Systemic (oral or injectable) corticosteroids.
  - Topical or intralesional corticosteroids in formulations/ doses/frequencies that, in the investigator's judgement, could lead to substantial systemic exposures (except as described in Section 8.2.9.2.2).

e. Vaccinated with a live attenuated vaccine (or exposed to a person vaccinated with a live attenuated vaccine) within the 6 weeks prior to the first dose of study intervention or is expected to be vaccinated or have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study intervention.

f. **Within 4 weeks** of first dose of study intervention or 5 half-lives (if known), whichever is longer: prohibited moderate to potent CYP3A inducers as listed in Section 10.8.

g. **Within 1 week** of first dose of study intervention or 5 half-lives (if known), whichever is longer:

- Herbal medications with unknown properties.
- Prohibited CYP3A substrates as described in Section 10.8.

h. Medications that may be associated with peripheral neuropathy or hearing loss:

- Chemotherapeutic agents or immunotherapy within 2 years before screening.
- Aminoglycosides or 2nd line injectable anti-TB drugs within 6 months before screening.
- Metronidazole or INH within 4 weeks before baseline.
- Loop diuretics within 2 weeks before screening.
- Quinine or quinidine within 1 week before screening.
- Any radiation therapy to the lumbosacral plexus.
- Current use of salicylates (other than low dose aspirin for prevention of cardiovascular / cerebrovascular disease).

Prior/Concurrent Clinical Study Experience

23. Participation in studies involving investigational products (eg, drugs or vaccines) within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to study entry and/or during study participation

Diagnostic Assessments

24. 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.

25. **ANY** of the following conditions at screening:
    a. Screening 12-lead 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 ms).
    b. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes.
26. **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed appropriate:
    a. Absolute neutrophil count $<1.2 \times 10^9$/L ($<1200/mm^3$);
    b. Hemoglobin <11.0 g/dL or hematocrit <33%;
    c. Platelet count $<150 \times 10^9$/L ($<150,000/mm^3$);
    d. Absolute lymphocyte count of $<0.8 \times 10^9$/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 could affect interpretation of study data or the participant's participation in the study.

Other Exclusions

27. Investigator site staff members or Pfizer employees directly involved in the conduct of the study, site staff members otherwise supervised by the investigator, and their respective family members.
28. Have history of alcohol or substance abuse.
29. Donation of blood in excess of 500 mL within 8 weeks prior to Day 1.

5.3. Lifestyle Considerations

5.3.1. Contraception

Participants who are WOCBP must agree to use one highly effective method of contraception (as specified in Section 10.4), as applicable.

The investigator or his/her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (See Section 10.4), and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA (Section 1.3), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation 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 8.2.13).

5.3.2. Meals and Dietary Restrictions

On study visit days when lipid panel will be collected (see the SoA [Section 1.3]), participants must comply with fasting requirements for at least 8 hours prior to the visit. Water and permitted non-study medications are allowed (see Section 6.5.1).

Participants must agree not to drink tonic water during the study.

5.3.3. Caffeine 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.

5.3.4. Elective Surgery

During the study, 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 randomly 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).

Screening laboratory tests with abnormal results may be repeated 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 upon discussion with, and agreement by, the sponsor.

Participants 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, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

In both the placebo-controlled phase (TP1) and active therapy extension phase (TP2), each participant will receive a total of 4 tablets QD during the initial 4-week period and a total of 1 tablet QD during the remainder of that study phase. To maintain blinding, participants who received PF-06651600 during the placebo-controlled phase will receive 1 tablet QD of PF-06651600 and 3 tablets of placebo QD for a total of 4 tablets QD during the initial 4-week period of the active therapy extension phase.

Placebo-Controlled Phase (TP1) by Dose Period				
Arm Name	**PF-06651600**		**Placebo**	
	Visits 2 – 3	Visits 3 - 6	Visits 2 – 3	Visits 3 - 6
	PF-06651600 200 mg QD (4-week dose)	PF-06651600 50 mg QD	Placebo (4-week dose)	Placebo
Intervention Number	PF-06651600	PF-06651600	Not applicable	Not applicable
Intervention Name	Ritlecitinib	Ritlecitinib	Placebo	Placebo
Type	Small molecule	Small molecule	Other	Other
Dosage Form	Tablet	Tablet	Tablets	Tablets
Dose Strength	50 mg	50 mg	0 mg	0 mg
Dosage	50 mg – 4 tablets	50 mg – 1 tablet	0 mg -4 tablets	0 mg -1 tablet
Route of Administration	Oral	Oral	Oral	Oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	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. Each blister card will be labeled as required per country requirement.	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. Each blister card will be labeled as required per country requirement.

Active Therapy Extension Phase (TP2) & Extension Phase (TP3)				
	Initial 4-Weeks Dose (4 Tablets)			**50 mg QD Dose (1 Tablet/Capsule) (All Participants)**
	Received Placebo in Placebo-Controlled Phase	**Received PF-06651600 in Placebo-Controlled Phase**		
ARM Name	PF-06651600 200 mg QD	PF-06551600 50 mg QD/Placebo		PF-06551600 50 mg QD
Intervention Number	PF-06651600	PF-06651600	Not applicable	PF-06651600
Intervention Name	Ritlecitinib	Ritlecitinib	Placebo	Ritlecitinib
Type	Small molecule	Small molecule	Other	Small molecule
Dosage Form	Tablet	Tablet	Tablet	Tablet/Capsule
Dose Strength	50 mg	50 mg	0 mg	50 mg
Dosage	50 mg – 4 tablets	50 mg – 1 tablet	0 mg - 3 tablets	50 mg – 1 tablet or capsule (TP3 only)
Route of Administration	Oral	Oral	Oral	Oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	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	Study Intervention will be provided in blister cards. Each	Study Intervention will be	Study Intervention will be provided in blister cards or

Active Therapy Extension Phase (TP2) & Extension Phase (TP3)				
	Initial 4-Weeks Dose (4 Tablets)			50 mg QD Dose (1 Tablet/Capsule) (All Participants)
	Received Placebo in Placebo-Controlled Phase	Received PF-06651600 in Placebo-Controlled Phase		
	labeled as required per country requirement.	blister card will be labeled as required per country requirement.	provided in blister cards. Each blister card will be labeled as required per country requirement.	bottles (TP3 only). Each blister card/bottle will be labeled as required per country requirement.

Abbreviation: 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

- The study intervention will be dispensed using an Interactive Response Technology (IRT) management system at each visit as specified in the SoA (Section 1.3). At the Month 1 visit, the participant will return the package containing the study intervention which was dispensed at the Day 1 visit for accountability.
- A qualified staff member will dispense the study intervention via unique container numbers on the blister cards or bottles (TP3 only) provided. The participant 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.
- 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.

  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. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

  Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should

actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP Manual.

Study interventions should be stored in their original containers.

Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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). such as the Investigational Product Accountability Log or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

Further guidance and information for the final disposition of unused study interventions are provided in the IP Manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers in the blister cards, or bottles (TP3 only) provided, in quantities appropriate according to the SoA (Section 1.3). A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the blister cards, or bottles (TP3 only) provided throughout the course of dosing and return the blister cards or bottles (TP3 only) to the site at the next study visit.

At the EOP visit (Month 6 or Month 9/EOP, as appropriate), additional double-blind therapy may be dispensed if the neurological and/or audiological/BAEP assessments (including the central read confirmation and any repeat assessments if deemed necessary by the central reader) are not yet completed. Additional double-blind therapy would be dispensed as a 32-day supply, but dosing may not extend past the end of the +21 day EOP visit window. Once neurological and audiological/BAEP EOP assessments are complete, active-therapy may be dispensed either on site or by shipping to the study participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

Study using IVRS/IWRS	All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.
Blind Break (IVRS/IWRS)	The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

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

6.3.1. Blinding

TP1 will be conducted in a double-blind manner. Participants, investigators, site and sponsor staff (except for the sponsor staff involved in the assignment or distribution of study intervention) will be fully blinded to the treatment assignments.

After the PCD (Section 4.4) TP2 will be conducted in a single-blind manner. Participants, investigators and site staff will remain blinded, but the sponsor staff will be un-blinded to the initial treatment assignments, in order to conduct the analysis for the PCD-CSR (Section 9.4.1). Although participants, investigators, site and sponsor staff will all be aware that active therapy will be provided to all participants in TP2 (and that after the first 4 weeks of TP2 all participants will be receiving the same dose of active treatment), study intervention packaging will remain blinded during this period.

After all participants have completed TP2, the study will be fully unblinded to the initial treatment assignments.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit during the Intervention Period. Compliance with the dosing of study intervention will be verified by delegated site personnel through a combination of counting returned tablets, or capsules (TP3 only) 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 (TP3 only), 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 5.3.4 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). With the exception of medications prohibited for use in Section 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 10.8.

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). Acetaminophen/paracetamol is allowed if dosed no more than 3.0 g/day for no more than 5 consecutive days. Participants are not allowed any other investigational drugs or treatments during the study.

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 Section 10.8. 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. During the study, if it is discovered that a subject has been taking a medication or treatment that could affect AA, the investigator should contact the Sponsor for each case to determine whether the subject must 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 during the study.

6.5.3. Vaccinations

Vaccination with a live attenuated vaccine is prohibited within the 6 weeks prior to the first dose of study intervention, during the study, and for 6 weeks following discontinuation of study drug. Vaccines (including COVID-19 vaccines) that are not live attenuated are permitted.

Similarly, current routine household contact with individuals who have been vaccinated with live attenuated vaccine must be avoided during study treatment and for 6 weeks following completion of study treatment. Following vaccination with live attenuated vaccine, 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, MMR (measles, mumps, rubella) vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live).

6.5.4. Surgery

During the study, 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 5.3.4 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 participant to permanently discontinue study intervention (ie, definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: treatment-related SAEs, serious infections, and other events as described in Section 10.7.2.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the assessments at the Early Termination (ET) and Follow-up visits (per the SoA [Section 1.3]). See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and 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, posttreatment study follow-up, and/or future collection of additional information.

Refer to Section 10.7 for discontinuation criteria.

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, 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 22E then the final visit in the Observation Period would be conducted at Month 51E (ie, the next closest scheduled visit occurring 24 months after Month 22).

7.1.2. Temporary Discontinuation

See Section 5.3.4 and Section 6.4.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;

- Lost to follow-up;
- Death;
- Study terminated by sponsor;

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA (Section 1.3) 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 SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD 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 (Section 1.3).
- 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 appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. The ICD is signed and dated by each participant in accordance with the procedures described in Section 10.1.3.
- Due to audiological and neurologic evaluations 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.

- 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 Section 10.4 and Section 8.2.13).
- The patient-reported outcome assessment should be completed before the other evaluations or treatments at all of the visits (when patient reported outcome assessments are to be administered) when possible. Vital signs and 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 total amount of blood collected from each participant over the duration of TP1 plus TP2, including all assessments at the screening and follow-up visits (for participants not proceeding to TP3), will be approximately 200 mL. The maximum amount of blood collected from each participant over the duration of TP3, including all assessments at the follow-up visits, will be approximately 118 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 318 mL Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

- Refer to Section 10.7 for guidelines on participant safety monitoring and discontinuation.

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. An experienced and qualified physician or healthcare professional may be permitted to perform the clinical evaluations of alopecia (ie, SALT). 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). 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

8.1.2.1. Severity of Alopecia Tool (SALT)

SALT is a quantitative assessment of AA severity based on scalp terminal hair loss.[52] Scalp hair loss due to AA (AA SALT score) is measured at screening. The overall SALT score, which does not distinguish the reason for hair loss, will be collected at visits shown in the SoA (Section 1.3).

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.

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

8.1.2.1.1. Non-AA SALT Score

In addition to the overall amount of scalp terminal hair loss, scalp hair loss due to etiologies other than AA will be assessed using the SALT tool. This will only be collected for participants known to have scalp hair loss due to other etiologies in addition to AA. The non-AA SALT score will be collected at visits shown in the SoA (Section 1.3).

8.1.2.1.2. Alopecia Areata Eligibility Assessment

In addition to the overall amount of scalp terminal hair loss (overall SALT), scalp hair loss due to AA (AA SALT) will be assessed at the screening visit to verify eligibility of participants.

8.1.3. Patient Reported Outcomes

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

The 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".

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Unscheduled visits, physical exams, or other study assessments may also be conducted at any time during the study to assess perceived safety issues.

Safety monitoring and discontinuation criteria are provided in Section 10.7.

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

- Baseline values will be defined as the last non-missing values collected before dosing on Day 1 for all participants.

8.2.1. Medical History, Physical Examinations, Height and Weight

- Complete AA disease history includes collection of details of AA at screening: AA history, AA diagnosis, number of years of current episode of hair loss, pattern of scalp hair loss, body hair loss, the use of topical treatments, systemic treatments and other treatments for AA.
  Note: Initiation of the current episode should be the last occurrence when the patient had substantial scalp hair (regardless of whether that hair growth occurred spontaneously or was the result of interventional treatment) prior to scalp hair loss.
- Medical history, including, but not limited to, comorbid conditions, history of drug, alcohol, tobacco use, dermatologic, auditory, and neurologic history, and infection history will be collected at screening and/or Day 1 (as applicable per the SoA [Section 1.3]) Refer to the CRF completion guidelines for specific information regarding medical history information to be collected for each group of participants.
- Smoking status and average weekly alcohol consumption (units/week) will also be collected for all participants.
- Height and weight will be measured without the participant wearing shoes or outerwear. Height (in or cm) and weight (lb or kg) will be measured and recorded in the source document at various time points according to the SoA (Section 1.3).

- 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 and auditory 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 and auditory 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 8.2.9.2 for additional details.

8.2.2. Vital Signs

- Oral, tympanic, or axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed. It is preferred that body temperature be collected using the tympanic or oral methods; however, the axillary method is 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 (BP) 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. 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 BP cuff should be used to measure BP each time.
- Pulse rate should be measured at approximately the same time as BP for a minimum of 30 seconds.
- BP and pulse 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.

8.2.3. Chest Radiography

CXR (posterior-anterior and lateral views are recommended; however local guidelines should be followed) or other appropriate diagnostic image (ie, computed tomography or MRI) must be taken at screening or within 3 months prior to screening visit for all participants. 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. Documentation of the reading by the qualified radiologist or pulmonologist must available in the source documentation.

8.2.4. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) 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 Section 10.7 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.
- ECG values of potential clinical concern are listed in Section 10.7.

8.2.5. Neurological Examination

Neurological examination must be performed by a qualified (board certified or equivalent) neurologist and will include a general neurological evaluation and a neuropathy assessment. The neuropathy assessment will assess for symptoms and signs of neuropathy. Refer to the Manuals for General Neurological and Neuropathy Assessments for additional details.

The neurologist may recommend additional evaluations and / or additional visits. They may also identify additional medical history or adverse events that need to be added to the CRF.

Additionally, at any time, participants with clinically meaningful changes from baseline in neurologic signs or symptoms should be documented in the CRF, and the monitor and sponsor study clinician should be notified.

The same neurologist should perform examinations on individual participants throughout the study, including during TP3 if a neurological evaluation by a neurologist is clinically indicated by the investigator.

See Section 10.7 for follow-up assessment of participants who discontinue due to a neurological AE.

8.2.6. Audiological Evaluations

All participants will have an audiological evaluation at times specified in the SoA (Section 1.3). When possible, the participant should have the evaluation performed by the same audiology professional, at the same evaluation center using the same equipment during the study.

In countries where licensed and certified audiologists are available, they are the recommended specialists for study-related audiometric testing and its clinical interpretation. In those countries in which an audiologist is not a licensed and certified specialty to interpret and manage audiometric test results, clinical interpretation should be performed by an appropriate specialist licensed and certified to interpret and manage audiometric test results (eg, otolaryngologist), while the actual audiometric testing procedure can be performed by a trained technician or equivalent who is able to perform all required tests.

Participants must have a full audiological assessment completed during screening prior to Day 1. Audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other. 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 all participants.

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

For participants who terminate early from the study, the audiological evaluation should be performed.

If there is a clinically meaningful, treatment-emergent decline in auditory function from the screening measurements, the participant must be promptly evaluated by an audiology professional 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. See Section 10.7 for follow-up assessment of participants who discontinue due to an auditory event.

The central reader will review the audiology results for each applicable visit.

Refer to the most current version of the Audiology Study Guide for details on audiological evaluation.

8.2.7. Brainstem Auditory Evoked Potential Evaluations

All participants will have a BAEP evaluation, as specified in the Manual for BAEP Evaluation, at the times specified in the SoA (Section 1.3). When possible, the participant should have the evaluations performed at the same evaluation center, by the same audiology professional using the same equipment, during the study. Audiology and BAEP evaluations should be done on the same day, with audiology assessment first. If they cannot be done on the same day, assessments must be within 7 days of each other.

A central reader will be used for BAEP to confirm that locally read BAEP waves were labelled appropriately and at their peak so that latency and amplitude data are accurate. Central reading will also ensure consistency in BAEP interpretation. The BAEP recording may be repeated (including additional recordings with modified parameters) or the original recording may be reassessed based on feedback from the central reader. Only results confirmed by the central reader as accurately interpreted will be used for analysis.

For participants who terminate early from the study, the BAEP evaluation should be performed.

For follow-up assessment of participants who discontinue due to an auditory adverse event see Section 10.7.

Refer to the most current version of the Manual for BAEP Evaluation for details on BAEP evaluation.

8.2.8. Skin Punch Biopsy, Evaluation of IENFD and Axonal Dystrophy

8.2.8.1. Skin Punch Biopsy

All participants will have skin punch biopsies performed at times specified in the SoA (Section 1.3). The participant should have the biopsies performed at the same center during the study.

Refer to the most current version of the Central Laboratory Manual for details on the skin punch biopsy procedure.

See Section 10.7 for follow-up assessment of participants who discontinue due to a neurological adverse event.

8.2.8.2. Histology for Axonal Dystrophy and IENFD

This will be performed by a central reader.

8.2.9. Special Safety Assessment

8.2.9.1. 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.

8.2.9.2. Dermatological Events

All participants will have a dermatological full body exam as noted in the SoA (Section 1.3).

Guidelines for the assessment of herpetiform rash and drug-related rash are noted in Section 8.2.9.2.1 and Section 8.2.9.2.2, respectively.

8.2.9.2.1. Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes zoster or herpes simplex) or eczema herpeticum, specimens for viral 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.

8.2.9.2.2. Drug-Related Rash

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

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

All 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 when possible. Detailed procedures to assure photographic quality and consistency will be provided separately in a photography instruction manual.

Within 30 days of receipt, the principal investigator (PI) should forward all de-identified biopsy results, culture results, photographs, and any additional relevant test results to the sponsor for review. Refer to the Canfield Photography User Manual for details.

8.2.10. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- 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 the SoA (Section 1.3). All other labs do not require fasting.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the 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 or within 28 days of the last dose of study intervention 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.
    - All protocol-required laboratory assessments, as defined in Section 10.2 must be conducted in accordance with the laboratory manual and the SoA (Section 1.3). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.
    - 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.
- See Section 10.5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.10.1. 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 when QFT-G is not available.

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 CXR will be performed as described in Section 8.2.3.

8.2.10.1.1. 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 if induration is <5 mm.

8.2.10.1.2. Screening Tuberculosis Testing

During the screening period, it must be determined and documented that participants do not have evidence of untreated or inadequately treated active or latent infection with TB per Exclusion criteria 21 in Section 5.2. The results of TB screening conducted 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).

8.2.10.1.3. Subsequent Tuberculosis Testing

Subsequent (post-screening) TB testing will be conducted at the time points indicated in the SoA (Section 1.3) for all participants as described below.

For participants with a negative QFT-G (or T-Spot or PPD) result during prior testing and no history of previous treatment for active or latent TB, the following testing will be conducted:

- QFT-G test or T-Spot test per Section 8.2.10.1. 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 the decision to restart treatment has been discussed and agreed with the sponsor, prior to restarting treatment. For this to happen, the participant must be evaluated, and the test result must be reviewed by a specialist (eg, pulmonologist or infectious disease specialist) to determine if the participant has active or latent TB. Participants with active or latent TB must be discontinued. If it is determined by a specialist (eg, pulmonologist or infectious disease specialist) that the participant does not have active or latent TB, the decision to restart treatment must be approved by Pfizer.

- Participants with a negative laboratory result may continue in the study and do not require a chest radiograph.

For participants with a history of adequate 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.

- CXR 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 identified as having active TB must be discontinued from the study and referred to a specialist (eg, pulmonologist or infectious disease specialist) for evaluation.

- Participants with a CXR or other appropriate diagnostic image (ie, computed tomography or MRI) negative for active TB may continue in the study.

8.2.10.2. Day 1 Viral Screen

A serum sample will be collected at Day 1 and submitted to the central lab for all participants. 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.

8.2.10.3. Hepatitis B Virus DNA (HBVDNA) Testing

For participants in countries in which hepatitis B prevalence has been reported at a rate of >5.0%[53] or if required by local standard of care, HBVDNA testing will be performed as reflex testing for any participant who is positive for HBcAb at screening. In addition, HBVDNA testing will be performed according to the SoA (Section 1.3) for subjects who were enrolled with a positive HBcAb and a negative HBsAg in those regions for which hepatitis B prevalence has been reported at a rate of >5.0% or if required by local standard of care. Testing at additional time points may be performed as per the local standard of care. Please refer to Section 10.6 for the testing algorithm, reflex testing, and eligibility criteria.

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

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

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"[54]. The version used is dictated by the actual study visit and the participant population (See the SoA [Section 1.3]).

At the screening or Day 1 visits, if the participant has had suicidal ideation associated with actual intent and a method or plan in the past year ("yes" answers on items 4, 5), the participant will not be included in the study. For participants, suicidal behavior in the past year ("Yes" answer on any question in the suicidal behavior section of the C-SSRS), is exclusionary. For participants who have had previous history of suicidal behaviors in the past >1 year, (a "Yes" answer to any of the suicidal behavior items of the C-SSRS), 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.

Any participants who are not eligible due to suicidal ideation or behavior 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.

8.2.12. 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.[55] Individuals with clinically significant depression as noted by a PHQ-8 total score ≥15 at screening must not be enrolled in the study.

8.2.13. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA (Section 1.3). Following a negative pregnancy test result at screening, appropriate

contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior to the participant's 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 51E/EOT visit. The pregnancy testing between visits may occur outside of the study site. Urine pregnancy kits will be provided to participants at each study visit (starting at Month 1) and site personnel will instruct participants on when and how to administer the pregnancy test and how to interpret the result. The participants 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 willingness to perform administered urine pregnancy test, and understanding of how to perform the test as well as how to interpret the test result. In addition, site personnel will contact participants 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 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 institutional review boards (IRBs)/ethics committees (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.

8.2.14. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the sponsor study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

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 caused the participant to discontinue the study intervention (see Section 7.1 and Section 10.7).

Each participant 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, except as indicated below, after the last administration of the study intervention.

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 Visit 19.

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.

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

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 definitively 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 AEs or SAEs 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 8.3.1.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. 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 AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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 Section 10.3.

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)/Independent Ethics Committees (IEC), 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/IEC, 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 pre-procedure 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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, a person receives 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 involved 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

Deaths and AEs related to cardiovascular events will be adjudicated (Section 9.6)

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 8.2.9 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

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

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 participant.

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/treating physician 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. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. 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

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

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. Immunogenicity Assessments

Immunogenicity assessments are not applicable in this study.

8.10. Health Economics

Not applicable: Health economic/medical resource utilization parameters are not evaluated in this study.

.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

For the primary safety endpoint, there is no formal hypothesis testing. The analyses will focus on estimation. Summary statistics for each group with 95% confidence intervals will be provided.

Estimands

Not applicable since there is no formal statistical hypothesis testing for this study.

9.2. Sample Size Determination

Approximately 60 adults 18 to 50 years of age will be randomized in a 1:1 allocation ratio to either the PF-06651600 200 mg QD/50 mg QD dose group or the placebo group.

For the primary safety endpoint, change from baseline in I-V interwave latency on BAEP at Month 9, the published standard deviations for I-V interwave latency on BAEP range from 0.1 to 0.3 ms. Assuming the standard deviation of 0.2 ms, and assuming standard deviation of change from baseline is similar as the standard deviation of actual score, the half-width of 95% confidence interval for the group will be 0.07 ms for 30 participants per group.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Efficacy	All randomized participants taking at least 1 dose of study intervention. Data will be summarized according to the intervention they were assigned.
Safety	All participants taking at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

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. This section is a summary of the planned statistical analyses of the primary, the secondary, and the exploratory endpoints.

9.4.1. Timing of the Analyses

There will be 3 Clinical Study Reports (CSRs) for this study: one PCD-CSR, and two supplemental CSRs.

The PCD-CSR will include the primary analysis for this study, which will be conducted following the PCD at Month 9 (TP1) (Section 4.4), and after the Month 9 data are cleaned and locked for all participants. The following data will be included:

- Efficacy data through Month 9 (TP1)
- All safety data collected through the PCD data cut-off date

The supplemental CSR 1 will be prepared after the last participant completes the 4-week follow-up visit, or the Month 15E visit (TP2) if the last participant is enrolling in TP3. This CSR will include:

- Efficacy through Month 15E (TP1+TP2)
- All safety data collected through the cut-off date for this CSR.

The supplemental CSR 2 will be focused on safety and efficacy data from TP3 and will be prepared after the last participant completes the last visit or discontinues from the study.

9.4.2. Efficacy Analyses

Efficacy data will be summarized by the treatment assignment based on efficacy population. The baseline is defined as the last measurement before the first dose in the placebo-controlled phase.

The secondary endpoints for SALT include both the overall SALT and AA SALT scores. The overall SALT score includes hair loss regardless of etiology (ie, scalp hair loss due to both non-AA and AA). The non-AA SALT score only takes into account scalp hair loss other than that due to AA and is required to be assessed only at:

- Month 9 (end of TP1) (or Month 6 for those participants, who enter the active therapy extension phase at Month 6),
- Month 15E (end of TP2) or Early Termination visit (as appropriate), and
- Month 51E (end of TP3) or Early Termination visit (as appropriate).

The AA SALT score at each visit will be calculated using non-AA SALT scores as follows:

- the non-AA SALT score collected at Month 9 (or Month 6) or the Early Termination visit (as appropriate) will be used for visits in TP1.

- the non-AA SALT score collected at Month 15E or the Early Termination visit (as appropriate) will be used for visits in TP2, and
- the non-AA SALT score collected at Month 51E or the Early Termination visit (as appropriate) will be used for visits in TP3.

- The formula for deriving the AA SALT score is given by: AA SALT score = overall SALT score – non-AA SALT score.

PCD CSR (Month 9; TP1)	
Endpoint	**Statistical Analysis Methods**
Primary	• There are no primary efficacy endpoints.
Secondary	• For PGI-C response, for the placebo-controlled phase, number and percentage with 95% confidence interval (based on Clopper-Pearson method) by treatment group, and treatment difference with 95% confidence interval (based on Chan and Zhang's exact method[56]) will be presented. Participants who discontinue from the study for any reason or who switch to active therapy extension phase before Month 9 will be considered as non-responders. • In the placebo-controlled phase, change from baseline in overall and AA SALT score will be analyzed using linear mixed-effects model with baseline, treatment group, visit and treatment group by visit interaction as fixed effects, and participant as a random effect with unstructured covariance matrix assumption. The estimated mean, mean difference, with 95% confidence interval based on the model will be presented at each time point.
Exploratory	• There are no exploratory efficacy endpoints included in this CSR

Supplementary CSR 1 (Month 15E; TP2)	
Endpoint	**Statistical Analysis Methods**
Primary	• There are no primary efficacy endpoints.
Secondary	• For PGI-C response in the active therapy extension phase, number, and percentage with 95% confidence interval (based on Clopper–Pearson method) by initial treatment group will be presented based on observed data. • For overall and AA SALT score in the active therapy extension phase, descriptive statistics will be presented by initial treatment group. Observed data will be used.
Exploratory	• There are no exploratory efficacy endpoints included in this CSR.

Supplementary CSR 2 (Month 51E; TP3)	
Endpoint	**Statistical Analysis Methods**
Primary	• There are no primary efficacy endpoints.
Secondary	• There are no secondary efficacy endpoints included in this CSR.

Supplementary CSR 2 (Month 51E; TP3)	
Endpoint	**Statistical Analysis Methods**
Exploratory	• For PGI-C response in TP3, number, and percentage with 95% confidence interval (based on Clopper–Pearson method) by initial treatment group will be presented based on observed data. • For overall and AA SALT score in TP3, descriptive statistics will be presented by initial treatment group. Observed data will be used.

9.4.3. Safety Analyses

The safety analyses will be summarized by initial treatment group in the safety population based on observed data. The baseline is defined as the last measurement before the first dose in the placebo-controlled phase.

All standard safety summary such as the incidence of safety events will be summarized by the initial treatment group for the placebo-control phase, the active therapy extension phase and TP3 extension phase. For initial active group, the overall summary for the whole study duration will also be provided.

PCD CSR (Month 9; TP1)	
Endpoint	**Statistical Analysis Methods**
Primary	• The primary endpoint is change from baseline in I-V interwave latency on BAEP at Month 9. It will be analyzed using linear mixed-effects model with baseline, treatment group, visit (Months 6 and 9) and treatment group by visit interaction as fixed effects, and subject as a random effect with unstructured covariance matrix assumption. For participants who switch to the active therapy extension phase at Month 6, only their data through Month 6 will be included in the analysis of the placebo-controlled period. The estimated means, with their standard errors and 95% confidence intervals based on the model will be presented.
Secondary	• Change from baseline in I-V interwave latency on BAEP during the placebo-controlled phase will be analyzed using linear mixed-effects model with baseline, treatment group, visit (Months 6 and 9) and treatment group by visit interaction as fixed effects, and participant as a random effect with unstructured covariance matrix assumption. The estimated means, with their standard errors and 95% confidence intervals based on the model will be presented. For data in the active therapy extension phase, descriptive statistics will be presented. • For change from baseline in IENFD at Month 9 and Month 15E and change from baseline in axonal dystrophy in skin punch biopsies at Month 9 and Month 15E: descriptive statistics will be presented. • Change and percent change from baseline in amplitude of wave V: the same method linear mixed-effect model as

PCD CSR (Month 9; TP1)	
Endpoint	**Statistical Analysis Methods**
	the I-V interwave latency will be used for Month 6 and Month 9 data. For data in the active therapy extension phase, descriptive statistics will be presented. • Absence of wave V on BAEP will be summarized descriptively using number and percentage of participants by treatment group at each intensity level. • The incidence rates of safety events, significant clinical abnormalities, vital signs and ECG will be summarized descriptively using number and percentage.

Supplementary CSR 1 (Month 15E; TP2)	
Endpoint	**Statistical Analysis Methods**
Primary	• There are no primary safety endpoints included in the supplemental CSR 1.
Secondary	• For change from baseline in I-V interwave latency on BAEP: descriptive statistics will be presented. • For change from baseline in IENFD at Month 9 and Month 15E and change from baseline in axonal dystrophy in skin punch biopsies at Month 9 and Month 15E: descriptive statistics will be presented. • Change and percent change from baseline in amplitude of wave V: descriptive statistics will be presented. • Absence of wave V on BAEP will be summarized descriptively using number and percentage of participants by treatment group at each intensity level. • The incidence rates of safety events, significant clinical abnormalities, vital signs and ECG will be summarized descriptively using number and percentage.

Supplementary CSR 2 (Month 51E; TP3)	
Endpoint	**Statistical Analysis Methods**
Primary	• There are no primary safety endpoints included in the supplemental CSR 2.
Secondary	• The incidence rates of safety events, significant clinical abnormalities and vital signs in TP3 will be summarized descriptively using number and percentage.

9.5. Interim Analyses

There is no formal interim analysis planned in this study. However, if required, interim analyses may be performed for study monitoring for internal decision making, due to regulatory requests, or to support regulatory submissions. As no statistical hypotheses will be tested in this study, there are no issues of protecting the Type I error rate.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use a data monitoring committee (DMC). The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Independent safety adjudication committees will be used for opportunistic infections, cardiovascular events, neurological /audiological events, and malignancy events.

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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws
- The protocol, protocol amendments, ICD, SRSD(s), 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent 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 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 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 was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.
- Participants must be re-consented to the most current version of the ICD(s) during their participation in the study.
- A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

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 9.6.

10.1.5.2. Adjudication/Review Committee Submission

There will be 4 adjudication committees: one for opportunistic infections, one for cardiovascular events, one for neurological/audiological safety, and one for malignancy. The identification of events requiring submission to an adjudication/review committee will be made by the study site and communicated to Pfizer or designee. In addition, events requiring

review, including opportunistic infections, cardiovascular, neurological/audiological or malignancy events may also 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. The Pfizer Study Team or designee will notify the study site of any events should they identify.

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

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 European Clinical Trials Database (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 standard operating procedures (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 participants) 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 accordance with the format and timelines set forth by US law.

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (Clinical Study Report [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 European Medicines Agency (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 ICDs, 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.
- Description of the use of computerized system is documented in the Study Monitoring Plan.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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 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 following safety laboratory tests will be performed at times defined in the SoA (Section 1.3) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues or as per local regulations.

- The tests detailed in Table 2 will be performed by the central laboratory. (See laboratory manual.)
- 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.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria and Section 8.2.13 Pregnancy Testing for screening pregnancy criteria. For details of timing of recommended pregnancy testing see the SoA (Section 1.3).

Table 2. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count %Reticulocytes MCV MCH Platelet count WBC count Neutrophils Eosinophils Monocytes Basophils Lymphocytes [1]	BUN and creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Direct and Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine Kinase[2] Follow-up testing for potential DILI cases[3]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[4] Urine culture[5]	At screening only: • FSH[6] • Pregnancy test (β-hCG)[7] • Hepatitis C antibody • HIV[8] • HbA1C • HbsAg • HbcAb • HbsAb[9] • HBVDNA[10] • HCVAb • HCVRNA[11] • QFT-G test or T-Spot test[12] • Viral Screen[13] • Skin biopsies/swabs[14] • Fasting Lipid profile[15]

Table 2. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other

NOTES:

1. 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 participants who have completed the Month 15E 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 Section 10.5.
4. Only if urine dipstick is positive for blood, nitrites, leukocyte esterase, and/or protein.
5. Urine culture will be performed if urinalysis is positive for nitrite and/or leukocyte esterase or if clinically indicated. For participants who have completed the Month 15E, urine samples and urinalysis will be performed only if considered clinically indicated by the investigator.
6. For confirmation of postmenopausal status only in females who are not using hormonal contraception or hormonal replacement therapy (HRT).
7. Pregnancy tests (urine) for women of childbearing potential. In the event that urine pregnancy tests are not permitted at an institution, serum pregnancy tests must be utilized. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC.
8. HIV testing per local regulations. Participants who are positive for HIV antibodies will be screen failed.
9. HBsAb will be performed as reflex testing for any participant who is HBsAg negative but HBcAb positive Please refer to Section 10.6 for testing algorithm, reflex testing, and full eligibility criteria.
10. 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 Section 8.2.10.3 and Section 10.6 for testing algorithm, reflex testing, and full eligibility criteria.
11. HCVRNA will be performed as reflex testing for any participant who is HCVAb positive.
12. The QFT G test is preferred; however, the T Spot test is also permitted as described in Section 8.2.10.1. A PPD test can be substituted for the QFT G test or T Spot test only under specific circumstances described in Exclusion criterion 21 in Section 5.2 and Section 8.2.10.1.
13. 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.
14. When required in cases of skin rash adverse events. See applicable sections for herpetiform rash (Section 8.2.9.2.1) and potential drug related rash (Section 8.2.9.2.2).
15. 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 15E Visit.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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, which 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 and Follow-Up of AE and/or SAE

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 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, will 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 professionals.
- 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 an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in 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, mullerian 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.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women 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 at least 14 days prior to FSH testing 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.

Contraception Guidance:

No contraception methods are required for male participants in the study.

The following applies to female participants who are considered WOCBP.

Permitted 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.

1. 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.

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

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

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some 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. 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 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 Alogrithm and Full Eligibility Criteria

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

1. At screening, HsBsAg 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 subject is included in the study, for subsequent visits HBVDNA testing must be performed according to the SoA (Section 1.3).

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.

[a] Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. 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: Guidelines for Participant Safety Monitoring and Discontinuations

These guidelines for participant safety monitoring and discontinuation are to be applied to all participants in Study B7981037. 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:

- Baseline values will be defined as the most recent pre-dose values before dosing on Day 1 for all participants.

10.7.1. 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:

Table 3. Laboratory Retesting Criteria

Laboratory Variable	Laboratory Value	Re-testing Timeframe[a]
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[b]	<600/mm^3 (<0.6 × 10^9/L)	Within 1 week
Serum Chemistry		
Creatine kinase[c]	>3 × ULN	Within 1 week
Aspartate aminotransferase	See Section 10.5 for potential cases of drug-induced liver injury.	Within 48 hours
Alanine aminotransferase	See Section 10.5 for potential cases of drug-induced liver injury.	Within 48 hours
Total bilirubin	See Section 10.5 for potential cases of drug-induced liver injury.	Within 48 hours

a. Based on awareness of the abnormal result.
b. 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.
c. 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 15E. For participants who have completed the Month 15E Visit, creatine kinase and urine myoglobin will not be tested.

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.

10.7.2. 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 or clinically meaningful, treatment-emergent changes in audiological assessments 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 15E Visit):

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

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 re-test. Refer to the re-testing timeframes for laboratory abnormalities in Section 10.7.1:

- 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: 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 15E).

  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 15E. For participants who have completed the Month 15E visit, creatine kinase and urine myoglobin will not be tested.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that meet ANY of the following:

  - >3× ULN with at least one total bilirubin value >2× ULN;

  - >3× ULN accompanied by signs or symptoms consistent with hepatic injury (eg, new onset elevated PT/INR);

  - Two sequential AST or ALT elevations >5× 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 should 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.

- Any participant that is discontinued from study intervention due to an auditory adverse event must have BAEP and auditory assessments performed at the time of discontinuation and repeated at 6 months after the last dose of study intervention. Refer to the Manual for BAEP Evaluations and the Audiology Study Guide for additional information.

- Any participant that is discontinued from study intervention due to a neurological adverse event must have skin biopsy and neurological evaluations, including the Neuropathy Assessment, performed at the time of discontinuation, and repeated at 6 months after the last dose of study intervention. Refer to the Manuals for General Neurological and Neuropathy Assessments for additional information.

10.8. Appendix 8: Prohibited and Permitted Concomitant CYP3A Inducers and Substrates

Please note that this list addresses only CYP3A inducers and sensitive and moderate sensitive CYP3A substrates. Other prohibited medications for this trial are listed in Section 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. If a medication is a sensitive or moderate sensitive CYP3A substrate and is not listed here, consultation with the Sponsor is required.

10.8.1. Prohibited Concomitant CYP3A Inducers and Substrates

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

a. 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.
b. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold. 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.
c. 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.
d. Notated as potent inducers.

10.8.2. Permitted Concomitant CYP3A Substrates

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

a. 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.
b. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold.

10.9. Appendix 9: 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 SoA (Section 1.3) 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).

In this appendix, safety assessment terms include 1) special safety assessments (audiological evaluations, including BAEP, by the audiologist, neurological evaluation by the neurologist, and the skin biopsy) and 2) usual safety assessments (all other safety evaluations).

10.9.1. Eligibility

While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant 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. Participants with active infections are excluded from study participation per Exclusion Criterion 19. When the infection resolves, the potential participant may be considered for re-screening. In addition, the following criteria apply:

- The participant must be able to perform all Screening and Day 1 procedures per the SoA (Section 1.3) at the study site (CXR, skin biopsy, SALT) and/or designated ancillary facility (eg, audiological evaluations and neurological evaluations) to determine whether the participant meets eligibility criteria for the study. This includes collection and resulting of laboratory assessments through the central laboratory vendor.

- The participant must meet eligibility criteria for the study and have had the initial Day 1 skin biopsy performed.

- At the time of Randomization it must be confirmed that the participant will be able to have the Month 1 and Month 3 safety laboratory tests collected/performed at the study site or an alternative clinical laboratory facility (including the participant's home, as available) according to the windows in Section 10.9.3.

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

10.9.2. 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 SoA (Section 1.3) or unplanned 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 (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review dosing logs and record investigational product, including doses taken and any interruptions in intake of investigational product (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. Refer to Appendix 4 and Section 10.9.3.1 of this appendix regarding pregnancy tests and to Section 5.3.1 of this protocol regarding contraception checks.
- Body temperature and collection method (eg, oral, tympanic, axillary), pulse rate, and respiratory rate (measured by study participant/caregiver).
- Collection of interim audiological history (using Part 1 in the Audiometry Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation with entry of clinically significant changes onto the AE section of the eCRF, as appropriate.
- Collection of interim neurological history (using General Neurology and Neuropathy Assessment Completion Guidelines) must be obtained, with entry of clinically significant changes onto the AE section of the eCRF, as appropriate.
- Administration of the C-SSRS performed by a qualified rater. As per Section 8.2.11.1, 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 investigational product to the participant.

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

The SALT and the PGI-C are not assessed if the visit is not onsite.

10.9.3. Alternative Facilities for Safety Assessments

10.9.3.1. Laboratory Testing (Usual Safety Assessments)

With the exceptions noted in Section 10.9.1 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 10.9.5.
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 15E);
- Urinalysis (for visits after Month 15E urinalysis will be performed only if considered clinically indicated by the investigator);
- Pregnancy testing (for WOCBP);
- Tuberculosis testing;
- Refer to the SoA (Section 1.3) for visits at which these tests are required and to Section 10.2 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 SoA (Section 1.3), 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 4. 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 investigational product 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 investigational product at the current visit. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

Special attention should be paid to ensure that laboratory results are checked against the Guidelines for Participant Safety Monitoring and Discontinuations in Section 10.7 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 investigational product to a participant.** The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. It should be confirmed that the participant is adhering to the contraception method(s) required in the protocol.

Table 4. Windows for Remote Visits, Laboratory Sample Collections, and Special Safety Assessments if Required due to Public Emergencies Including COVID-19

Visit Identifier	Visit Month (Day in Study)	Remote Visit Window (Day in Study)[a]	Lab Collection Window (Day in Study)[b]	Special Safety Assessment Window (Day in Study)[c]
3	Month 1 (Day 31)	±3 days (Day 28-34)	-7/ +14 days (Day 24-45)	NA
4	Month 3 (Day 91)	±7 days (Day 84-98)	-14/ +30 days (Day 77-121)	NA
5	Month 6 (Day 181)	±7 days (Day 174-188)	-14/ +30 days (Day 167-211)	-14/+30 days (Day 167-211)
6	Month 9 (Day 271)	±7 days (Day 264-278)	-14/ +14 days (Day 257-285)	-14/ +60 days (Day 257-331)[c]
7	Month 3E (Day 91E)	±7 days (Day 84E-98E)	-14/ +30 days (Day 77E-121E)	NA
8	Month 6E (Day 181E)	±7 days (Day 174E-188E)	-14/ +30 days (Day 167E-211E)	NA
9	Month 9E (Day 271E)	±7 days (Day 264E-278E)	-14/ +30 days (Day 257E-301E)	-14/ +30 days (Day 257E-301E)
10	Month 12E (Day 361E)	±7 days (Day 354E-368E)	-14/ +30 days (Day 347E-391E)	NA
11	Month 15E (Day 451E)	±7 days (Day 444E-458E)	-14/ +30 days (Day 437E-481E)	-14/ +30 days (Day 437E-481E)
12	Month 21E (Day 631E)	±7 days (Day 624E-638E)	-14/ +30 days (Day 617E-661E)	NA
13	Month 27E (Day 811E)	±7 days (Day 804E-818E)	-14/ +30 days (Day 797E-841E)	-14/ +30 days (Day 797E-841E)
14	Month 33E (Day 991E)	±7 days (Day 984E-998E)	-14/ +30 days (Day 977E-1021E)	NA
15	Month 39E (Day 1171E)	±7 days (Day 1164E-1178E)	-14/ +30 days (Day 1157E-1201E)	-14/ +30 days (Day 1157E-1201E)
16	Month 45E (Day 1351E)	±7 days (Day 1344E-1358E)	-14/ +30 days (Day 1337E-1381E)	NA
17	Month 51E (Day 1531E)	±7 days (Day 1524E-1538E)	-14/ +30 days (Day 1517E-1561E)	-14/ +30 days (Day 1517E-1561E)

a. These are the same as the windows in the protocol SoA (Section 1.3).
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

Table 4. Windows for Remote Visits, Laboratory Sample Collections, and Special Safety Assessments if Required due to Public Emergencies Including COVID-19

Visit Identifier	Visit Month (Day in Study)	Remote Visit Window (Day in Study)[a]	Lab Collection Window (Day in Study)[b]	Special Safety Assessment Window (Day in Study)[c]

visit must be available and reviewed by the investigator prior to shipping investigational product at the current visit.

c. The visit window for the on-site visit (Special Safety Assessments) for Month 9 is -7/+60 days and (Section 10.9.4). During TP3, the only special safety assessment is the audiological assessment.

10.9.3.2. Electrocardiograms

If the participant is unable to visit the study site for an ECG after the Screening visit, the participant may visit an alternative facility, or alternatively in the participant's home, if available, to have the ECG performed according to the guidelines in Section 8.2.4. Qualified study site personnel must order, receive, and review results. For participants in TP3, ECG will not be recorded.

10.9.3.3. Audiological and Neurological Specialist Evaluations

At visits after Screening which require audiological or neurological evaluation, if the participant is unable to visit the designated ancillary center for audiological or neurological evaluation, the audiological history (Part 1 in the Audiometry Guide Worksheet for Post Day 1 visits) and neurological history (General Neurology and Neuropathy Assessment Completion Guidelines) must be collected at the study site; during the remote visit per Section 10.9.2; or during the home health visit per Section 10.9.6. Clinically significant changes should be recorded as AEs in CRF. The audiological evaluations, including the BAEP, and the neurological evaluations must be performed per Section 8.2.6 at the next available opportunity, even if outside of the protocol-specified visit window. Only the audiological evaluation is collected during TP3.

10.9.3.4. Skin Biopsies

At visits after Day 1 which require a skin biopsy, if the participant is unable to visit the study site, then the skin biopsy must be performed at the next available opportunity, even if outside of a protocol-specified visit window. Not collected during TP3.

10.9.4. Month 9 Visit Window

The visit window for the special safety assessments at Month 9 in the setting of a public health emergency is expanded to -7 / +60 days. The usual safety assessments are to be completed as above. The full month 9 visit including the special safety assessments (audiological evaluations, neurological evaluation, and the skin biopsy) have until +60 days to be completed onsite or at the designated ancillary center. If required Special Safety Assessments (Section 10.9) cannot be performed at Month 9, the participant will not be allowed into the active therapy extension phase and must follow Early Termination procedures (Section 7.1).

Double-blind investigational product is dispensed until all the specialized safety assessments have been completed. The site staff should contact the IMPALA Help Desk for assistance.

Active therapy investigational product is dispensed only after all the special safety assessments have been completed and is the start of the extension portion of the study.

10.9.5. 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 contract research organization (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 10.9.2. 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 (TP3 only), 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 (TP3 only) dispensed at a previous visit.

All blister cards, or bottles (TP3 only) and dosing logs must be returned to the study site at the next on-site visit.

10.9.6. Home Health Visits

If available, a home health care service may be utilized to facilitate scheduled visits per the SoA (Section 1.3) 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 ICD 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 and documented in site's source documents (or per local guidelines/regulations) prior to conducting the first home health visit.

The C-SSRS, SALT, and PGI-C cannot be assessed at a home visit.

The following may be performed during a home health visit:

- Review dosing logs and record study intervention, 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 (Section 10.4). Refer to Section 8.2.13 of the protocol and Section 10.9.3.1 regarding pregnancy tests.

- Collection of updated audiological history (Part 1 in the Audiometry Guide Worksheet for Post Day 1 visits) at visits requiring audiological evaluation. with entry of clinically significant changes onto the AE section of the eCRF, as appropriate.
- Collection of interim neurological history (using General Neurology and Neuropathy Assessment Completion Guidelines) must be obtained, with entry of clinically significant changes onto the AE section of the eCRF, as appropriate.
- Body temperature and collection method (eg, oral, tympanic, axillary), pulse rate, and respiratory rate (measured by study participant/caregiver).
- ECG per Section 8.2.4 (only up to Month 15E).
- Hematology.
- Serum chemistry (CK only up to Month 15E).
- Lipid panel (for visits on or before Month 15E).
- Urinalysis. (for visits after Month 15E, urinalysis will be performed only if considered clinically indicated by the investigator)
- Pregnancy testing (for WOCBP).
- Physical examination.

10.9.7. 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 investigational product 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 investigational product per Section 10.7.2 of the protocol.

10.9.8. Efficacy Assessments

The SALT and PGI-C (Section 8.1.2 and Section 8.1.3) are only to be collected during on-site visits.

10.10. Appendix 10: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	alopecia totalis
AU	alopecia universalis
AUC	area under the concentration-time curve
BAEP	brainstem auditory evoked potential
BCR	B cell receptor
BMX	bone marrow tyrosine kinase on chromosome X
BP	blood pressure
BTK	Bruton's tyrosine kinase
CFB	change from baseline
CFP-10	culture filtrate protein 10 kiloDalton
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum plasma concentration
COE	cross-over extension
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease-2019
CRF	case report form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CXR	chest radiograph
CYP	cytochrome P450
dB	decibels
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DNCB	1-chloro-2,4-dinitrobenzene
DPCP	diphenylcyclopropenone
E	Active therapy extension phase
EBA	eyebrow assessment

Abbreviation	Term
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
EOP	end of placebo-controlled phase/beginning of active therapy extension phase
EOS	end of study
EOT	end of treatment
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 cells
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBVDNA	hepatitis B virus deoxyribonucleic acid
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
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IENF	intraepidermal nerve fiber
IENFD	intraepidermal nerve fiber density
IFN	interferon

Abbreviation	Term
Ig	immunoglobulin
IL	interleukin
IMPALA	name of Pfizer's interactive voice response system
IND	investigational new drug application
INH	isoniazid
INR	international normalized ratio
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
LFT	liver function test
LTE	long term extension
MMF	mycophenolate mofetil
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTX	methotrexate
NA	not applicable
NK	natural killer
NOAEL	no observed adverse effect level
NRS	numerical rating scale
PCD	primary completion date
PGI-C	Patient's Global Impression of Change
PHQ-8	Patient Health Questionnaire – 8 items
PI	principal investigator
PK	pharmacokinetics
PN	peripheral neuropathy
PPD	purified protein derivative
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
QT_{cF}	QT corrected using Fridericia's correction factor
RA	rheumatoid arthritis
RNA	ribonucleic acid

Abbreviation	Term
SADBE	squaric acid dibutylester
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SBE	single-blind extension
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
TdP	Torsades de pointes
TEAE	treatment-emergent adverse event
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TESAE	treatment emergent serious adverse event
TH1	type 1 helper
TP	Treatment Period
T-Spot test	T-SPOT®.*TB*
TXK	tyrosine kinase expressed in T cells
TYK2	tyrosine kinase 2
US	United States
ULN	upper limit of normal
UVB	Ultraviolet B
WOCBP	woman of childbearing potential

10.11. Appendix 11: Protocol Amendment 1 History

Document History		
Document	Version Date	Summary and Rationale for Changes
Amendment 1	23 April 2021	• In the Schedule of Activities for Screening and Day 1, "Audiological evaluation and history by an audiologist" the name of the Audiology Study Guide was updated. Rationale: it was updated to its finalized name. • In the Schedule of Activities for the Intervention Period, the header note in the table (Row 4/Column 11) was updated per the PACL 25 Jun 2020. Rationale: updated per the PACL and for clarity. • In the Schedule of Activities for the Intervention Period, "Audiological Evaluation by an audiologist" the name of the Audiology Study Guide was updated to its finalized name. Rationale: it was updated to its finalized name. • In the Schedule of Activities for the Intervention Period, "Pregnancy test" Notes were updated to enable pregnancy tests for outside testing to be provided by the site. Rationale: Enables testing for pregnancy between visits with a test at appropriate level of accuracy. • In the Schedule of Activities for the Intervention Period / Month 6 and Month 9/EOP, added a note that for the EOP visit only (Month 6 or Month 9/EOP, as appropriate), the window for audiological/BAEP central read (including any repeat assessments if deemed necessary by the central reader) is -7/+21 days. All other assessments, including the primary audiological/BAEP assessments, must be completed within ±7 days. Rationale: Allows for audiological/BAEP central read and any repeats. • In the Schedule of Activities for the Intervention Period / Skin punch biopsy for evaluation of axonal dystrophy and IENFD, a note was added that at the EOP visit (Month 6 or Month 9, as appropriate), the skin biopsy must be collected before Active Therapy administration. Rationale: Ensures that secondary safety evaluations are completed prior to the start of active therapy extension phase. • In the Schedule of Activities for the Intervention Period, Study Intervention Dispensing Notes were updated to clarify that at the Month 6 visit (only for those eligible participants who enter the active therapy extension phase at Month 6 [see Section 4.1.]) or 9/EOP visit, if the neurological or audiological/BAEP assessments have not yet been completed, double-blind therapy continues to be dispensed until the neurological and audiological/BAEP assessments (including the

Document History		
Document	Version Date	Summary and Rationale for Changes
		central read confirmation and any repeat assessments if deemed necessary by the central reader) are completed. Active therapy is dispensed (via on-site visit or shipping) only once all the above procedures are completed. Refer to the IRT reference manual for dispensing additional double-blind therapy. Rationale: Ensures that primary and secondary safety evaluations are completed prior to the start of active therapy extension phase. • In the Schedule of Activities for the Intervention Period, "Home pregnancy test" section added. Rationale: Present in protocol but absent from SoA. • In the Schedule of Activities for Early Termination and Follow-up, header note (Row 2/Column 3) footnote added that there is no Visit 12 Rationale: Footnote added to affirm that it is absent. • In the Schedule of Activities for Early Termination and Follow-up, "Audiological Evaluation", the name of the Audiology Study Guide was updated to its finalized name. Rationale: it was updated to its finalized name. • In Section 4.1 Study Design, Overall Design, the ability to add participants due to issues related to peripheral nerve punch biopsy integrity, if needed was added. Rationale: Approximately 60 participants are to have interpretable peripheral nerve punch biopsies. • In Section 4.1, statement added "The skin biopsy must be collected before the start of Active Therapy Extension Phase." Rationale: Ensures that secondary safety evaluations are completed prior to the start of active therapy extension phase. • In Section 5.1 Inclusion criterion 2, clarified that the central reader must confirm that the participant has normal hearing prior to randomization. Rationale: Clarified based on questions from site staff. • In Section 5.2. Exclusion Criteria, Medical Conditions, 1, actions in response to C-SSRS responses were clarified Rationale: Clarified based on questions in similar studies. • In Section 5.2. Exclusion Criteria, Medical Conditions, 21b, added recommended CXR views. Rationale: Added to align with description in Section 8.2.3. • In Section 5.2. Exclusion Criteria, Prohibited Prior/Concomitant Therapy, 22e, clarified wording

Document History		
Document	Version Date	Summary and Rationale for Changes
		Rationale: Clarified in response to questions from Investigators. • Section 5.2. Exclusion Criteria, Prohibited Prior/Concomitant Therapy, 22, on QT prolonging drugs removed. Rationale: An analysis of applicable nonclinical and clinical data indicates 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 5.2 Exclusion Criteria, 23, Updated to clearly exclude participation in investigational vaccine trials. Rationale: Update explicitly excludes concurrent participation in studies of investigational vaccines. • Section 6.2.1. Preparation and Dispensing was updated to add that at the EOP visit (Month 6 or Month 9/EOP, as appropriate), additional double-blind therapy may be dispensed if the neurological and/or audiological/BAEP assessments (including the central read confirmation and any repeat assessments if deemed necessary by the central reader) are not yet completed. Additional double-blind therapy would be dispensed as a 32-day supply, but dosing may not extend past the end of the +21 day EOP visit window. Once neurological and audiological/BAEP EOP assessments are complete, active therapy may be dispensed either on site or by shipping to the study participant. Rationale: Allows continued double-blind dosing until safety assessments are completed, within a defined window (+21 days). • Section 6.5.3. Vaccinations, was updated given the widespread use of vaccines against COVID-19 Rationale: This change was made to provide affirmatory clarity regarding COVID-19 vaccination before, during, and after the study. • Section 8.2.6. Audiological Evaluations, clarification that the central reader reviews the audiological results. Rationale: To provide clarity for study sites. • Section 8.2.6. Audiological Evaluations, the name of the Audiology Study Guide was updated. Rationale: it was updated to its finalized name. • Section 8.2.7. Brainstem Auditory Evoked Potential Evaluations removed “local” from the definition of which results are used for analysis. Rationale: Clarifies that only results which have undergone central read are used for analysis. • Section 8.2.9.2.2 Canfield Rash Manual updated to Canfield Photography User Manual.

Document History		
Document	Version Date	Summary and Rationale for Changes
		Rationale: name as written was incorrect. • Section 8.2.10.1.3. Subsequent Tuberculosis Testing, was updated regarding actions to be taken in the event of a positive result in an ongoing participant. Rationale: Updated to include evaluation by local specialists. • In Section 8.2.11.1. Columbia Suicide Severity Rating Scale (C-SSRS), actions in response to C-SSRS responses were clarified in alignment with exclusion criterion 1. Rationale: Updated for greater clarity. • Section 8.2.14. The name of the 'Rater Qualifications Manual' was updated to 'Rater Assessment Manual' Rationale: It was updated to its finalized name. • Section 8.3.6. Cardiovascular and Death Events, was updated to reflect the adjudication process Rationale: Reference to the adjudication was added. • Section 8.3.8. Adverse Events of Special Interest, was updated to add a reference to the section with the definition and the reporting process. Rationale: This was updated for clarity. • Section 8.10. Health Economics, was deleted Rationale: This section was deleted as per PACL 25 Jun 2020. • Section 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information, was updated to remove the word 'adolescents'. Rationale: There are no adolescents in this study. • Section 10.6. Appendix 6. Reference for Global Prevalence of Hepatitis B virus infection changed to footnote from in-line text. Rationale: for consistency of style. • Section 10.7.1. Monitoring, a footnote was added to the table in reference to the timeframe for re-testing Rationale: This was updated to reflect that the timeframe depends on the timing of the awareness of the abnormal result. • Section 10.7.2. Monitoring, Laboratory Abnormalities a second sentence was added regarding the timeframes for retesting Rationale: This was updated to reflect that the timeframe depends on the timing of the awareness of the abnormal result. • Section 10.7.2. Monitoring, Discontinuation/End of Treatment Monitoring, bullet 2, the name of the Audiology Study Guide was updated. Rationale: it was updated to its finalized name. • Section 10.9. Appendix 9: Alternative Measures During Public Emergencies, was added to permit the study to continue during a health emergency.

Document History		
Document	Version Date	Summary and Rationale for Changes
		Rationale: Added to permit the study to continue while maintaining treatment continuity and safety oversight. • Throughout document: administrative changes. Rationale: Added for clarity, internal consistency, and grammatical correctness.
Original protocol	08 May 2020	N/A

11. REFERENCES

1. Gilhar, A, Etzioni, A, Paus, R. Alopecia areata. N Engl J Med. 2012;366(16):1515-25.
2. Hordinsky, MK. Overview of alopecia areata. J Investig Dermatol Symp Proc. 2013;16(1):S13-5.
3. Kassira, S, Korta, DZ, Chapman, LW, et al. Review of treatment for alopecia totalis and alopecia universalis. Int J Dermatol. 2017;56(8):801-10.
4. Tosti, A, Bellavista, S, Iorizzo, M. Alopecia areata: a long term follow-up study of 191 patients. J Am Acad Dermatol. 2006;55(3):438-41.
5. NAAF website. NAAF website at https://www.naaf.org/alopecia-areata/alopecia-areata-and-emotional-wellness-in-children. Accessed 08 Aug 2019.
6. Hunt, N, McHale, S. The psychological impact of alopecia. BMJ. 2005;331(7522):951-3.
7. McGarvey, EL, Baum, LD, Pinkerton, RC, et al. Psychological sequelae and alopecia among women with cancer. Cancer Pract. 2001;9(6):283-9.
8. Colon, EA, Popkin, MK, Callies, AL, et al. Lifetime prevalence of psychiatric disorders in patients with alopecia areata. Compr Psychiatry. 1991;32(3):245-51.
9. Ruiz-Doblado, S, Carrizosa, A, Garcia-Hernandez, MJ. Alopecia areata: psychiatric comorbidity and adjustment to illness. Int J Dermatol. 2003;42(6):434-7.
10. Chen, W, Mempel, M, Traidl-Hofmann, C, et al. Gender aspects in skin diseases. J Eur Acad Dermatol Venereol. 2010;24(12):1378-85.
11. Sellami, R, Masmoudi, J, Ouali, U, et al. The relationship between alopecia areata and alexithymia, anxiety and depression: a case-control study. Indian J Dermatol. 2014;59(4):421.
12. Villasante Fricke, AC, Miteva, M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015;8:397-403.
13. Liakopoulou, M, Alifieraki, T, Katideniou, A, et al. Children with alopecia areata: psychiatric symptomatology and life events. J Am Acad Child Adolesc Psychiatry. 1997;36(5):678-84.
14. Dubois, M, Baumstarck-Barrau, K, Gaudy-Marqueste, C, et al. Quality of life in alopecia areata: a study of 60 cases. J Invest Dermatol. 2010;130(12):2830-3.
15. Ghajarzadeh, M, Ghiasi, M, Kheirkhah, S. Associations between skin diseases and quality of life: a comparison of psoriasis, vitiligo, and alopecia areata. Acta Med Iran. 2012;50(7):511-5.
16. Masmoudi, J, Sellami, R, Ouali, U, et al. Quality of life in alopecia areata: a sample of tunisian patients. Dermatol Res Pract. 2013;2013:983804.
17. de Hollanda, TR, Sodre, CT, Brasil, MA, et al. Quality of life in alopecia areata: a case-control study. Int J Trichology. 2014;6(1):8-12.
18. Baghestani, S, Zare, S, Seddigh, SH. Severity of Depression and Anxiety in Patients with Alopecia Areata in Bandar Abbas, Iran. Dermatol Reports. 2015;7(3):6063.
19. Jankovic, S, Peric, J, Maksimovic, N, et al. Quality of life in patients with alopecia areata: a hospital-based cross-sectional study. J Eur Acad Dermatol Venereol. 2016;30(5):840-6.
20. Rencz, F, Gulacsi, L, Pentek, M, et al. Alopecia areata and health-related quality of life: a systematic review and meta-analysis. Br J Dermatol. 2016;175(3):561-71.

21. Zhang, M, Zhang, N. Quality of life assessment in patients with alopecia areata and androgenetic alopecia in the People's Republic of China. Patient Prefer Adherence. 2017;11:151-5.
22. Hordinsky, MK. Current Treatments for Alopecia Areata. J Investig Dermatol Symp Proc. 2015;17(2):44-6.
23. Hordinsky, M, Donati, A. Alopecia areata: an evidence-based treatment update. Am J Clin Dermatol. 2014;15(3):231-46.
24. Alkhalifah, A, Alsantali, A, Wang, E, et al. Alopecia areata update: part II. Treatment. J Am Acad Dermatol. 2010;62(2):191-202, quiz 3-4.
25. Messenger, AG, McKillop, J, Farrant, P, et al. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. Br J Dermatol. 2012;166(5):916-26.
26. Delamere, FM, Sladden, MM, Dobbins, HM, et al. Interventions for alopecia areata. Cochrane Database Syst Rev. 2008(2):CD004413.
27. Gilhar, A. Collapse of immune privilege in alopecia areata: coincidental or substantial? J Invest Dermatol. 2010;130(11):2535-7.
28. Bertolini, M, Zilio, F, Rossi, A, et al. Abnormal interactions between perifollicular mast cells and CD8+ T-cells may contribute to the pathogenesis of alopecia areata. PLoS One. 2014;9(5):e94260.
29. Guttman-Yassky, E, Ungar, B, Noda, S, et al. Extensive alopecia areata is reversed by IL-12/IL-23p40 cytokine antagonism. J Allergy Clin Immunol. 2016;137(1):301-4.
30. Fuentes-Duculan, J, Gulati, N, Bonifacio, KM, et al. Biomarkers of alopecia areata disease activity and response to corticosteroid treatment. Exp Dermatol. 2016;25(4):282-6.
31. Xing, L, Dai, Z, Jabbari, A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043-9.
32. Kennedy Crispin, M, Ko, JM, Craiglow, BG, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight. 2016;1(15):e89776.
33. Craiglow, BG, King, BA. Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol. 2014;134(12):2988-90.
34. Jabbari, A, Dai, Z, Xing, L, et al. Reversal of Alopecia Areata Following Treatment With the JAK1/2 Inhibitor Baricitinib. EBioMedicine. 2015;2(4):351-5.
35. Harris, JE, Rashighi, M, Nguyen, N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016;74(2):370-1.
36. Mackay-Wiggan, J, Jabbari, A, Nguyen, N, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight. 2016;1(15):e89790.
37. King, BA, editor Treating alopecia areeata, vitiligo, and atopic dermatitis: JAK inhibitors, something new for dermatology. Am Acad Dermatol Scientific Meeting; 19 Feb 2018.
38. Shapiro, J, editor Hair Today, Gone Tomorrow! . Maui Derm for Dermatologists meeting; 31 Jan 2018.
39. Liu, LY, Craiglow, BG, Dai, F, et al. Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients. J Am Acad Dermatol. 2017;76(1):22-8.
40. Berg, LJ, Finkelstein, LD, Lucas, JA, et al. Tec family kinases in T lymphocyte development and function. Annu Rev Immunol. 2005;23:549-600.

41. Schwartzberg, PL, Finkelstein, LD, Readinger, JA. TEC-family kinases: regulators of T-helper-cell differentiation. Nat Rev Immunol. 2005;5(4):284-95.
42. Berglof, A, Hamasy, A, Meinke, S, et al. Targets for Ibrutinib Beyond B Cell Malignancies. Scand J Immunol. 2015;82(3):208-17.
43. Ito, T, Ito, N, Saatoff, M, et al. Maintenance of hair follicle immune privilege is linked to prevention of NK cell attack. J Invest Dermatol. 2008;128(5):1196-206.
44. Picardo, M, Dell'Anna, ML, Ezzedine, K, et al. Vitiligo. Nat Rev Dis Primers. 2015;1:15011.
45. Deshpande, SN, Houston, L., Keeith, R.W. . Hearing Testing, Auditory Brainstem Response (ABR). In: Kountakis SE, editor. Encyclopedia of Otolaryngology, Head and Neck Surgery. Berlin, Heidelberg: Springer; 2013.
46. England, JD, Gronseth, GS, Franklin, G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2009;72(2):177-84.
47. Lauria, G, Bakkers, M, Schmitz, C, et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. J Peripher Nerv Syst. 2010;15(3):202-7.
48. Valentine, WM. Toxic Peripheral Neuropathies: Agents and Mechanisms. Toxicol Pathol. 2019:192623319854326.
49. Burakgazi, AZ, Messersmith, W, Vaidya, D, et al. Longitudinal assessment of oxaliplatin-induced neuropathy. Neurology. 2011;77(10):980-6.
50. Khoshnoodi, MA, Truelove, S, Burakgazi, A, et al. Longitudinal Assessment of Small Fiber Neuropathy: Evidence of a Non-Length-Dependent Distal Axonopathy. JAMA Neurol. 2016;73(6):684-90.
51. Wyrwich, KWKH, Knight S. et al. The Role of Patients in the Development of the Alopecia Areata Investigator Global Assessment (AA-IGA), a Clinican-Reported Measure Evaluating Clinically Meaningful Success in Clinical Trials. Alopecia Areata Research Summit; New York, NY2018.
52. Olsen, EA. Investigative guidelines for alopecia areata. Dermatol Ther. 2011;24(3):311-9.
53. Polaris Observatory, C. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383-403.
54. Posner, K, Oquendo, MA, Gould, M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-43.
55. Kroenke, K, Spitzer, RL. The PHQ-9: A new depression diagnostic and severity measure. Psychiatric Annals. 2002;32(9):505-15.
56. Chan, IS, Zhang, Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55(4):1202-9.